Volume 15 | 4/2025

Issn 2160-9381

Impact Factor: 2.3

Dermatology Practical & Conceptual

OFFICIAL JOURNAL OF THE INTERNATIONAL DERMOSCOPY SOCIETY

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Long-term persistence with guselkumab: a 5-year multicenter retrospective study across 14 dermatology centers in Italy - *Nicoletta Bernardini, Giacomo Caldarola, Antonio Giovanni Richetta, Maria Esposito, Federica Trovato, Paolo Amerio, Edvige Morea, Claudio Bonifati, Dario Graceffa, Pier Luigi Bruni, Domenico Giordano, Severino Persechino, Annamaria Mazzotta, Gaia Moretta, Gianluca Pagnanelli, Sabatino Pallotta, Jasmine Anedda, Cristina Mugheddu, Emanuele Miraglia, Vincenzo Panasiti, Elisa Molinelli, Oriana Simonetti, Maria Concetta Fargnoli, Ketty Peris, Giovanni Pellacani, Concetta Potenza, Annunziata Dattola*

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Dermatology Practical & Conceptual

OFFICIAL JOURNAL OF THE INTERNATIONAL DERMOSCOPY SOCIETY

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Special Issue on Artificial Intelligence in Dermatology: A Call for Collaborative Innovation
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DOI: https://doi.org/10.5826/dpc.1504a7043

ORIGINAL ARTICLE

Long-term persistence with guselkumab: a 5-year multicenter retrospective study across 14 dermatology centers in Italy
Nicoletta Bernardini, Giacomo Caldarola, Antonio Giovanni Richetta, Maria Esposito, Federica Trovato, Paolo Amerio, Edvige Morea, Claudio Bonifati, Dario Graceffa, Pier Luigi Bruni, Domenico Giordano, Severino Persechino, Annamaria Mazzotta, Gaia Moretta, Gianluca Pagnanelli, Sabatino Pallotta, Jasmine Anedda, Cristina Mugheddu, Emanuele Miraglia, Vincenzo Panasiti, Elisa Molinelli, Oriana Simonetti, Maria Concetta Fargnoli, Ketty Peris, Giovanni Pellacani, Concetta Potenza, Annunziata Dattola
DOI: https://doi.org/10.5826/dpc.1504a6646

Guselkumab demonstrates high long-term treatment persistence in real-world clinical practice, with over 70% of patients remaining on therapy after 5 years. Prior exposure to IL-17 inhibitors was the primary factor linked to discontinuation.

Factors Associated with Exacerbation in Psoriasis compared to Eczema
Thanaphon Anutraungkool, Suteeraporn Chaowattanapanit, Charoen Choonhakarn, Panita Limpawattana, Narachai Julanon, Rachot Wongjirattikarn, Krauwan Kruahong, Anongnit Mokkarat, Kittisak Sawanyawisuth
DOI: https://doi.org/10.5826/dpc.1504a5630

Internal factors, particularly stress and inadequate sleep, are more strongly associated with psoriasis exacerbation. In contrast, external factors such as humidity and dust predominantly trigger eczema flare-ups, supporting disease-specific prevention strategies.

Risk Factors and Epidemiology of Acne Severity and Acne Scar Development: A Comprehensive Clinical Study
Fatma Etgü, Gul Sekerlisoy Tatar
DOI: https://doi.org/10.5826/dpc.1504a6108

Early onset, male sex, and severe acne are significant risk factors for acne scarring. Identifying these risk factors early and initiating timely treatment can reduce scarring and improve outcomes.

Predictive Factors of Secukinumab Response in Korean Hidradenitis Suppurativa Patients: Insights from a 48-Week Trial
Ngoc Ha Nguyen, Sang Gyu Lee, Seoyoon Ham, Ju Hee Lee, Young In Lee
DOI: https://doi.org/10.5826/dpc.1504a5933

Faster initial responses to secukinumab in hidradenitis suppurativa patients are observed in those with milder disease, earlier treatment, and no previous biological therapy. Secukinumab also significantly reduced antibiotic usage.

Artificial Intelligence in Patient Education for Androgenetic Alopecia: A Comparative Study of ChatGPT, Gemini, and Deepseek R1
Seçil Yigen Iritaş
DOI: https://doi.org/10.5826/dpc.1504a5929

In our comparative analysis, responses to patient questions on androgenetic alopecia were evaluated for accuracy, readability, and user experience. ChatGPT 4.0 and Gemini Flash 1.5 were reliable, whereas DeepSeek R1 showed limitations.

GRWD1 Drives Melanoma Growth Through NF-B Signaling Pathway
Dursun Turkmen, Rafet Ozbey, Berna Ozdem, Saadet Alan, Ayten Kilincli Cetin , Fatma Bengisu Baran , Berat Dogan , Nihal Altunisik, Zekiye Kanat , Serpil Sener, Ibrahim Tekedereli
DOI: https://doi.org/10.5826/dpc.1504a5918

GRWD1 promotes melanoma progression by activating NF-B signaling, enhancing proliferation and migration while inhibiting apoptosis. Its overexpression correlates with poor prognosis, suggesting GRWD1 as a potential therapeutic target.

Ultraviolet-Induced Fluorescence and Sub-Ultraviolet Reflectance Dermatoscopy of Grover's Disease (Transient Acantholytic Dermatosis): a Retrospective Single-Center Cohort Study
Paweł Pietkiewicz, Cristian Navarrete-Dechent, Adhikari Adarsha, Carmen Cantisani, Mohamad Goldust, Natalia Salwowska, Norbert Kiss
DOI: https://doi.org/10.5826/dpc.1504a5980

sUVRD frequently reveals eccrine duct involvement in Grover's disease, suggesting pathogenic significance. Routine dermatoscopy may improve early detection in atypical, oligosymptomatic patients. A plausible association with skin cancer require further research.

Re-evaluation of the Anatomical Distribution Patterns in Large Congenital Melanocytic Nevus
Sevkiye Aydogdu, Can Baykal
DOI: https://doi.org/10.5826/dpc.1504a5113

Our study identified one novel clinical pattern and three subgroups within existing classifications of large congenital melanocytic nevi based on comparisons with their embryological origins.

Stabilizing Progressive Vitiligo With Systemic Treatment: Identifying Factors Associated With Patients Requiring Prolonged Treatment Duration
Ting-Ting Yang, Cheng-Che Lan
DOI: https://doi.org/10.5826/dpc.1504a5210

Older vitiligo patients and patients with lesions including face are more likely to have their disease stabilized with 16 weeks of oral mini-pulse corticosteroid or methotrexate without recurrence within six months.

Dermoscopic Features of Acral Palmoplantar Nevi: Age and Site Correlation in a North African Cohort

Meryem Soughi, Oumaima Bouraqqadi, Zakia Douhi, Sara Elloudi, Hanane Baybay, Fatimazahra Mernissi

DOI: https://doi.org/10.5826/dpc.1503a5065

This study aimed to examine the different dermoscopic patterns of palmar-plantar nevi and their correlation with age and location in our population.Recognition of these patterns is crucial for establishing an accurate diagnosis, distinguishing acral nevi from ALMs, and avoiding unnecessary excisions. The interpretation of dermoscopic patterns must take into account the anatomical location on the plantar surface as well as the patient's age.

Brodalumab efficacy in psoriasis patients with inadequate response to IL-23 or IL-12/23 inhibitors: multicenter Italian retrospective analysis - IL PSO (Italian Landscape Psoriasis)

Diego Orsini, Maria Concetta Fargnoli, Martina Burlando, Anna Campanati, Elena Campione, Claudio Guarneri, Alessandra Narcisi, Paolo Pella, Paolo Romita, Massimo Travaglini, Leonardo Zichichi, Luisa Maria Halina Arancio, Chiara Assorgi, Ginevra Baggini, Riccardo Balestri, Luca Bianchi, Alexandra Maria Giovanna Brunasso, Anna Elisabetta Cagni, Giacomo Caldarola, Gianluca Calianno, Antonio Carpentieri, Martino Carriero, Andrea Carugno, Franco Cona, Antonio Costanzo, Emanuele Cozzani, Giacomo Dal Bello, Paolo Dapavo, Annunziata Dattola, Antonio Di Tano, Federico Diotallevi, Marianna Donnarumma, Elena De Col, Maria Esposito, Carmen Silvia Fiorella, Marco Galluzzo, Francesca Graziola, Giovanni Carlo Lazzaro Danzuso, Agostina Legori, Matteo Licciardello, Viviana Lora, Piergiorgio Malagoli, Matteo Megna, Federica Mola, Gaia Moretta, Andrea Muracchioli, Attilia Musumeci, Maria Letizia Musumeci, Gianluca Pagnanelli, Vincenzo Panasiti, Eugenio Provenzano, Simone Ribero, Daniele Rizzo, Marco Rubatto, Oriele Sarno, Davide Strippoli, Fabrizio Vaira, Dario Graceffa

DOI: https://doi.org/10.5826/dpc.1504a6010

This study shows that brodalumab is effective and safe in psoriasis patients unresponsive to IL-23 or IL-12/23 inhibitors, achieving rapid and sustained PASI and DLQI improvements with mostly mild adverse events.

Treatment Failure in Scabies: Assessment of Risk Factors in a Multicenter Cross-Sectional Study

Yasemin Erdem, Algun Polat Ekinci, Mucahit Ergun, Ceylan Bulat, Artun Kırker, Hamit Dogus Turgut, Afra Cesur, Ilknur Kıvanc Altunay, Zeynep Topkarci

DOI: https://doi.org/10.5826/dpc.1504a5360

Treatment failure in scabies remains a current and significant problem. Incorrect application of topical medications and improper implementation of hygiene measures are among the major factors contributing to treatment failure.

Non-Invasive Skin Imaging of Pseudoxanthoma Elasticum Using Dynamic Optical Coherence Tomography: Insights from a Case-Control Study

Camilla Chello, Alessandro Laghi, Ludovica Melchiorri, Ilaria Zubba, Emanuele Miraglia, Marco Ardigò, Giovanni Pellacani, Sandra Giustini

DOI: https://doi.org/10.5826/dpc.1503a5260

Dynamic optical coherence tomography (D-OCT) has the potential to transform the early diagnosis and monitoring of pseudoxanthoma elasticum by providing a noninvasive alternative to traditional skin biopsies.

Post COVID Alopecia in the Indian Subcontinent - A Harbinger of Disease Severity

Anshitha Vurimindi Kadudas, Tina Priscilla Katta, Neha Gala, Anu Mohandas, Manmohan Gavvala, Rishita Pogula, Sai Rashmitha Pagadala, Anvi K. Reddy, Spurthi Subramanyam

DOI: https://doi.org/10.5826/dpc.1504a5417

COVID-19 remains a primary cause of alopecia. Post-COVID alopecia impacts 37.8% of individuals, with female sex, infection severity, and stress as crucial determinants. Early recognition ensures enhanced therapeutic results.

GRINCH Index: Measuring Patient Satisfaction During Christmas Holiday Gift Programs

Giulio Gualdi, Laura Bigi, Clara De Simone, Paolo Amerio, Francesco Loconsole, Federico Bardazzi, Lidia Sacchelli, Michela Starace, Andrea Conti, Manuela Baldari, Anna Balato, Giovanna Brunasso, Giacomo Caldarola, Anna Campanati, Gabriella Fabbrocini, Maria Concetta Fargnoli, Claudio Guarneri, Piergiorgio Malagoli, Andrea Paradisi, Francesca Prignano, Mario Puviani, Valentina Dini, Simone Soglia, Ilaria Salvi, Martina Burlando

DOI: https://doi.org/10.5826/dpc.1504a5527

This study introduces the GRINCH index to assess patient satisfaction via holiday gift-giving. Results show higher gift rates among older dermatologists and chronic patients, highlighting the value of strong doctor-patient relationships.

PRAME immunohistochemical expression in recurrent/traumatized melanocytic nevi and the pitfall of expression by reactive fibroblasts

Emma Carraturo, Giuseppe D'Abbronzo, Giuseppe Argenziano, Gabriella Brancaccio, Camila Scharf, Elvira Moscarella, Renato Franco, Andrea Ronchi

DOI: https://doi.org/10.5826/dpc.1504a5564

This study evaluated PRAME immunohistochemical expression in recurrent/traumatized melanocytic nevi (RTMN), showing no positivity in melanocytic components but significant expression in fibroblastic scar tissue. These findings highlight the diagnostic implications of PRAME in RTMN.

Elective First-Line Use of Dimethyl Fumarate in Psoriasis: Insights from an Italian Cohort

Alessandro Giunta, Maria Esposito, Elena Campione, Martina Burlando, Giacomo Caldarola, Viviana lora, Federico Diotallevi, Ersilia Tolino, Gianmarco Silvi, Emanuele Cozzani, Ruslana Gaeta Shumak, Rosaria Fidanza, Paolo Antonetti, Lorenzo Maria Pinto, Valentina Mirisola, Maria Concetta Fargnoli, Luca Bianchi, Francesca Prignano

DOI: https://doi.org/10.5826/dpc.1504a5458

Dimethyl fumarate (DMF) demonstrates consistent efficacy and safety as a first-line treatment for moderate psoriasis, particularly in patients with initial disease. Despite early adverse events, its long-term tolerability and suitability for patients with comorbidities make it an essential option in systemic therapy.

Tildrakizumab as a Potential Option for Early Psoriatic Arthritis in Patients with Metabolic Comorbidities and Psoriasis: a Case Series

Fabio Artosi, Caterina Lanna, Ruslana Gaeta Shumak, Cristiana Borselli, Gaetana Costanza, Antonia Rivieccio, Diego Orsini, Sara Lambiase, Laura Diluvio, Luca Bianchi, Elena Campione

DOI: https://doi.org/10.5826/dpc.1504a5570

Tildrakizumab, showed significant efficacy also on early, mild psoriatic arthritis in patients affected also by psoriasis and metabolic comorbidities, with marked improvement in joint, skin, and quality-of-life scores, despite prevalent metabolic comorbidities. These findings suggest a potential disease-modifying role of IL-23 inhibition in early PsA.

Unveiling Infantile Hemangiomas: A Comprehensive Study of Patterns, Presentations, and Complications

Prashansa Jaiswal, Jyoti Singh, Aishwarya Dua, Aaditya Sirohi, Febin Ashraf

DOI: https://doi.org/10.5826/dpc.1504a5515

Infantile hemangiomas appear most frequently in preterm female infants who develop these growths mainly on their head and neck

region. Early identification of precursor skin lesions enables doctors to start appropriate treatment during the optimal time which reduces both the need for cosmetic procedures and functional impairments.

Association Between Altered Gut Microbiota and Acne Vulgaris: A Comparative Study of Trimethylamine N-Oxide Levels in Patients and Healthy Controls

Eylül Ceren Bal Bayazıtlı, Gülhan Aksoy Saraç, Andaç Uzdoğan, Onur Acar, Hatice Busra Karaman, Alperen Külhan, Akın Aktaş

DOI: https://doi.org/10.5826/dpc.1504a5486

Elevated serum TMAO levels in acne vulgaris highlight the gut–skin axis and suggest dietary and microbiota-related factors may contribute to acne development.

Spontaneous Regression of Well-Differentiated Squamous Cell Skin Cancer Following Partial, Diagnostic Biopsy: Retrospective Cohort in Queensland

David Wilkinson, Julia Sottovia, Sonja Hoogstad

DOI: https://doi.org/10.5826/dpc.1504a5632

We report high rates of apparent spontaneous regression, following partial, diagnostic biopsy of well-differentiated squamous cell cancer. Preliminary observations suggest the phenomenon may occur in about one third of patients.

Dupilumab: an Additional Arrow in the Quiver for Prurigo Nodularis? Data From a Real-Life Setting

Roberta Di Caprio, Stefano Caccavale, Eugenia Veronica Di Brizzi, Caterina Giorgio, Aleksandra Stefaniak, Giuseppe Argenziano, Anna Balato

DOI: https://doi.org/10.5826/dpc.1504a5639

Our findings support the use of dupilumab as an effective treatment option for PN, with significant improvements in pruritus, quality of life, and disease severity compared to antidepressant therapy.

Dermoscopy as a Predictor of Photodynamic Therapy Outcomes in Actinic Keratoses and Bowen's Disease: Prospective Study in Solid Organ Transplant Patients

Laura Bernal Masferrer, Tamara Gracia Cazaña, Marcial Álvarez Salafranca, Isabel Bernad Alonso, Sara España Fernández de Valderrama, Mariana Claudia Matei, Francisco Javier Paul Ramos, Yolanda Gilaberte

DOI: https://doi.org/10.5826/dpc.1504a5645

Dermoscopy may help predict response to photodynamic therapy in actinic keratoses and Bowen's disease among solid organ transplant recipients. White structureless areas in actinic keratoses and rosettes in Bowen's disease were associated with treatment resistance.

All Eyes on Dermoscopy: Features of Benign Conjunctival Melanocytic Lesions

Dimitrios Sgouros, Panagiota Theofilogiannakou, Georgia Pappa, Konstantinos Liopyris, Eftychia Kitsiou, Anna Syrmali, Sofia Theotokoglou, Emmanouil Karampinis, Aimilios Lallas, Zoe Apalla, Alexander Katoulis

DOI: https://doi.org/10.5826/dpc.1504a5596

This study outlines the clinical and dermoscopic characteristics of benign conjunctival melanocytic lesions and underscores the need for further research to validate potential associations with total body nevus count.

Real-World Safety of Oral Isotretinoin in Patients During Sunny Months: Retrospective Cohort Study

Elisa Marzola, Emma Pedarzani, Giorgia Valpiani, Sofia Fraternale, Giulia Toni, Vincenzo Bettoli, Monica Corazza, Alessandro Borghi

DOI: https://doi.org/10.5826/dpc.1504a5612

Reducing the daily dose of oral isotretinoin during sunny months may decrease side effects without compromising effectiveness. This suggests no need to suspend or delay oral isotretinoin during sunny seasons.

Autoantibodies against Components of Sensory Nerve Formations in the Intervertebral Disks and Adjacent Structures are Antigens Recognized by the Sera from Patients Affected by a New Variant of Endemic Pemphigus in El Bagre, Colombia

Ana Maria Abreu-Velez, Jorge Mario Velez Arango, Yulieth Alexandra Upegui Zapata, Adriana Milena Olarte Aponte, Melisa Sofia Naranjo Vegas , Ivan Naranjo Vegas, Jose Antonio Vega Alvarez, Takashi Hashimoto, Michael S Howard

DOI: https://doi.org/10.5826/dpc.1504a5649

An orphan autoimmune disease (a new variant of endemic pemphigus foliaceus, EPF; denominated pemphigus Abreu-Manu, or El Bagre-EPF) is present endemically in El Bagre, Colombia. We discover autoantibodies to cells junctions, neural receptors, at the intervertebral area, making this disease the ideal to study spine problems.

Differential Expression of Claudin-3 and Claudin-1 in Mycosis Fungoides: Implications for Disease Monitoring

Akın Aktaş, Funda Erduran, Burcu Tuğrul, Funda Eren, Esra Fırat Oğuz

DOI: https://doi.org/10.5826/dpc.1503a5679

Mycosis fungoides lesions exhibit differential expression of claudin-1 and claudin-3, reflecting progressive disruption of epidermal tight junctions. These findings suggest their potential value as biomarkers for disease monitoring.

Retrospective Analysis of Second Primary Malignancies in Patients with Mycosis Fungoides and Sézary Syndrome in Croatia

Mikela Petkovic, Ivana Ilic, Romana Ceovic

DOI: https://doi.org/10.5826/dpc.1504a5683

Patients with mycosis fungoides face an increased risk of developing second primary malignancies. Despite this, current guidelines lack recommendations for additional cancer screening. Regular preventive screenings are advised for early detection.

Pigment Network Analysis in Melanoma and Nevi: Retrospective Study from Snippets to Full Dermoscopic Images

Noa Kremer, Isabella N. Dana, Emmanouil Chousakos, Larissa M. Pastore, Halpern C. Halpern, Stephen W. Dusza, Jochen Weber, Ofer Reiter , Aimilios Lallas, Cristian Navarrete-Dechent, Ralph Braun, Harold Rabinovitz, Gustavo Carvalho, Rashek Kazi, Rozina B. Zeidan , Shirin Bajaj, Nicholas R. Kurtansky, Ashfaq Marghoob

DOI: https://doi.org/10.5826/dpc.1504a5700

Expert classification of the pigment network, especially in melanomas, is influenced by viewing the whole lesion versus snippets, with both the objective morphology of the network and the subjective interpretation of other lesion features playing a role.

Therapeutic Modulation Of Peripheral Blood Cells And Inflammatory Indices During 52 Weeks Of Risankizumab In Responder Patients With Moderate-to-Severe Psoriasis: Results From A Multicenter Prospective Study

Antonella Di Cesare, Elia Rosi, Emanuele Trovato, Leonardo Pescitelli, Salvatore Panduri, Flavia Manzo Margiotta, Alessandra Michelucci, Eugenio Capalbo, Martina Dragotto, Michela Magnano, Susanna Rossari, Imma Savarese, Gionata Buggiani, Nicola Milanesi, Elisa Lorenzoni, Federica Ricceri, Marco Romanelli, Pietro Rubegni, Nicola Pimpinelli, Francesca Prignano

DOI: https://doi.org/10.5826/dpc.1504a5733

Biologic therapies act on specific immune-pathogenic pathways and potentially on systemic inflammation as well. Risankizumab modulates relevant peripheral inflammatory indices such as neutrophils-to-lymphocyte-ratio, pan-immune-inflammation-value, systemic-immune-inflammation-index, and systemic-immune-response-index, especially in super-responder patients, with potential impact on long-term psoriatic patients' prognosis.

Predictors of Early Response and Relapse in Chronic Spontaneous Urticaria Treated with Omalizumab: The Role of Age, Sex, Disease Duration, and UAS7

Mehmet Enes Güner, Perihan Ozturk, Ozan Can Yaray, Esra Merve Evran Kılıç, Mine Müjde Kuş

DOI: https://doi.org/10.5826/dpc.1504a6169

Lower baseline UAS7 and shorter disease duration predict early response to omalizumab in CSU. Younger age and female sex may be associated with a lower risk of relapse.

REVIEW

Clinicopathological factors Predicting Melanoma Recurrence: A Study from South East Ireland

Aneela Razzaq, Maryam Shahad, Anam Allah Ditta

DOI: https://doi.org/10.5826/dpc.1504a6006

Advancing age, tumor stage, Breslow thickness, Clark stage, ulceration, and lymphovascular invasion are significant predictors of melanoma recurrence. Early identification of high-risk patients can guide tailored surveillance and management.

Rethinking Melanocytic Tumors: A Critical Appraisal of the WHO Classification and the Myth of Nevus-to-Melanoma Progression

Giuseppe Argenziano, Giulia Briatico, Eugenia Veronica Di Brizzi, Camila Scharf, Gabriella Brancaccio, Elvira Moscarella, Maria Maddalena Nicoletti, Pasquale Verolino, Aimilios Lallas, Harald Kittler

DOI: https://doi.org/10.5826/dpc.1504a6994

This review challenges the WHO melanoma classification, arguing most melanomas arise de novo. It proposes a simplified, clinically driven reclassification to improve diagnosis, reduce overinterpretation, and better guide treatment.

Targeted Therapies and Pharmacologic Advances in Mucous Membrane Pemphigoid: A Comprehensive Review

Vera Nikolaevna Busol, Nikita Victorovich Kudryashov

DOI: https://doi.org/10.5826/dpc.1504a5749

More research is required in relation to the pathogenesis of MMP and the search for novel well-tolerated options with minimal adverse effects for monotherapy or in combination with other pharmacological agents.

Advanced Skin Imaging Techniques for Patients with Skin of Color: Clinical and Technological Insights

Dorra Guermazi, Elie Saliba

DOI: https://doi.org/10.5826/dpc.1504a5762

This review highlights advancements in skin imaging technologies and their challenges in skin of color, emphasizing the need for inclusive research, AI-driven diagnostics, and tailored imaging techniques to ensure equitable dermatologic care.

Evaluation of Clinical Studies of Patients With Dermatophyte Infections Caused by Trichophyton indotineae: Treatment Response and Resistance to Antifungal Medications

Funda Tamer, Muhterem Polat

DOI: https://doi.org/10.5826/dpc.1504a5517

Trichophyton indotineae is a newly described dermatophyte species that causes widespread and treatment-resistant fungal skin infections. Available data are insufficient to establish standard treatment regimens for these refractory cutaneous infections.

Sleep Disturbances and Acne: A Comprehensive Review

Michelle Samaniego, Montserrat Alonso, Nehaa Sohail, Ladan Mostaghimi

DOI: https://doi.org/10.5826/dpc.1504a5530

Acne and sleep are bidirectionally linked, with poor sleep worsening acne through hormonal and immune pathways, and acne impairing sleep through physical and psychological factors, highlighting the need for targeted interventions.

Meta-Research Study on the Quality of Randomized Controlled Trials Evaluating Drug Therapy for Impetigo

Juliana Cavaleiro Rodrigues, Kamilla Mayr Martins Sá, Giullia Carvalho Mangas Lopes, Marcella Cosmo Piovesan, Elaine Marcílio Santos, Ana Luiza Martimbianco

DOI: https://doi.org/10.5826/dpc.1504a5668

Many randomized clinical trials (RCTs) on pharmacological treatments for impetigo in children and adolescents exhibit methodological limitations, particularly in randomization, blinding, and protocol registration. Strengthening study design and reporting standards is essential to improving the reliability of evidence and guide clinical decision-making.

Tretinoin for Photodamaged Facial Skin: Systematic Review and Meta-Analysis of Randomized Controlled Trials

Hsin-Yin Huang, Leon Tsung-Ju Lee

DOI: https://doi.org/10.5826/dpc.1504a5172

According to this systematic review and meta-analysis, treatment with tretinoin resulted in significant improvement in both fine and coarse facial wrinkles caused by photodamage relative to vehicle.

Training Primary Care Practitioners In Dermoscopy Diagnostic Algorithms Enhances Diagnostic Accuracy and Triage of Suspected Skin Cancer: Scoping Review Evidence

Alexandre Ladet, Sandra Lawton, Michael Boffa

DOI: https://doi.org/10.5826/dpc.1503a5208

In some Western regions with limited dermatologist access, primary care physicians need to properly triage suspicious skin lesions. This review shows that training them in dermoscopy using simple algorithms effectively improves diagnostic proficiency

Psoriasis and Alopecia: Unveiling the Links

Mohammad Reza Pourani, Yasaman Khajeamiri, Fahimeh Abdollahimajd, Omid Zargari

DOI: https://doi.org/10.5826/dpc.1504a5283

Psoriasis and alopecia are related through several pathways, which can be classified as follows: 1. Psoriatic alopecia; 2. Drug-induced alopecia, especially from TNF- inhibitors; 3. Concomitant psoriasis and alopecia areata.

Skin-Immune-Neuro-Gastro-Endocrine (SINGE) System: Lighting the Fire on Atopic Dermatitis Research

Meshi Paz, Peter Lio

DOI: https://doi.org/10.5826/dpc.1504a5329

The Skin-Immune-Neuro-Gastro-Endocrine (SINGE) system provides a unified framework for understanding multisystem pathophysiology, redefining atopic dermatitis as a systemic condition.

Clinical Efficacy and Safety of Intralesional Bevacizumab in Dermatology: Insights from a Systematic Review

Fereshte Rastegarnasab, Najmeh Tavousi, Mahsa Pourmahdi-Boroujeni , Kimia Afshar, Shadi Behfar, Bahareh Abtahi-Naeini

DOI: https://doi.org/10.5826/dpc.1504a5430

Intralesional bevacizumab has some off-label applications in dermatology beyond its previous advantages for the treatment of cancer and ophthalmological conditions: hereditary hemorrhagic telangiectasia, vascular malformation, vascular proliferation, lichen planus, and basal cell carcinoma.

RESEARCH LETTER

Photodynamic Therapy with 5-Aminolevulinic Acid for Cosmetic-Induced Acne Fulminans: Case Report and Literature Review

Ran An, Rui Liu, Hui Gu

DOI: https://doi.org/10.5826/dpc.1504a6693

Dermoscopic Features and Diagnostic Criteria of Galli-Galli Disease: A Clinical Update

Simonetta Piana, Enrico Zendri

DOI: https://doi.org/10.5826/dpc.1504a4640

Dermatoscopic Patterns in Keloid, Hypertrophic, and Atrophic Scars: Cross-Sectional Analysis and Clinical Correlation
Leandra D'orsi Metsavath, Geise Cristine Espíndola, Elizabeth Leocadia Fernandes, Keila Seabra Teles Ferreira, Gisele Viana Oliveira, Marcio Roberto Silva, Leonne Di Carlo Del Vecchio, Jussara Aparecida Silva
DOI: https://doi.org/10.5826/dpc.1504a5315

Imiquimod induced vitiligo:An HLA case investigated
Eleni Klimi
DOI: https://doi.org/10.5826/dpc.1504a5797

Combination of Fractional CO2 Laser and Imiquimod in Pigmented Basal Cell Carcinoma: Preliminary Clinical Observations
Luca Ambrosio, Giovanni Di Lella, Caterina Longo, Giovanni Pellacani, Iris Zalaudek, Claudio Conforti
DOI: https://doi.org/10.5826/dpc.1504a5586

Eruptive Clear Cell Acanthomas with Atypical Dermoscopic Features
Luca Ambrosio, Antonio Di Guardo, Vincenzo Roberti, Andrea Ascione, Claudio Conforti, Giovanni Pellacani
DOI: https://doi.org/10.5826/dpc.1504a5595

Nevus Unius Lateris and Nevus Anemicus in a Patient With Neurofibromatosis Type 1: Noninvasive Imaging With Line-Field Confocal Optical Coherence Tomography and High-Resolution Video Dermoscopy
Linda Tognetti, Francesca Falcinelli, Laura Calabrese, Pietro Rubegni
DOI: https://doi.org/10.5826/dpc.1504a5633

Line-Field Confocal Optical Coherence Tomography in Merkel Cell Carcinoma and Histopathological Correlation
Maria Elisabetta Greco, Antonio Di Guardo, Andrea Ascione, Giuseppe Soda, Giovanni Pellacani, Flavia Persechino
DOI: https://doi.org/10.5826/dpc.1504a5647

Trends in Gender Representation at US Dermatology Grand Rounds (2000-2025): A Cross-Sectional Study
Maggie H. Zhou, Wei Li, Faith Chukwu, Amit Singal, Shari R. Lipner
DOI: https://doi.org/10.5826/dpc.1504a5653

Langerhans Cell Histiocytosis and Mastocytosis: A Rare Association
Romain Boisseau, Lea Scaramuzzino, Grégory Bosphore, Kim Heang Ly
DOI: https://doi.org/10.5826/dpc.1504a5660

Betamethasone-Calcipotriol Foam: A Promising Treatment for Erythema Annulare Centrifugum With LC-OCT Monitoring
Caterina Mariarosaria Giorgio, Gaetano Licata, Eugenia Veronica Di Brizzi, Elvira Moscarella, Giuseppe Argenziano, Vittorio Tancredi
DOI: https://doi.org/10.5826/dpc.1504a5695

Treatment Strategies for Atopic Dermatitis in Adults Who Exhibit Non-Allergic Comorbidities Real-Life Data from a Tertiary Greek Hospital
Eleni Paschou, Aimilios Lallas, Katerina Bakirtzi , Dimitra Kiritsi , Efstratios Vakirlis, Eleni Sotiriou
DOI: https://doi.org/10.5826/dpc.1504a5766

Colchicine-Responsive Granuloma Faciale: A Case Report with Dermoscopic Clues
Esra Kılıç Manavlı, Gülhan Gürel, Derya Aksu, Burcu Belen Aydoğmuş
DOI: https://doi.org/10.5826/dpc.1504a5778

One Clue, Two Outcomes: Benign vs Malignant Through Dermoscopy
Patricija Šimkūnaitė, Melita Virpšaitė, Iveta Gylienė, Jorinta Jokubaitė, Tadas Raudonis
DOI: https://doi.org/10.5826/dpc.1504a5780

A case of infective endocarditis presenting with skin findings
Zeynep Busra Balik, Gulsen Akoglu
DOI: https://doi.org/10.5826/dpc.1504a5816

Graham-Little-Piccardi-Lassueur syndrome, favorable response to isotretinoin treatment
Silvia Guerrero-Cornejo, Vicente Orellana-Westermeyer, Josefa Catalán-Lobo
DOI: https://doi.org/10.5826/dpc.1504a5851

Cutaneous and orbital myeloid sarcoma as the initial clinical presentation of acute myeloid leukemia in an infant.
Leonne Di Carlo Del Vecchio, Jan Lapins, Elizabeth Leocadia Fernandes, Marcia Lanzoni de Alvarenga Lira, Fernanda Magalhães, Meliane Moleta
DOI: https://doi.org/10.5826/dpc.1504a5858

Oral Erosive Lichen Planus Successfully Treated with Baricitinib
Samuele Savian, Roberto Maglie, Efenesia Maria Baffa, Carlo Pipitò, Vincenzina Rubino, Emiliano Antiga
DOI: https://doi.org/10.5826/dpc.1504a5848

IMAGE LETTER

Cutaneous Lesions from Schistosoma haematobium
Andrea Danese, Sina Sokol, Elena De Rui, Salvatore Scarso, Francesco Bellinato, Silvia Vaienti, Giampiero Girolomoni, Paolo Gisondi
DOI: https://doi.org/10.5826/dpc.1504a6479

Hair Collar Sign with Naevus Flammeus: a Possible Sign of Aplasia Cutis Congenita
Li Han, Lang Rao, Yong-bo Wu, Yan-yi Deng, Bo Luo
DOI: https://doi.org/10.5826/dpc.1504a6116

Type 2 Lepra Reaction with Borderline Lepromatous Leprosy
Qiuping Chen, Jifeng Liu
DOI: https://doi.org/10.5826/dpc.1504a6738

Poroma vessels can be better identified by high magnification dermoscopy compared to conventional dermoscopy
Roberta Giuffrida, Linda Tognetti, Dario Valguarnera, Claudio Conforti, Iris Zalaudek, Fabrizio Guarneri
DOI: https://doi.org/10.5826/dpc.1504a6050

Dermoscopic Features of Morbilliform Rash in Dengue Fever: A Clinical Insight
Caterina Mariarosaria Giorgio, Eugenia Veronica Di Brizzi, Giuseppe Argenziano, Claudia Di Sarno, Raffaele Di Sarno, Gaetano Licata
DOI: https://doi.org/10.5826/dpc.1504a5245

Dermatomyositis-Like Lesion: an Atypical Cutaneous Presentation in Adult-Onset Still Disease
Shirui Chen, Lin Li, Liming Xiang, Xia Chen, Cunhuo Jiang
DOI: https://doi.org/10.5826/dpc.1504a5243

Bywaters Lesions: Clinical, Dermoscopic, and Histopathological Insights
Sara Salvagno, Silvia Baravalle, Chiara Colato, Antonio Carletto, Francesco Bellinato, Giampiero Girolomoni, Paolo Gisondi
DOI: https://doi.org/10.5826/dpc.1504a5754

Inverted Follicular Keratosis of the Nail Unit: A Rare Case
Hanane Rachadi, Fadoua Chemsy, Fouzia Hali, Farida Marnissi, Soumiya Chiheb
DOI: https://doi.org/10.5826/dpc.1504a5542

Legius Syndrome: A clinical observation of a father-son pair
Lin Wang, Yiyun Wu, Wenting Xu, Cheng Tan
DOI: https://doi.org/10.5826/dpc.1504a5771

Line-field confocal optical coherence tomography features of Merkel cell carcinoma
Gerardo Palmisano, Jacques Lasudry, Lucas Boussingault, Véronique del Marmol, Ketty Peris, Mariano Suppa
DOI: https://doi.org/10.5826/dpc.1504a5743

Hutchinson's Sign Without Melanonychia: A Key For The Diagnosis Of Invasive Melanoma Of The Nail Matrix
Alejandra Jaramillo Arboleda, María Fernanda Torres Calderón, Francesco Piscazzi, Maria Paz Micieli Galeazzi, Llucia Alos, Susana Puig Sardá
DOI: https://doi.org/10.5826/dpc.1504a5888

LETTER TO THE EDITOR

Is Dermoscopy Destroying Clinical Dermatology?
Claudio Conforti, Luca Ambrosio, Roberta Giuffrida, Caterina Longo, Giovanni Pellacani, Iris Zalaudek
DOI: https://doi.org/10.5826/dpc.1504a5823

Melanomas Arising On Tattos: The "Disruption Sign"
Sabina Vaccari, Raffaele Cirella, Martina Lambertini, Marco Morante, Beatrice Raone, Emi Dika
DOI: https://doi.org/10.5826/dpc.1504a5890

The Efficacy and Safety of Nemolizumab in Patients with Prurigo Nodularis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials
Hicham Titou
DOI: https://doi.org/10.5826/dpc.1504a5967

IMAGING EXCELLENCE FROM
CANFIELD

Dermatology Practical & Conceptual

Special Issue on Artificial Intelligence in Dermatology: A Call for Collaborative Innovation

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Citation: Kittler H, Tschandl P, Barata C, Ge Z, Malvehy J, Argenziano G. Special issue on artificial intelligence in dermatology: A call for collaborative innovation. *Dermatol Pract Concept.* 2025;15(4):7043. DOI: https://doi.org/10.5826/dpc.1504a7043

Accepted: October 21, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Artificial intelligence is transforming medicine, and dermatology stands at the forefront of this transformation. Over the past decade, machine learning has progressed from experimental image classification to systems capable of matching or even surpassing expert performance in specific diagnostic tasks [1, 2]. While convolutional neural networks (CNNs) and image-based skin cancer diagnosis dominated the early stages of this development [3], recent advances point toward more general and versatile foundational models that can address a wide variety of downstream tasks beyond diagnosis [4, 5]. Yet the excitement surrounding these breakthroughs is accompanied by equally significant challenges. The real test for AI in dermatology is not performance in a carefully curated sandbox like setting, but its meaningful integration into the complexities of real-world care [6, 7].

It is precisely at this pivotal moment that *Dermatology: Practical and Conceptual* is launching a Special Issue on Artificial Intelligence in Dermatology. The issue will be accompanied by an inaugural summit on *AI in Dermatology* to be held on 29 September 2026 in Vienna, Austria. With this combined initiative we aim to create a forum for rigorous, interdisciplinary scholarship and to invite clinicians, engineers, policy makers, and patient advocates to shape the future of AI in dermatology together.

The need for such a forum has never been greater. AI models are now entering clinics, regulatory bodies are beginning to grant approvals, and health systems are experimenting with deployment. Yet clinical evidence still lags behind technical promise. Most models have been validated retrospectively, on narrowly defined image sets, and outside

the varied conditions of daily practice. There is an urgent need for prospective clinical trials, robust external validations, and health economic analyses to determine whether AI systems genuinely improve patient outcomes and workflow efficiency.

Equally important is the recognition that AI is not merely a technological add on but a catalyst for rethinking how dermatological care is organized. The next generation of tools will be embedded in clinical pathways, influencing everything from triage and differential diagnosis to follow up and education. Such integration will only succeed if AI is conceived and built through genuine co-development. Clinicians must articulate the clinical questions that matter most and ensure that outputs are interpretable and actionable at the bedside. Engineers and data scientists need to translate these questions into robust, reproducible models while remaining attentive to the nuances of clinical practice. Patients should have a voice in defining priorities and acceptable trade-offs, ensuring that issues of consent, accessibility, and user experience are addressed from the outset. Policy makers and regulators must help craft forward looking frameworks for safety, reimbursement, and accountability. Only through this continuous dialogue among all stakeholders can AI become a trustworthy partner that augments rather than replaces human expertise.

This special issue and the accompanying summit aim to nurture precisely such dialogue. We welcome contributions that range from cutting edge model developments to careful clinical evaluations, from theoretical reflections on ethics and regulation to case studies of real-world deployment. We are particularly interested in work that crosses disciplinary boundaries and in manuscripts that document lessons learned from collaborative projects in which clinicians, engineers, and patients have worked side by side. By bringing together these diverse perspectives, the issue will not only showcase scientific advances but also chart a path for responsible and inclusive innovation.

The invitation to authors is broad and inclusive. Whether your expertise lies in computer vision, clinical dermatology, ethics, data governance, patient empowerment, basic research, public health or health policy, we welcome your insights and especially encourage contributions that reflect international perspectives, recognizing that patterns of skin disease and access to dermatological care vary widely across regions and that AI must serve global as well as local needs. By dedicating a special issue to Artificial Intelligence in Dermatology, *Dermatology: Practical and Conceptual* aims to create more than a record of the current state of the art. We invite you to join this endeavor and to help define what responsible, clinically meaningful, and patient centered AI in dermatology should look like. The submission deadline is 15 May 2026. Manuscripts should be submitted through the *DPC* online submission system under the article category "Special Issue: AI in Dermatology." Submission fees will be waived for this special issue, and, as is customary for *DPC*, no publication fees will be charged. All submissions will undergo rigorous double blind peer review and accepted original articles will be showcased at the accompanying summit, where they will reach an international audience of leading AI specialists, industry innovation leaders, and distinguished clinicians.

Our goal is to provide a lasting reference and source of guidance at a time when AI is prepared to influence every aspect of skin health. We hope that the articles collected here will inspire new collaborations, inform research, clinical and policy decisions, and help ensure that the benefits of AI are shared equitably.

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Dermatology Practical & Conceptual

Long-Term Persistence with Guselkumab: A 5-Year Multicenter Retrospective Study across 14 Dermatology Centers in Italy

Bernardini Nicoletta[1], Caldarola Giacomo[2], Richetta Antonio Giovanni[3], Esposito Maria[4], Trovato Federica[5], Amerio Paolo[6], Morea Edvige[6], Bonifati Claudio[7], Graceffa Dario[8], Bruni Pier Luigi[9], Giordano Domenico[10], Persechino Severino[10], Mazzotta Annamaria[11], Moretta Gaia[5], Pagnanelli Gianluca[5], Pallotta Sabatino[5], Annedda Jasmine[12], Mugheddu Cristina[12], Miraglia Emanuele[13], Panasiti Vincenzo[14], Molinelli Elisa[15], Simonetti Oriana[15], Fargnoli Maria Concetta[4], Peris Ketty[2], Pellacani Giovanni[3], Potenza Concetta[1], Dattola Annunziata[3]

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Key words: Psoriasis, Guselkumab, Drug survival, Real-world evidence, Biologic therapy

Citation: Bernardini N, Caldarola G, Richetta AG, et al. Long-Term Persistence with Guselkumab: a 5-year Multicenter Retrospective Study across 14 Dermatology Centers in Italy. *Dermatol Pract Concept*. 2025;15(4):6646. DOI: https://doi.org/10.5826/dpc.1504a6646

Accepted: October 8, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: Annunziata Dattola, Nicoletta Bernardini, Giacomo Caldarola, Concetta Potenza, Giovanni Pellacani, and Antonio Giovanni Richetta have made substantial contributions to the conception, the design of the manuscript, the analysis and interpretation of the data, and drafting the manuscript. All authors contributed to drafting the manuscript and read and approved the final version of the manuscript.

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ABSTRACT

Introduction: Psoriasis is a chronic systemic inflammatory disease that requires long-term treatment strategies to maintain sustained disease control. Treatment persistence is an important real-world indicator of therapeutic effectiveness and tolerability. Guselkumab, an IL-23 inhibitor, has shown favorable persistence in several studies, but extended long-term data remain limited.

Objectives: To assess 3- and 5-year drug survival rates of guselkumab in patients with moderate-to-severe plaque psoriasis and to examine the relationship between persistence and clinical variables such as PASI, BMI, prior biologic exposure, and involvement of difficult-to-treat areas.

Methods: This was a multicenter retrospective observational study conducted across 14 dermatology centers in Italy. Adult patients with moderate-to-severe plaque psoriasis who started guselkumab were included. Data collected included demographics, clinical history, disease severity, comorbidities, and treatment details. Drug survival was analyzed using Kaplan–Meier curves and Cox proportional hazards models.

Results: A total of 247 patients were included. At three years, 80.2% of patients remained on guselkumab, and at five years, 72.8% continued treatment. Persistence was not significantly influenced by BMI, PASI, or age. However, prior biologics exposure was associated with a higher risk of discontinuation (hazard ratio (HR): 1.84; *P*=0.0208), especially in those previously treated with IL-17 inhibitors (HR:2.14; *P*=0.0150). The involvement of difficult-to-treat areas did not significantly affect persistence, although a trend toward reduced discontinuation was observed in patients with genital involvement (*P*=0.0539).

Conclusions: Guselkumab demonstrated high long-term persistence in real-world clinical practice. Drug survival remained consistently high across various subgroups, with prior IL-17 inhibitor exposure being the main predictor of decreased persistence.

Introduction

Psoriasis is a chronic systemic inflammatory condition that affects both the skin and multiple organ systems and is frequently associated with comorbidities such as metabolic syndrome, cardiovascular disease, and inflammatory bowel disorders [1-4]. The pathogenesis of psoriasis involves complex interactions between genetic predispositions and environmental triggers, leading to an inflammatory response mediated by dendritic cells, T cells, keratinocytes, and cytokines such as TNFα and the IL-23/IL-17 pathways [1,5]. This inflammatory cascade not only affects the skin, causing characteristic erythematous, indurated, and scaly plaques, but also contributes to systemic inflammation, which is implicated in the development of the above-mentioned comorbidities [1,2].

Moderate-to-severe psoriasis significantly impacts patients' quality of life and creates a substantial long-term disease burden, necessitating ongoing disease management. The chronic nature of psoriasis leads to considerable physical, social, and psychological impairments, affecting not only patients but also their families [6,7].

The introduction of biologics targeting interleukin pathways (IL-12/23, IL-17, IL-23) has revolutionized the management of psoriasis and psoriatic arthritis. IL-12/23 inhibitors like ustekinumab, and IL-23 inhibitors such as guselkumab, tildrakizumab, and risankizumab have demonstrated varying levels of treatment persistence, which is an essential measure of long-term efficacy and safety and an essential feature leading to patient satisfaction in real-world settings [8].

Guselkumab has demonstrated high drug survival rates in the treatment of moderate-to-severe psoriasis across various real-world studies [9-13]. However, real-life evidence regarding guselkumab persistence over extended follow-up and the factors influencing it remains limited.

The aim of this work was to retrospectively assess the long-term persistence of guselkumab in a cohort of patients with psoriasis as well as to explore the associations between persistence and key variables such as BMI, PASI, previous biologic treatments, and the involvement of difficult-to-treat areas.

Materials and Methods

Study Design and Population

This multicenter retrospective observational study was conducted across 14 dermatology centers in Italy (listed in Table S1). It included adult patients (aged 18 years or older) with moderate-to-severe plaque psoriasis who initiated guselkumab treatment as a part of routine clinical practice.

Both bio-naïve and bio-experienced patients were eligible. Clinical data were collected retrospectively from medical records, starting from the initiation of treatment. Follow-up was assessed at three years (primary endpoint) and five years (secondary endpoint), as specified in the study protocol.

Data Collection

Collected variables included demographic (age, sex) and anthropometric variables (weight, height, BMI), clinical history (age at disease onset, disease duration, family history), comorbidities (especially cardiometabolic and gastrointestinal), and previous biologic therapies. Psoriasis characteristics included baseline PASI scores and involvement of difficult-to-treat areas (scalp, nails, genital, and pretibial regions). Data on treatment discontinuation, including timing and documented reasons, were also collected.

Outcome Measures

The primary endpoint was the survival of the drug guselkumab, defined as persistence in treatment over time, evaluated for up to three years after treatment initiation.

Secondary endpoints included evaluating the drug survival with guselkumab for up to five years after treatment initiation, based on baseline PASI, BMI, prior biologics exposure (overall and by drug class), and involvement of difficult-to-treat anatomical sites.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics. Continuous variables are reported as means and standard deviations (SD), and categorical variables as counts and percentages.

Kaplan–Meier curves were used to assess drug survival over time. Factors associated with treatment discontinuation were evaluated using multivariate Cox proportional hazards models, including age, sex, BMI, PASI, bio-experience, prior biologics exposure (overall and by drug class), and site-specific involvement. A p-value of <0.05 was considered statistically significant. Analyses were performed using R (version 4.0.5) and GraphPad Prism 4.0 (GraphPad Software Inc., La Jolla, CA, USA).

Ethics Statement

The study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The Ethics Committees of the participating centers waived the requirement for formal approval and informed consent as the study was non-interventional and based on retrospective, anonymized data collection.

Results

Patients' Baseline Characteristics

A total of 247 patients with moderate-to-severe plaque psoriasis who received guselkumab treatment were included in the analysis. The mean age was 53.2 years (SD: 13.9), with a slight predominance of males (57.5%). The average weight was 78.8 kg (SD: 15.2), and mean BMI was 27.2 kg/m² (SD: 4.9). According to BMI classification, 1.2% of patients were underweight, 32.8% had normal weight, 39.3% were overweight, and 23.1% were classified as obese. The mean PASI index was 14.51 (SD: 8.76). Approximately half of the cohort (53%) had prior exposure to biologic therapies. Other baseline characteristics of the study population are detailed in Table 1.

Overall Drug Survival

A total of 247 patients treated with guselkumab were included in the persistence analysis. As shown in Figure 1, at three years, 198 of the 247 patients (80.2%) were still receiving treatment, while 49 patients (19.8%) had discontinued. At five years, 67 patients (27.1%) had discontinued treatment for various reasons, while 180 patients (72.8%) continued the therapy.

Drug Survival based on BMI

Treatment persistence with guselkumab was analyzed according to baseline weight, stratifying patients into two groups: ≤90 kg and >90 kg, as shown in Figure 2A.

At 12 months, the persistence rates were 97.0% for patients weighing ≤90 kg and 95.0% for those >90 kg (P=0.556). At 24 months, persistence declined slightly to 92.0% and 89.0%, respectively (P=0.244). At 36 months, the rates were 88.0% and 82.0% (P=0.656), followed by 84.0% and 75.0% at 48 months (P=0.999) and 80.0% and 70.0% at 60 months (P=0.998). No statistically significant difference was observed.

Treatment persistence with guselkumab was also evaluated according to baseline body mass index (BMI), as shown in Figure 2B. Patients were categorized into three groups: BMI <20, BMI 21–30, and BMI >30. At 12 months, persistence rates were 95.0% in the BMI <20 group, 96.0% in the BMI 21–30 group, and 94.0% in the BMI >30 group. The differences between groups at this time point were not statistically significant (BMI 21–30 vs <20: P=0.098; BMI >30 vs 21–30: P=0.098). Over time, persistence rates declined gradually across all BMI categories. At 24 months, persistence was 91.0% in both the <20 and 21–30 BMI groups, and 87.0% in the >30 group. At 36 months, persistence reached 85.0%, 87.0%, and 80.0%, respectively, with no statistically significant difference observed (e.g., P=1.000 for <20 vs 21–30; P=0.9731 for >30 vs 21–30).

Table 1. Patients' Baseline Characteristics.

Characteristic	Count	%	Mean ± SD
Age (years)			53.2 ± 13.9
Sex: Male	142.0	57.5	
Weight (kg)			78.8 ± 15.2
BMI (kg/m²)			27.2 ± 4.9
BMI Underweight	3.0	1.2	
BMI Normal weight	81.0	32.8	
BMI Overweight	97.0	39.3	
BMI Obese	57.0	23.1	
PASI			14.51 ± 8.76
Bio-experienced: Yes	131.0	53.0	
Cardiometabolic comorbidities	76.0	30.8	
Gastrointestinal comorbidities:	4.0	1.6	
Nail involvement:	70.0	28.3	
Scalp involvement:	144.0	58.3	
Genital involvement:	66.0	26.7	
Pretibial involvement:	134.0	54.3	

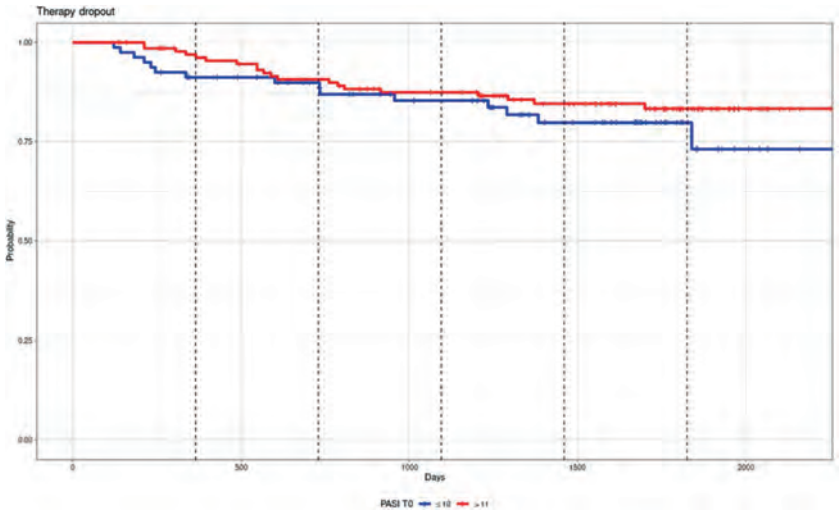


Figure 1. Kaplan-Meier curve showing treatment persistence with guselkumab in the overall study population (N=247). The analysis includes all reasons for discontinuation, both clinical and non-clinical. At three years, 198 patients (80.2%) remained on treatment; at five years, 180 patients (72.8%) continued therapy, while 67 patients (27.1%) had discontinued.

By 48 months, rates were 78.0%, 83.0%, and 72.0%, respectively, and at 60 months, they were 72.0%, 78.0%, and 66.0%, again with all comparisons showing P>0.3. No statistically significant difference in treatment persistence was observed between BMI groups at any time point.

Drug Survival based on Disease Severity

Treatment persistence with guselkumab was assessed according to baseline PASI score, as shown in Figure 3. Patients were stratified into two groups: PASI <10 and PASI >11. At 12 months, persistence rates were 95.5% in the PASI <10 group and 95.3% in the PASI >11 group, with no statistically significant difference (*P*=0.051). Over time, persistence declined similarly across both groups. At 24 months, persistence was 90.9% for PASI <10 and 91.0% for PASI >11 (*P*=0.539). At 36 months, rates were 86.4% and 86.6%, respectively (*P*=0.715). At 48 months, persistence reached 84.1% and 83.6% (*p*=0.998) and at 60 months, 79.5% and 78.4% (*P*=0.998), again with no statistically significant difference observed.

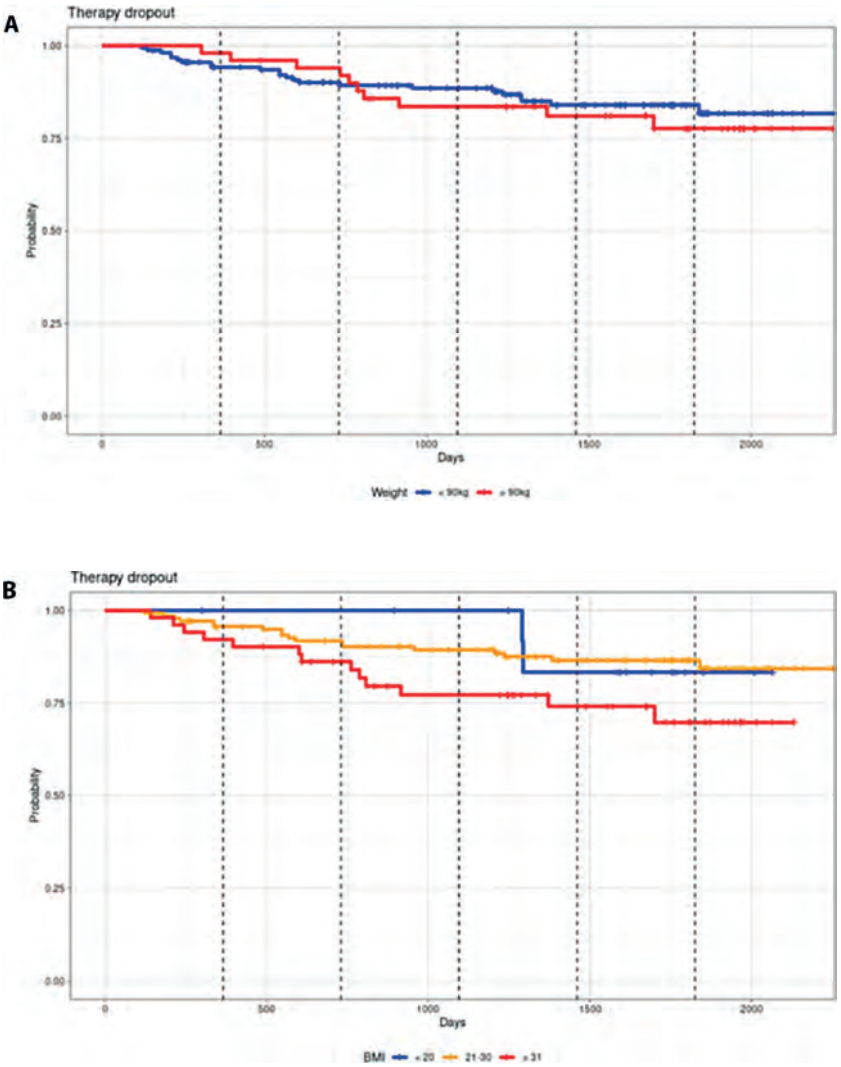


Figure 2. Treatment persistence with guselkumab stratified by baseline weight (A) and BMI (B). (A) Patients were categorized into two weight groups: <90 kg and >90 kg. (B) Patients were stratified by BMI into three categories: (<20), (21-30), and (≥31).

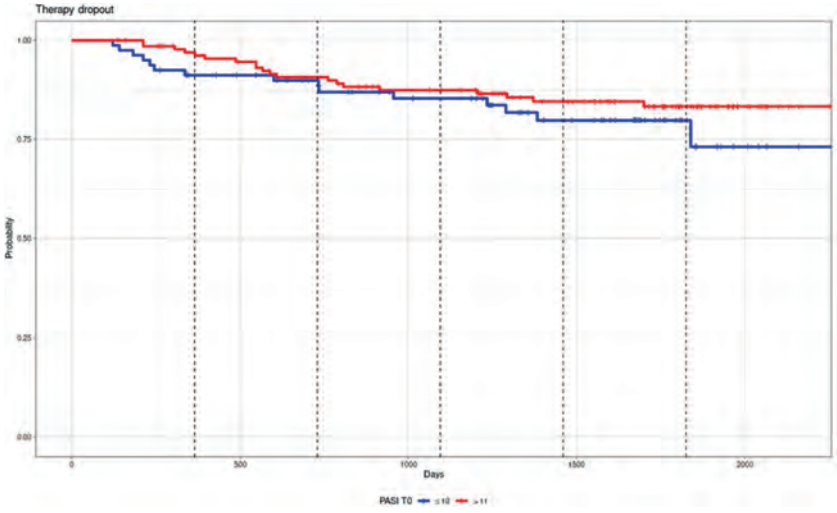


Figure 3. Treatment persistence with guselkumab stratified by baseline PASI score. Patients were grouped into three categories according to disease severity at baseline: PASI <10 and PASI >11.

Drug Survival based on Prior Exposure to Biologic Therapies

Treatment persistence with guselkumab was evaluated according to prior exposure to biologic therapies, as illustrated in Figure 4. Patients were classified as either bio-naïve or bio-experienced. At 12 months, persistence was 95.7% in the bio-naïve group and 90.8% in the bio-experienced group (*P*=0.960). At 24 months, 91.3% of bio-naïve patients and 82.4% of bio-experienced patients remained on therapy (*P*=0.411), and at 36 months, the rates were 87.8% and 77.9%, respectively (*P*=0.340). By 48 months, persistence declined to 85.2% in the bio-naïve group and 73.3% in the bio-experienced group (*P*=0.999), and at 60 months, it reached 82.6% and 68.7%, respectively (*P*=0.999). These differences were not statistically significant.

Multivariate Analysis

A multivariate Cox regression analysis was performed to assess factors associated with treatment discontinuation (Table 2). Variables included in the model were age, sex, BMI, baseline PASI, and prior exposure to biologic therapies (bio-experience).

Among these, prior biologic experience emerged as the only statistically significant predictor of discontinuation (HR = 1.84, coefficient=0.6101; SE=0.2640; z=2.311; *P*=0.0208), indicating a higher risk of treatment interruption in bio-experienced patients.

Other variables, including BMI (coefficient: 0.0330; *P*=0.1628), age (coefficient: –0.0059; *P*=0.5238), sex (coefficient: 0.4376; *P*=0.0828), and PASI (coefficient: –0.0038; *P*=0.8394) were not significantly linked with persistence outcomes.

A separate model evaluated the impact of previous biologic class exposure (Table 3). Prior use of IL-17 inhibitors was significantly associated with an increased risk of discontinuation (coefficient: 0.7613; SE=0.3128; z=2.433; *P*=0.0150), corresponding to an HR of 2.14. No statistically significant association was found for prior exposure to anti-TNF-α agents (coefficient: 0.3182; HR: 1.37; *P*=0.2190), IL-12/23 inhibitors (coefficient: 0.2939; HR:

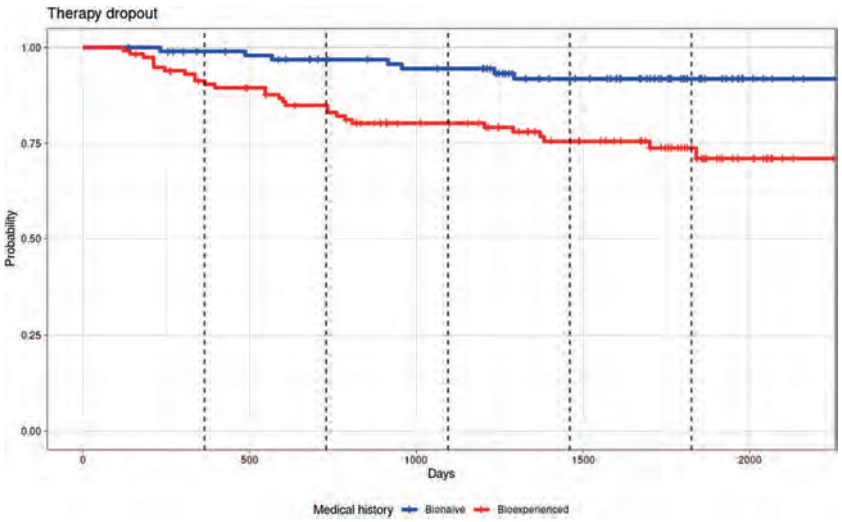


Figure 4. Treatment persistence with guselkumab stratified by prior exposure to biologic therapies. Patients were categorized as bio-naïve (no previous biologic treatment) or bio-experienced (previously treated with one or more biologics).

Table 2. Multivariate Cox Regression Analysis of Factors associated with Treatment Discontinuation. The model included baseline BMI, age, sex, PASI, and previous exposure to biologic therapies.

Variable	coef	exp(coef)	SE(coef)	z	p-value	
BMI	0.032964	1.033514	0.023617	1.396	0.1628	
Age	-0.005853	0.994164	0.009181	-0.637	0.5238	
Sex	0.437617	1.549012	0.252292	1.735	0.0828	
PASI	-0.003767	0.996240	0.018592	-0.203	0.8394	
Bio-experience	0.610064	1.840549	0.263955	2.311	0.0208	*

Table 3. Multivariate Cox Regression Analysis Evaluating the Impact of Prior Biologic Drug Classes on Treatment Discontinuation with Guselkumab.

Variable	N patients (y/n)	Coef	exp(coef)	se(coef)	z	p	
Anti-TNF-α	82/165	0.3182	1.3750	0.258800	1.2290	0.2190	
IL12/IL23 Inhibitor	45 / 202	0.2939	1.3420	0.303500	0.9680	0.3330	
IL17 Inhibitor	38 / 209	0.7613	2.1410	0.312800	2.4330	0.0150	*
IL23 Inhibitor	2 / 242	-1.5120	0.0000	0.244292	-0.0060	0.9950	

1.34; *P*=0.3330), or IL-23 inhibitors (coefficient: –1.5120; HR: ≈ 0.22; *P*=0.9950).

A further multivariate analysis investigated the association between psoriasis involvement in difficult-to-treat areas and the treatment persistence. Genital involvement was associated with a trend toward reduced discontinuation (estimate: –0.1173; SE: 0.0605; t = –1.938; *P*=0.0539). Nail (estimate: 0.0595; *P*=0.3253), scalp (estimate: 0.0744; *p*=0.1755), and pretibial involvement (estimate: –0.0560; *p*=0.2799) were not significantly associated with treatment persistence.

Discussion

Psoriasis is a clinically heterogeneous lifelong skin disease characterized by various forms, including plaque, flexural, guttate, pustular, and erythrodermic. It affects approximately 60 million people globally [14], and its prevalence in Italy ranges from 1.8% to 4.8%, with an incidence between 107.742 and 230.62 per 100,000 person-years [15]. Guselkumab is a monoclonal antibody that targets interleukin (IL)-23, approved for treating adults with moderate-to-severe plaque psoriasis [16]. It has demonstrated sustained efficacy and safety over five years, with significant improvements in Psoriasis Area and Severity Index (PASI) scores and Dermatology Life Quality Index (DLQI) scores [17,18].

Additionally, guselkumab has demonstrated significant drug survival in patients with moderate-to-severe psoriasis across various real-world settings. An Australian multicenter retrospective study aimed to determine the drug survival rates of biologics available in Australia for treating chronic plaque psoriasis, analyzing data from 306 patients and 566 treatment courses collected from two outpatient dermatology clinics between April 2006 and December 2020. Results indicated that guselkumab had the longest drug survival rates at 94.2% at both one and five years, followed by ixekizumab with rates of 87.2% at one year and 59.4% at five years [19]. Mastorino et al. evaluated the drug survival, effectiveness, and safety of guselkumab for treating moderate-to-severe psoriasis over 208 weeks, involving 202 patients. The estimated drug survival rate at almost four years (208 weeks) was 68.5%, with factors such as being a super responder and having cardiovascular comorbidities associated with a reduced risk of drug interruption [20]. A retrospective study analyzed real-world data from the Czech Republic BIOREP registry involving 333 patients treated with guselkumab for psoriasis. Drug survival remained high at 91.6%, 87.0%, and 85.5% after 12, 24, and 36 months, respectively [21].

In our study, we observed a high long-term treatment persistence, with 80.2% of patients still receiving treatment after three years. This result aligns with the findings reported by Torres et al., who noted 3-year persistence rates of over 80% for guselkumab in a large international real-world cohort [22]. After five years, 72.8% continued the therapy. This high long-term persistence rate matches previous reports in the literature and reflects the favorable tolerability and sustained effectiveness of guselkumab in real-life clinical practice [19-21,23]. The analysis considers all causes of discontinuation, including both clinical and non-clinical factors, providing a comprehensive overview of treatment retention.

Treatment persistence with guselkumab was evaluated based on baseline weight and BMI. In the present cohort, patients were stratified by body weight into two categories: ≤90 kg and >90 kg. Persistence rates at 12 months were high in both groups (97.0% and 95.0%, respectively) and gradually declined over time. At 24 months, persistence was 92.0% in the ≤90 kg group and 89.0% in the >90 kg group; at 36 months, 88.0% and 82.0%; at 48 months, 84.0% and 75.0%; and at 60 months, 80.0% and 70.0%, respectively.

In the analysis by body mass index (BMI), patients were classified into three categories: BMI <20, BMI 21–30, and BMI >31. At 12 months, persistence rates were 95.0% in the BMI <20 group, 96.0% in the BMI 21–30 group, and 94.0% in the BMI >31 group. These rates declined progressively over time: at 24 months, persistence was 91.0%, 91.0%, and 87.0%, respectively; at 36 months, 85.0%, 87.0%, and 80.0%; at 48 months, 78.0%, 83.0%, and 72.0%; and at 60 months, 72.0%, 78.0%, and 66.0%, respectively, for the BMI <20, BMI 21–30, and BMI >31 categories. These findings indicate that treatment persistence with guselkumab was

consistently high and did not appear to be significantly influenced by baseline weight or BMI. These results align with findings from other studies, which have shown that drug survival is not affected by patient weight or BMI [21,24].

Chiricozzi et al. investigated how age affects the drug survival of IL-17 and IL-23 inhibitors in patients with moderate-to-severe plaque psoriasis, analyzing 4,178 patients and 4,866 treatment lines in a large retrospective multicenter cohort. The results showed that aging negatively affects overall treatment persistence, but this impact was notably stronger for IL-17 inhibitors. Conversely, IL-23 inhibitors maintained high drug survival even in elderly patients, indicating greater resilience to age-related discontinuation [25]. These findings suggest that, unlike IL-17 inhibitors, the persistence of IL-23 inhibitors is minimally influenced by patient age. This age-related trend was also confirmed in our study, where patient age did not significantly affect the long-term drug survival of guselkumab.

In the Australian Psoriasis Registry, guselkumab demonstrated high drug survival rates, with 93.1% at nine months for bio-experienced patients, compared to 100% for bio-naïve patients. Overall drug survival was 99.0%, 83.3%, and 77.1% at three, 15, and 27 months, respectively. The study found that bio-naïve patients had more prolonged drug survival than those with prior biologic therapy [26]. Li et al. conducted a retrospective analysis of 386 patients with plaque psoriasis treated with biologics (ixekizumab, secukinumab, guselkumab, and adalimumab) over a 52-week period, revealing that guselkumab had the highest drug survival rate at 72.2%. Additionally, results showed that, among bio-naive patients, drug survival rates tended to be higher compared to bio-experienced patients, although these differences were not statistically significant [27]. According to these studies, in our work, treatment persistence with guselkumab was analyzed based on previous exposure to biologic therapies. Patients were categorized as bio-naïve or bio-experienced. At 12 months, persistence was 95.7% in the bio-naïve group and 90.8% in the bio-experienced group. This difference remained evident over time: at 60 months, 82.6% of bio-naïve patients were still on treatment, compared to 68.7% of bio-experienced patients. These data suggest a higher long-term persistence among patients who had not previously received biologic therapies, indicating that a previous exposure to biologics may be associated with an increased likelihood of treatment discontinuation. The multivariate analysis investigating the impact of previous biologic drug classes on guselkumab persistence revealed that the prior use of IL-17 inhibitors was significantly associated with a higher risk of treatment discontinuation (coefficient: 0.7613; P=0.0150). No statistically significant association was observed for prior exposure to anti-TNF-α agents (P=0.2190), IL-12/23 inhibitors (P=0.3330), or IL-23 inhibitors (p=0.9950). These findings suggest that, as already reported for other biological treatments, being bio-experienced lowers the likelihood of retaining the current drug; moreover, in our cohort, we demonstrated that specifically a history of treatment with IL-17 inhibitors may predict reduced persistence with guselkumab, whereas prior use of other biologic classes does not appear to have a significant impact.

Interestingly, the involvement of difficult-to-treat areas did not appear as a significant predictor of treatment discontinuation in the multivariate analysis, except for genital psoriasis, which showed a trend toward a lower dropout risk (P=0.0539). This observation may reflect a higher observed benefit among patients with diseases in sensitive or high-impact locations, potentially improving treatment adherence.

This study presents some limitations. First, the retrospective design may have introduced selection and information biases, and some clinical data, such as patient-reported outcomes or reasons for discontinuation, may be incomplete or have been recorded inconsistently across centers. Moreover, the lack of formal diagnostic assessment for comorbid psoriatic arthritis may have affected persistence estimates in certain cases.

Future prospective studies integrating clinical, patient-reported, and biomarker data are necessary to better characterize long-term treatment trajectories with guselkumab.

Acknowledgments: Editorial and writing assistance was provided by CTP, srl, and Enrica Piras. Statistical analyses were provided by CTP, srl, and Camilla Ceccarani.

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Dermatology Practical & Conceptual

Supplementary File

Table S1. Participating centers and number of patients treated with guselkumab.

Center
UOC Dermatology – Polo Pontino – Sapienza University, Rome
Policlinico Umberto I, Rome
Dermatology Clinic, University of Cagliari
San Gallicano Dermatological Institute – Rome
IDI-IRCCS – Rome
Dermatology Clinic, Azienda Ospedali Riuniti – Ancona
Dermatology Clinic – Santa Maria Hospital – Terni
UOC Sant'Andrea – Rome
Policlinico Gemelli – Rome
Department of Clinical Sciences and Biotechnology – L'Aquila
ASL Roma 6 – Frascati, Rome
San Camillo IRCCS – Rome
Campus Bio-Medico University – Rome
UOC Dermatology University of Chieti-Pescara

Dermatology Practical & Conceptual

Factors Associated with Exacerbation in Psoriasis Compared to Eczema

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Key words: Psoriasis, Eczema, Aggravating factors, Exacerbation

Citation: Anutraungkool T, Chaowattanapanit S, Choonhakarn C, et al. Factors Associated with Exacerbation in Psoriasis compared to Eczema. *Dermatol Pract Concept*. 2025;15(4):5630. DOI: https://doi.org/10.5826/dpc.1504a5630

Accepted: July 19, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Psoriasis and eczema are chronic inflammatory skin diseases. Environmental factors play an important role in the pathogenesis and exacerbation of both conditions.

Objective: This study aimed to investigate factors associated with exacerbation of psoriasis and eczema and compare those factors between both diseases, with the aim of identifying the significant differences between the two conditions.

Methods: A cross-sectional study was conducted on adult patients diagnosed with psoriasis and eczema in Thailand. Demographic characteristics, clinical data, and aggravating factors were collected and compared between both groups. Demographic characteristics and clinical data were analyzed using descriptive statistics, while aggravating factors were analyzed by logistic regression analysis.

Results: A total of 280 patients participated in this study: 192 psoriasis patients and 88 eczema patients. In 97.3% of psoriasis patients and 99.7% of eczema patients, aggravating factors were reported during disease exacerbation. Mental stress and inadequate sleep were significantly associated with psoriasis exacerbation, while humid environment and dust were significantly associated with eczema exacerbation rather than psoriasis exacerbation.

Conclusion: Internal factors, such as mental stress and inadequate sleep, have a greater influence on the worsening of psoriasis, whereas external factors, including a humid environment and dust, have a more significant impact on eczema flare-ups than on psoriasis exacerbation.

Introduction

Psoriasis is a chronic, recurrent immune-mediated inflammatory skin disease, affecting 2-3% of the world's population [1]. It has a great impact on patients' quality of life. The pathogenesis is complex and remains unclear. However, genetic susceptibility combined with environmental factors and immune dysfunction have been shown to play a significant role in pathogenesis. Dysregulation and interaction of T cells, particularly Th1 and Th17 cells, result in the production of various cytokines (IFN-γ, IL-2, IL-12, IL-17, IL-22, and IL-23), stimulating keratinocyte proliferation, and ultimately forming psoriatic plaques [2]. Many factors have been reported to trigger psoriasis, including rash scratching, psychological stress, environmental pollution, UV radiation exposure, medications (e.g., imiquimod, lithium, beta-blockers, anti-TNF antibodies), infection, smoking, and alcohol consumption [1,3-6]. Moreover, unbalanced dietary intake and foods such as red meat and gluten-containing food may aggravate psoriasis flare-ups [7,8].

Similarly, endogenous eczema, including atopic dermatitis, nummular eczema, dyshidrosis, lichen simplex chronicus, and prurigo nodularis, is a chronic inflammatory skin disorder influenced by genetic, environmental, and immunologic factors. In atopic dermatitis, Th2 cytokines dominate the acute phase, contributing to barrier dysfunction and pruritus, while Th1, Th22, and Th17 cytokines drive chronic changes such as epidermal thickening [9]. In prurigo nodularis, T cells, mast cells, and eosinophils release mediators such as IL-31 and histamine, leading to intense pruritus [10]. Various triggering factors have been reported to exacerbate atopic dermatitis flares, such as sweating, foods, stress, hot and humid environment, cold and dry environment, and sun exposure, whereas stress and scratching are the main aggravating factors of prurigo nodularis [11,12].

Objectives

This study was conducted to better understand the differences in aggravating factors between psoriasis and endogenous eczema and to provide appropriate recommendations to prevent flare-ups of these diseases. Our study aimed to explore factors associated with psoriasis and eczema exacerbation and to determine the differences in those factors between both conditions.

Methods

The cross-sectional study was conducted at the Dermatology Clinic of Khon Kaen University's Hospital in Thailand. All patients aged 18 years or older diagnosed with psoriasis or endogenous eczema, including atopic dermatitis, nummular eczema, dyshidrosis, lichen simplex chronicus, and prurigo nodularis, between 20 July 2019 and 20 December 2022 were enrolled in the study. Psoriasis and eczema were diagnosed based on clinical manifestations. Psoriasis is characterized by well-defined erythematous plaques with silvery-white scales, with or without scalp and nail involvement. Eczema is characterized by pruritus, a chronic and relapsing course, and typical morphological features. In cases where the clinical appearance was not typical, a histopathological examination was performed to confirm the diagnosis. For analysis purposes, all endogenous eczema subtypes were grouped as a single eczema category. Patients who could not read the questionnaires or declined to sign the informed consent were excluded. A structured questionnaire was developed ad hoc for this study to capture relevant triggers reported by patients, incorporating potentially important factors identified through a literature review. The questionnaires covered patients' demographic data, duration of disease, co-morbidities, pruritus, potential aggravating factors such as scratching, illness, foods, weather, chemicals, mental stress, smoking, alcohol drinking, medications or herbal use, and inadequate sleep. The severity of pruritus during disease exacerbation was assessed using an 11-point numeric rating scale (NRS-11), ranging from 0 (no itch) to 10 (worst imaginable itch).

Sample Size Calculation

The determination of the sample size was based on the recommended guideline from statisticians for multiple logistic regression analysis, which suggests that the number of participants with psoriasis and eczema should be five to ten times greater than the number of risk factors. Given that nine factors were associated with the disease according to previous data in Thailand, approximately 90 subjects with psoriasis and eczema were deemed necessary [13].

Statistical Analysis

The statistical analysis was conducted using STATA version 10.0 (StataCorp, College Station, Texas). Descriptive statistics were employed, presenting categorical data as numbers and percentages. Numerical data are described as mean ± standard deviation (SD) for normally distributed parameters or median ± interquartile range (IQR) for non-normally distributed parameters. For univariate analysis, crude odds ratios (OR) and 95% confidence intervals (CI) were calculated to assess the strength of association. Factors with a p-value of <0.20 in univariate analysis were then included in a stepwise multiple logistic regression model. A p-value of <0.05 was considered indicative of a statistically significant difference. Adjusted odds ratios (AOR) and 95% CI were utilized to determine the strength of association in the multiple logistic regression model.

Results

A total of 192 psoriasis patients and 88 eczema patients participated in the study. The baseline characteristics of the patients are shown in Table 1. The median duration of disease was 102 months (range: 36–204) for psoriasis and 24 months (range: 12–60) for eczema patients. Comorbidities were found in 38.5% of psoriasis patients and 52.3% of eczema patients. The most common comorbidity associated with psoriasis and eczema was hypertension. Allergic rhinitis or asthma was more frequently reported in patients with eczema than in those with psoriasis (P=0.001; Table 1). A family history of the same disease was more commonly found in psoriasis patients than in eczema patients (P=0.025; Table 1). Pruritus was a common feature in both psoriasis and eczema patients; however, patients with eczema had greater itching severity than those with psoriasis, as demonstrated by the NRS-11.

Regarding aggravating factors, 187 (97.3%) of the 192 psoriasis patients and 86 (97.7%) of the 88 eczema patients reported having aggravating factors during disease exacerbation, as shown in Table 2. The most common aggravating factor reported in psoriasis was weather (76%), followed by scratching (67.3%), foods (66.7%), mental stress (65.6%), and inadequate sleep (64.6%). Similarly, the most common aggravating factor reported in eczema was weather (75%), followed by scratching (54.5%), foods (46.6%), inadequate sleep (30.7%), and mental stress (23.9%).

The comparison of aggravating factors between psoriasis and eczema patients using univariate analysis is demonstrated in Table 2. Scratching, illness, pickled food, monosodium glutamate, mental stress, and inadequate sleep showed a statistically significant difference in psoriasis patients compared to eczema patients. All those factors and factors with a p-value of less than 0.2 by univariate analysis, including cold and humid conditions, were subjected to subsequent multiple logistic regression.

According to multiple logistic regression analysis (Table 3), mental stress (AOR, 5.27, 95% CI: 2.47–10.52, P<0.001) and inadequate sleep (AOR 2.14, 95% CI: 1.31–5.08, P=0.006) were significantly associated with psoriasis exacerbation rather than eczema exacerbation. In contrast, a humid environment (AOR 0.33, 95% CI: 0.14–0.79, P=0.013) and dust (AOR 0.37, 95% CI: 0.19–0.72, P=0.004) were significantly associated with eczema exacerbation rather than psoriasis exacerbation.

Discussion

Several studies have reported that environmental factors play a significant role in the occurrence and exacerbation of psoriasis [1,3-6], especially in genetically predisposed patients,

Table 1. Comparison of baseline characteristics between psoriasis and eczema patients.

Variables	Psoriasis (N=192)	Eczema (N=88)	*P*-values
Age (years), med (IQR 1,3)	53.5(38,62)	57(46.5,64.3)	0.025
Female, N (%)	89(46.4%)	32(36.4%)	0.118
Weight (kg), med (IQR 1,3)	62(55.8,71.4)	63(55,73)	0.879
Height (cm), med (IQR 1,3)	162(158,168.3)	162(155,167.3)	0.864
Comorbidities, N (%)	74(38.5%)	46(52.3%)	0.032
• DM	23(12.0%)	6(6.8%)	0.194
• Hypertension	43(22.4%)	13(14.8%)	0.613
• Dyslipidemia	8(4.2%)	8(9.1%)	0.108
• CKD	5(2.6%)	1(1.1%)	0.444
• Allergic rhinitis/asthma	5(2.6%)	12(13.6%)	0.001
• Hyperthyroidism	5(2.6%)	1(1.1%)	0.444
• Others*	16(8.3%)	15(30.7%)	0.034
History of smoking	15(7.8%)	8(9.1%)	0.72
History of alcohol drinking	28(14.6%)	11(12.5%)	0.641
Family history of the same disease	20(10.4%)	1(1.1%)	0.025
Disease duration (month), med (IQR 1,3)	102(36,204)	24(12,60)	<0.001
Itching, N (%)	153(79.7%)	78(88.6%)	0.071
NRS-11, med (IQR 1,3)	4(1,5)	5(3,7)	0.001

Note: N; numbers of variable, med; median, IQR; inter-quartile range, DM; diabetes mellitus, CKD; chronic kidney disease, NRS-11; 11-point numeric rating scale. *Other comorbidities in psoriasis group: gout 5, solid tumor 2, coronary arterial disease 2, systemic lupus erythematosus 1, lumbar spondylosis 1, thalassemia 1, stroke 1, glomerulonephritis 1, gastroesophageal reflux disease 1, cirrhosis 1. Other comorbidities in eczema group: gout 3, rheumatoid arthritis 2, benign prostatic hyperplasia 1, Nonalcoholic fatty liver disease 1, lumbar spondylosis 1, epilepsy 1, coronary arterial disease 1, myasthenia gravis 1, solid tumor 1, lymphoma 1, cardiac arrhythmia 1, stroke 1.

Table 2. Comparison of aggravating factors between psoriasis and eczema patients using bivariate logistic regression.

Factors	Psoriasis (N=192)	Eczema (N=88)	Crude OR	95%CI	p-value
Aggravating factors were suspected	187(97.3%)	86(97.7%)			
Scratching	133(67.3%)	48(54.5%)	1.88	(1.12-3.16)	0.017
Illness	39(17.2%)	6(6.8%)	3.48	(1.42-8.57)	0.007
Foods	128(66.7%)	41(46.6%)	2.29	(1.37-3.84)	0.002
• Seafood	85(44.2%)	28(31.8%)	1.70	(1.01-2.90)	0.050
• Pickled foods	40(20.8%)	8(9.1%)	2.63	(1.17-5.89)	0.019
• Traditional pickled fish ("Pla-Ra")	27(14.1%)	5(5.7%)	1.61	(0.58-4.52)	0.364
• Chicken	21(10.9%)	7(8.0%)	1.42	(0.58-3.48)	0.442
• Beef	25(13.0%)	8(9.1%)	1.50	(0.65-3.47)	0.346
• Pork	4(2.1%)	2(2.2%)	0.91	(0.16-5.09)	0.919
• Monosodium glutamate	25(13.0%)	4(4.5%)	3.14	(1.06-9.32)	0.039
• Others*	25(13.0%)	6(6.8%)	2.05	(0.81-5.18)	0.131
Weather	146(76.0%)	66(75%)	1.06	(0.58-1.89)	0.850
• Hot	98(51.0%)	48(54.5%)	0.87	(0.52-1.44)	0.586
• Cold	60(31.3%)	19(21.6%)	1.65	(0.91-2.99)	0.097
• Humidity	21(10.9%)	16(18.2%)	0.55	(0.27-1.12)	0.100
Environment	79(41.2%)	43(48.8%)	0.73	(0.44-1.22)	0.227
• Dust	61(31.8%)	36(40.9%)	0.67	(0.39-1.13)	0.137
• Chemicals	46(23.9%)	20(22.7%)	1.07	(0.59-1.94)	0.822
Smoking	19(9.9%)	5(5.7%)	1.82	(0.66-5.05)	0.248
Alcohol drinking	42(21.9%)	13(14.8%)	1.62	(0.82-3.19)	0.168
Herb use	6(3.1%)	2(2.3%)	1.39	(0.27-7.01)	0.692
Mental stress	126(65.6%)	21(23.9%)	6.09	(3.43-10.81)	<0.001
Inadequate sleep	124(64.6)	27(30.7%)	4.12	(2.40-7.07)	<0.001

*Other food in psoriasis group: fresh bamboo shoots 5, duck 4, egg 3, fruits 2, fresh-water fish 2, shrimp paste 2, insect 2, flour 2, soy milk 1, potatoes 1, fresh-water shrimp 1. Other food in eczema group: fresh bamboo shoots 2, insect 1, duck 1, honey 1, cheese 1.

Table 3. Comparison of aggravating factors between psoriasis and eczema patients using multiple logistic regression.

Factors	Adjusted OR	95% CI	p-value
Scratching	0.98	0.52-1.87	0.957
Illness	1.39	0.48-4.03	0.539
Seafood	1.06	0.54-2.06	0.873
Pickled foods	1.64	0.65-4.10	0.294
Monosodium glutamate	2.16	0.62-7.52	0.228
Cold	1.92	0.93-3.91	0.074
Humidity	0.33	0.14-0.79	0.013
Dust	0.37	0.19-0.72	0.004
Alcohol drinking	0.77	0.33-1.76	0.530
Mental stress	5.27	2.47-10.52	<0.001
Inadequate sleep	2.14	1.31-5.08	0.006

as well as in the exacerbation of eczema [14-20]. This study showed that almost all psoriasis and eczema patients had aggravating factors associated with the exacerbation of the diseases. This may be due to a chronicity of diseases leading to patients' recognition of trigger factors. Previous studies found that stressful events, smoking, and alcohol consumption were common trigger factors in psoriasis exacerbation, while sweating, emotional stress, and house dust were common trigger factors for flare-ups of atopic dermatitis [21,22]. Our study found that the most common aggravating factors in both psoriasis and eczema were weather, scratching, foods, mental stress, and inadequate sleep, some of which were consistent with previous studies. Our study also found that mental stress and inadequate sleep were strongly associated with psoriasis exacerbation rather than with eczema exacerbation, while a humid environment and dust were significantly associated with eczema exacerbation rather than with psoriasis exacerbation. This could be because individuals with eczema may have a compromised skin barrier that makes their skin more sensitive.

A systematic review study in northern and central Europe revealed that half of psoriasis patients experience seasonal-dependent disease, consistent with our study. Most cases indicated improvement in psoriasis in the summer and a deterioration in winter [23]. In contrast with our study, 51% of psoriasis patients reported worsening in hot weather and 31.3% in cold weather. This may be due to sweat-induced itching in summer, causing further Koebnerization. Moreover, an uncommon subset of patients with psoriasis–photosensitive psoriasis–exhibit exacerbation in the summer months [24]. Photosensitive psoriasis patients have a strong association with HLA-Cw*0602 [24]. This may be another explanation for the high rate of worsening in hot weather in our study; further investigation regarding seasonal variation and genetic association is needed. Regarding eczema, seasonal variation is one factor influencing disease flare-ups. In general, most patients tend to experience disease flare-ups in winter with low ambient humidity [25]. However, hot weather can exacerbate eczema symptoms. A previous study classified eczema into two patterns: a summer-type pattern (aggravation of symptoms in summer) and a winter-type pattern (aggravation of symptoms in winter) [26]. Our study found that most patients with eczema experienced disease worsening in summer (54.5%) rather than in winter (21.6%). Moreover, we found that a humid climate had a significant effect on eczema exacerbation compared to the psoriasis group. This may be due to warmth and humidity causing an increase in perspiration and producing excessive sweat, which provokes itch and the itch-scratch cycle.

Scratching is a well-known aggravating factor in both psoriasis and eczema. In our study, scratching was the second most common aggravating factor in both conditions. The Koebner phenomenon, i.e., the emergence of skin lesions following various injuries or trauma, is commonly found in psoriasis patients. The pathogenesis is related to the activation of lesional mast cells and their mediators, leading to an increased expression of nerve growth factor and vascular endothelial growth factor [27]. The development of new psoriatic lesions can occur after various mechanical injuries such as tattooing, surgical incisions, needle acupuncture, cupping therapy, and even scratching due to itching as part of this phenomenon. In eczema, scratching can worsen the symptoms by inducing the itch-scratch cycle.

Diet has been suggested to play a role in the pathogenesis of psoriasis [7,28]. Some studies have indicated that fasting periods, low-energy diets, vegetarian diets, and n-3 polyunsaturated fatty acids from fish oil have shown beneficial effects in psoriasis [29]. Meanwhile, saturated fatty acids, simple sugars, red meat, or alcohol can exacerbate psoriasis via inflammatory cytokine activation [7,8]. In our study, there was a surprisingly high report of food as an aggravating factor compared to only 14% in a previous study [27]. The types of food most frequently reported in our study were seafood, pickled food, and pickled fish ("Pla-Ra"), which were not mentioned before. In contrast to previous studies suggesting that fish oil in seafood improves psoriatic rash, our study reported seafood as an aggravating factor [30–34]. This difference may be attributed to the fact that seafood in our region lacks fish oil fatty acids, unlike the mackerel, sardine, salmon, or herring found in regions studied in previous research. The proposed theories behind a high reported rate of food-aggravating factors in our study could be due to an under-detected rate in previous studies due to an unawareness of these factors, to speculative explanations such as local food preservation processes involving pickling, or even the presence of bacteria or parasites in undercooked food that might lead to oxidative stress and increased free radicals, which are linked to skin inflammation in psoriasis, and/or to contamination of heavy metals in seafood in our region [35]. There are supporting studies indicating that heavy metals, especially cadmium, may contribute to psoriasis and eczema [36]. Patients with psoriasis have shown higher blood cadmium levels than the general population [37]. Additionally, studies have supported a positive association between cadmium, lead, and mercury with eczema [38–42]. In Thailand, a study found higher cadmium levels in urine among the population in the north and northeastern regions, where our study was conducted, compared to other regions, and people are primarily exposed to cadmium

through the inhalation of contaminated dust in the air and the ingestion of contaminated water and food [43]. Major food groups contributing to cadmium exposure include rice and grains, shellfish, and seafood [44.] This could speculatively explain why our study identified seafood and dust as significant aggravating factors in both psoriasis and eczema.

Beyond heavy metal contamination in food, the idea of food as an exacerbating factor for eczema has been controversial. Eczematous reactions due to food, especially in children with atopic eczema, have been reported [23,24]. Another distinct type of dermatitis called "systemic contact dermatitis" has also been reported to be aggravated by food [26]. However, seafood was not a common food aggravating these types of eczematous reactions in previous findings, contrary to our results. Based on our results, further studies are needed to clarify the relationship between specific types of food in psoriasis and eczema. Investigating the theory of pathomechanism behind both the food preservation process and heavy metal contamination requires further exploration. Measuring blood levels of heavy metals in patients consuming this type of food is necessary to validate this hypothesis.

Mental stress is one of the major aggravating factors in psoriasis. Psoriasis patients often suffer from embarrassment due to appearance, itching, or pain of the skin lesions, which leads to anxiety, depression, mental stress, or even suicidal ideation. At the same time, mental stress itself can exacerbate skin lesions. A previous study reported that psychological stress can cause skin flares in up to 40% of psoriasis patients [45]. In a large systematic review involving 32,537 patients, 54% reported preceding stressful events prior to exacerbation, and 46% of patients suspected that stress aggravated the rash [46]. The mechanism between stress and psoriasis is still unclear. However, dysregulation and complex interplay among the hypothalamic–pituitary–adrenal (HPA) axis, sympathetic–adrenal–medullary (SAM) axis, peripheral nervous system, and immune-mediated pathways are involved in stress-associated psoriasis exacerbation [47]. Similarly, mental stress is one of the most mentioned aggravating factors in eczema. A previous study found that emotional stress can cause disease flares in up to 48% of atopic dermatitis patients [22]. However, our study found that stress was the most significant aggravating factor associated with psoriasis exacerbation (65.6%) compared to eczema exacerbation (23.9%).

Sleep disturbance is a common associated condition in psoriasis and eczema. Previous studies have shown that up to 77.1% of patients with psoriasis experience sleep disturbance [48,49]. Various factors can cause sleep disturbance in psoriasis, including pruritus, anxiety, depression, systemic inflammation, and comorbidities [50]. The relationship between psoriasis and sleep deprivation is bidirectional. Sleep deprivation leads to an increase in proinflammatory cytokines, including IL-6 and tumor necrosis factor-α (TNF-α), which in turn can cause keratinocyte hyperproliferation in psoriasis patients [40]. Therefore, poor sleep quality may trigger psoriasis, and psoriasis may worsen the quality of sleep. Similarly, itching can cause sleep disturbance in patients with eczema, and poor sleep quality can induce eczema exacerbation. A previous study found that a lack of sleep can cause eczema exacerbation in up to 29% of cases [22]. Our study found that inadequate sleep was another factor significantly associated with psoriasis exacerbation (64.6%) compared to eczema exacerbation (30.7%).

Our study also showed that industrial dust is a prominent aggravating factor for eczema, especially when compared to psoriasis. Previous studies have shown that air pollutants, including particulate matter (PM2.5, PM10), nitrogen dioxide (NO2), sulfur dioxide (SO2), and carbon monoxide (CO), are significantly associated with the incidence of eczematous rashes [15,51,52]. Exposure to the pollutants has an adverse effect on the skin by increasing the level of free radicals, inducing cutaneous inflammation, activating mechanisms linked to the aryl hydrocarbon receptor, and altering the skin microflora [52]. Although our study did not directly collect data on the levels of these pollutants, the high rate of industrial dust reported by eczema patients as an aggravating factor could imply a connection with these pollutants, especially PM2.5, based on the current pollution situation in Thailand.

Patient education on aggravating factors is crucial to prevent flare-ups of chronic inflammatory skin diseases, particularly psoriasis and eczema.

Our study explored the aggravating factors of psoriasis, focusing on detailed aspects of foods and climate, and evaluated these factors in a comparison to eczema. However, there are some limitations to this study. First, our study had a small sample size and was conducted at a single center. Additionally, the reliance on self-reported data introduces potential recall bias. The lack of objective environmental exposure measurements such as specific pollutant levels or quantitative dietary assessments, limits the ability to establish precise relationships between exposure and outcomes. Further multicenter studies with objective exposure measurements are needed to clarify the pathogenesis of food-related and environmental exacerbations in psoriasis and eczema.

Conclusions

Weather, scratching, foods, mental stress, and inadequate sleep were common aggravating factors in both psoriasis and eczema. However, internal factors such as mental stress and inadequate sleep have a greater influence on the worsening of psoriasis, whereas external factors including humid environment and dust have a more significant impact on eczema

flare-ups than on psoriasis exacerbation. Providing advice to patients regarding aggravating factors is beneficial to prevent flare-ups of both chronic inflammatory skin conditions.

Ethics Approval Statement: The study received approval from the university's ethics committee [HE621284], and written informed consent was obtained from all participants before enrollment.

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Dermatology Practical & Conceptual

Risk Factors and Epidemiology of Acne Severity and Acne Scar Development: A Comprehensive Clinical Study

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Key words: Acne, Acne scarring, Acne severity, Acne scar severity, Risk factors

Citation: Etgu F, Sekerlisoy Tatar G. Risk Factors and Epidemiology of Acne Severity and Acne Scar Development: A Comprehensive Clinical Study. *Dermatol Pract Concept*. 2025;15(4):6108. DOI: https://doi.org/10.5826/dpc.1504a6108

Accepted: August 28, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Acne vulgaris, affecting around 9.4% of the global population, is a common disorder of the pilosebaceous unit. Approximately 95% of affected individuals develop some degree of scarring, which, along with active acne, contributes significantly to psychosocial morbidity.

Objectives: This study aimed to evaluate the factors influencing acne severity, the development of acne scars, and the severity of scarring in patients with acne vulgaris.

Methods: A cross-sectional study was conducted between May and November 2024 at the dermatology outpatient clinic of Ordu University, Turkey. Demographic data, characteristics of acne lesions, treatment history, and various potential risk factors for acne and scarring were recorded. Acne severity and scar severity were evaluated using standardized grading systems.

Results: A total of 269 patients (175 females, 94 males) were included, with acne scars observed in 71.3%. Younger age, earlier, and adolescent-onset acne were significantly associated with greater acne severity and scarring. Male sex and severe acne further increased the risk and severity of scars. Patients with scarring reported higher emotional stress. Post-lesional hyperpigmentation and erythema predicted more severe scarring. Prior use of topical agents and systemic antibiotics was linked to increased scar risk, while systemic isotretinoin had a protective effect.

Conclusions: Early identification of risk factors and timely intervention may help reduce the burden of acne scarring and improve patients' quality of life. Recognizing predictors of acne severity and scarring can guide clinicians in implementing preventive strategies and optimizing long-term outcomes.

Introduction

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit characterized by the presence of comedones, papules, pustules, and cysts. Its lifetime prevalence approaches 100%, and it affects individuals globally [1,3]. With a reported prevalence of 9.4%, acne ranks as the eighth most prevalent disease worldwide [2]. It affects approximately 85% of adolescents and often persists into adulthood, particularly in females over the age of 25 [1,2].

Several factors have been implicated in acne severity, including female sex, older adolescent age, parental education, positive family history, oily skin type, and higher body mass index (BMI) [4]. The relationship between acne and dietary factors or smoking remains less clearly defined. Further studies are necessary to elucidate these associations [4].

Acne scarring occurs in up to 95% of patients with acne [5,7], although the prevalence in the general population ranges from 1% to 11% [7]. Even mild-to-moderate acne can result in clinically significant scarring [5]. Given that acne lesions commonly occur on visible areas, scarring can lead to considerable psychosocial burden. Currently, there is no universal consensus on optimal treatment modalities for acne scars [6,7], and many patients present with multiple scar types, complicating management strategies [6]. Consequently, early identification of high-risk patients is essential to implementing timely and effective interventions to prevent scarring [5].

This study aimed to evaluate the risk factors associated with acne severity, acne scar development, and acne scar severity in individuals with acne vulgaris.

Materials and Methods

Study Population, Setting, and Ethics

This cross-sectional study was conducted between May 2024 and November 2024 in the dermatology outpatient clinic of Ordu University, Ordu, Türkiye. Ethical approval was obtained from the university's Ethics Committee (Approval No: 2024/34). Sample size calculations indicated a minimum of 104 participants for a 95% confidence interval. Participants aged 18–65 years with a diagnosis of acne vulgaris who consented to participate were included. Patients with other dermatological conditions affecting acne-prone areas were excluded. Informed consent was obtained from all participants. The study adhered to the Declaration of Helsinki and the Guidelines for Good Clinical Practice. This study was reported in accordance with the STROBE guidelines (see Table S1).

Study Design

Two senior dermatologists evaluated each participant for diagnosis, classification, and severity assessment of both acne and acne scarring. Demographic and clinical data, including age, marital status, employment, disease duration, age at onset, history of adolescent acne, skin type, family history, lesion location and type, post-lesional hyperpigmentation and erythema, and scar morphology, were recorded. Scar types included icepick, rolling, and boxcar scars. Additional data included prior acne treatments, smoking/alcohol use, cosmetic usage, use of potential triggering medications, emotional stress level (0–10 Likert scale), seasonal acne variation, and dietary habits, including dairy consumption. In female patients, menstrual irregularities and clinical signs of hyperandrogenism were also documented.

Acne Severity: Global Acne Grading System (GAGS)

The Global Acne Grading System (GAGS), developed by Doshi et al. in 1997, evaluates acne severity across six anatomical regions with assigned multipliers. Lesions are graded from 0 (none) to 4 (nodules), and the region score is calculated by multiplying the lesion grade by the region multiplier. The final score classifies acne as: 1–18 (mild), 19–30 (moderate), 31–38 (severe), and >39 (very severe) [8].

Acne Scar Classification

According to Jennings et al., acne scars are categorized as atrophic, hypertrophic, keloidal, or papular. Atrophic scars are further divided into icepick, rolling, and boxcar subtypes [6].

Acne Scar Severity

A 4-point scale was used to assess scar severity: Grade 1 (macular changes), Grade 2 (mild), Grade 3 (moderate), and Grade 4 (severe) [9]. Clinical grading of acne scars was performed using the Goodman and Baron qualitative scar grading scale, a widely accepted and validated method. Two senior dermatologists calibrated their scoring before the study to ensure consistency. Blinding was not feasible as dermatologists performed direct patient examinations and collected clinical data, including acne type and lesion characteristics. The calibration and standardized assessment procedures aimed to minimize inter-rater variability and improve scoring reliability.

Assessment of Clinical Signs of Hyperandrogenism

Hyperandrogenism is a clinical condition caused by excess androgen production from the ovaries and adrenal glands or increased peripheral conversion. Its manifestations include seborrhea, acne, infertility, hirsutism, and virilization [10]. In this study, only clinical signs relevant to dermatology, such as adult female acne, hirsutism, and female pattern hair loss, were assessed, without biochemical evaluation.

Statistical Analysis

MedCalc version 20.009 (Ostend, Belgium) was used for statistical analyses. Normality of continuous variables was assessed using the Kolmogorov-Smirnov test and Q-Q plots. Mean, standard deviation (SD), median, and interquartile ranges (IQR), are reported for continuous variables; categorical data are summarized using frequency and percentage. Independent t-tests and Mann-Whitney U tests were used for group comparisons. Logistic regression analysis was performed to identify risk factors associated with acne severity and scarring. Univariable odds ratios (uORs), multivariable odds ratios (mORs), and their 95% confidence intervals (CIs) are reported. To evaluate factors associated with the presence and severity of acne scarring, a multivariable logistic regression model was applied. A p-value of <0.05 was considered statistically significant.

Power Analysis

The power (1-β) of the study was calculated using G*Power version 3.1.2 software. The test family was specified as z tests, and the statistical test used was logistic regression. The type of power analysis was set to "Post hoc; Compute achieved power—given α, sample size, and effect size." Based on previous studies, a two-tailed test was applied, with α = 0.05, H_0 = 0.59, X distribution = Binomial, and a sample size of N=269. The calculated power (1-β) value was 0.87, indicating that the study had sufficient power to detect the observed effect size.

Results

The study included 269 patients, of whom 75 (65.1%) were females and 94 (34.9%) were males. The mean age of the participants was 25 ± 6.6 years, with an average acne onset age of 19.5 ± 6.2 years. The average duration of acne was 5.7 ± 5.6 years. Stress levels were measured with a mean score of 6.2 ± 2.7, and the mean GAGS score was 23.4 ± 7.9.

Based on the GAGS score, acne severity was classified as mild in 26.4%, moderate in 59.1%, severe in 12.3%, and very severe in 2.2% of participants. Acne scarring was present in 71.3% of patients, with severity graded as Grade 1 in 23.8%, Grade 2 in 36.8%, Grade 3 in 22.8%, and Grade 4 in 16.6%. Detailed demographic information is shown in Table 1.

Risk Factors Associated with Acne Severity

Patients with severe acne were significantly younger (mean age 23 ± 5.5 vs. 25 ± 9; *P*=0.000) and had an earlier onset of acne (16.5 ± 6 vs. 19 ± 10; *P*=0.001). A history of adolescent acne increased the likelihood of severe acne, with patients having a 1.87 times higher odds of developing severe acne

Table 1. Demographic Characteristics of the Study Group.

Variables		N	%
Adolescent acne	**No**	153	56.9
	Yes	116	43.1
Skin type	**Dry**	122	45.4
	Oily	147	54.6
Family history of acne	**No**	126	46.8
	Yes	143	53.2
Family history for acne scar	**No**	198	73.6
	Yes	71	26.4
Forehead	**No**	54	20.1
	Yes	215	79.9
Cheek	**No**	19	7.1
	Yes	250	92.9
Nose	**No**	205	76.2
	Yes	64	23.8
Chin	**No**	93	34.6
	Yes	176	65.4
Submandibular area	**No**	175	65.1
	Yes	94	34.9
Back	**No**	148	55.0
	Yes	121	45.0
Chest	**No**	198	73.6
	Yes	71	26.4
Postlesional hyperpigmentation	**No**	106	39.4
	Yes	163	60.4
Erythema	**No**	65	24.2
	Yes	204	75.8
Previous treatment	**No**	100	37.2
	Topical	120	44.6
	Antibiotic (Oral)	40	14.9
	İsotretinoin(Oral)	9	3.3
Smoking	**No**	221	82.2
	Yes	48	17.8
Alcohol	**No**	258	95.9
	Yes	11	4.1
Regular use of cosmetics	**No**	96	35.7
	Yes	173	64.3
Triggering medication	**No**	226	84.0
	Yes	43	16.0
Dairy consumption	**No**	164	61.0
	Yes	105	39.0
Menstruation history	**Regular**	142	52.8
	Irregular	32	12.3
	Not applicable	94	34.9
Hyperandrogenism	**No**	154	57.2
	Yes	21	7.8
	İNot applicable	94	34.9

(odds ratio (OR)=1.87; 95% CI: 1.14–3.08; *P*=0.013). Acne lesions located on the forehead (OR=0.0001) were significantly linked with higher acne severity. Table 2 presents a detailed univariable analysis of the factors associated with acne severity. These findings emphasize the multifactorial nature of acne severity and highlight the importance of lesion localization in predicting severity.

Risk Factors Associated with Acne Scarring

Previous treatments played a significant role; patients who received topical treatments had an increased risk of scarring (OR2.02; 95% CI: 1.12–3.65; *P*=0.019), and those treated with oral antibiotics had an even higher risk (OR=4.11; 95% CI: 1.48–11.4; *P*=0.006). Conversely, oral isotretinoin was associated with a significantly reduced risk of acne scarring (OR=0.16; 95% CI: 0.03–0.85; *P*=.031), suggesting a protective effect. These findings underline the importance of appropriate treatment choices and their potential to prevent scarring. Table 3 provides a detailed univariable analysis of the clinical and demographic factors associated with the development of acne scars.

Risk Factors for Acne Scar Severity

Several factors were identified as significant predictors of acne scar severity. Patients with a history of adolescent acne had a significantly higher likelihood of severe scarring (OR2.66; 95% CI: 1.41–5.01; *P*=0.002). Additionally, involvement of specific anatomical areas such as the forehead (OR=4.46; 95% CI: 1.64–12.2; *P*=0.003), cheek (OR=7.00; 95% CI: 0.87–55.9; P=0.034), and back (=2.32; 95% CI: 1.28–4.18; P=0.005) were all strongly related to more severe scarring.

Post-inflammatory changes such as hyperpigmentation (OR = 1.88; 95% CI: 1.01–3.51; P = 0.045) and erythema (OR = 2.22; 95% CI: 1.04–4.74; P = 0.038) also contributed to increased scar severity. Nasal involvement did not significantly impact scar severity (OR = 0.302; 95% CI: 0.1–0.88; P = 0.028). Table 2 provides a detailed univariable analysis of the clinical and demographic factors associated with the severity of acne scarring.

Post-inflammatory changes such as hyperpigmentation (OR=1.88; 95% CI: 1.01–3.51; P=0.045) and erythema (OR=2.22; 95% CI: 1.04–4.74; P=0.038) also contributed to increased scar severity. Nasal involvement did not significantly impact scar severity (OR=0.302; 95% CI: 0.1–0.88; P=0.028). Table 2 provides a detailed univariable analysis of the clinical and demographic factors associated with the severity of acne scarring.

Risk Factors for Acne Scarring: Multivariable Analysis

A multivariable logistic regression analysis was performed to identify factors associated with acne scarring. Stress levels (OR = 1.453; P < 0.0001) and global acne severity (OR = 1.079; P = 0.033) were significant risk factors for scarring. Topical treatments (OR = 3.158; P = 0.007) and oral antibiotics (OR = 4.263; P = 0.026) increased the odds of scarring, while oral isotretinoin was protective (OR = 0.088; P = 0.037).

Postlesional hyperpigmentation (OR = 2.436; P = 0.031) was also significantly associated with scarring, but erythema did not show a significant impact (P = 0.365). Other factors such as age, sex, acne onset, and family history did not significantly affect scarring risk.

Risk Factors for Acne Scar Severity: Multivariable Analysis

A multivariable logistic regression analysis identified key factors associated with the severity of acne scarring. Higher global acne severity (OR = 1.195; P = 0.000) and postlesional hyperpigmentation (OR = 4.751; P = 0.001) were significantly linked to more severe scarring. Regular cosmetic use had a protective effect (OR = 0.413; P = 0.041). Scarring on the nose was less severe compared to other regions (OR = 0.302; P = 0.028). Other factors, such as stress, acne duration, and prior treatments, were not significantly associated

Table 4 summarizes the factors contributing to acne severity, the development of acne scarring, and the severity of acne scars. The factors associated with acne severity are derived from the univariable analysis, while those related to acne scarring and acne scar severity are based on the multivariaable analysis results.

Discussion

This study assessed the factors influencing acne severity, scar formation, and scar severity. Younger age, adolescent acne history, and earlier onset were significantly associated with more severe acne and scarring. Male sex and high acne severity emerged as risk factors for scar development and severity.

It is well established that patients with acne vulgaris experience a reduced quality of life, diminished psychological well-being, lower satisfaction with their appearance, greater social impairment, and a higher tendency toward depressive temperament. Therefore, identifying and effectively managing the factors associated with acne is crucial for the appropriate treatment of this prevalent chronic dermatological condition [11].

Several studies have examined factors affecting acne frequency and severity. A systematic review of 35 articles found that older adolescents are more frequently affected than were younger adolescents and adults [4]. Similarly, our study showed greater severity in those with adolescent-onset acne. While acne is generally more common in females—consistent with our findings—it has been reported as more severe in

Table 2. Univariable Analysis of Factors Associated with Acne Severity and Acne Scar Severity (N=269).

		GAGS (≤25) (n = 153)		GAGS>25 (n = 116)		Acne Severity			Acne scarring (Grade 1-2) (n = 117)		Acne scarring (Grade 3-4) (n = 76)		Acne Scar Severity		
		N	%	N	%	uOR	95% CI	p-value	N	%	N	%	uOR	95% CI	p-value
Sex	Female	101	66.0	74	63.8	1.00	Reference		75	64.1	40	52.6	1.00	Reference	
	Male	52	34.0	42	36.2	1.10	0.66-1.82	0.705	42	35.9	36	47.4	1.60	0.89-2.89	0.113
Adolescent acne	No	76	49.7	40	34.5	1.00	Reference		55	47.0	19	25.0	1.00	Reference	
	Yes	77	50.3	76	65.5	1.87	1.14-3.08	0.013*	62	53.0	57	75.0	2.66	1.41-5.01	0.002*
Skin type	Dry	68	44.4	54	46.6	1.00	Reference		52	44.4	34	44.7	1.00	Reference	
	Oily	85	55.6	62	53.4	0.91	0.56-1.49	0.731	65	55.6	42	55.3	0.98	0.55-1.76	0.968
Family history of acne	No	71	46.4	55	47.5	1.00	Reference		52	44.4	36	47.4	1.00	Reference	
	Yes	82	53.6	61	52.6	0.96	0.59-1.55	0.869	65	55.6	40	52.6	0.88	0.49-1.58	0.690
Family history of	No	112	73.2	86	74.1	1.00	Reference		85	72.6	56	73.7	1.00	Reference	
	Yes	41	26.8	30	25.9	0.95	0.55-1.65	0.863	32	27.4	20	26.3	0.94	0.49-1.82	0.874
Forehead	No	50	32.7	4	3.4	1.00	Reference		28	23.9	5	6.6	1.00	Reference	
	Yes	103	67.3	112	96.6	13.50	4.74-38.95	<0.0001*	89	76.1	71	93.4	4.46	1.64-12.2	0.003*
Cheek	No	18	11.8	1	0.9	1.00	Reference		10	8.5	1	1.3	1.00	Reference	
	Yes	135	88.2	115	99.1	15.33	2.01-116.6	0.000*	107	91.5	75	98.7	7.00	0.87-55.9	0.034*
Nose	No	123	80.4	82	70.7	1.00	Reference		91	77.8	58	76.3	1.00	Reference	
	Yes	30	19.6	34	29.3	1.70	0.96-2.99	0.065	26	22.2	18	23.7	1.08	0.54-2.15	0.813
Chin	No	70	45.8	23	19.8	1.00	Reference		39	33.3	15	19.7	1.00	Reference	
	Yes	83	54.2	93	80.2	3.41	1.95-5.94	<0.0001*	78	66.7	61	80.3	2.03	1.02-4.02	0.041*
Submandibular area	No	109	71.2	66	56.9	1.00	Reference		81	69.2	40	52.6	1.00	Reference	
	Yes	44	28.8	50	43.1	1.87	1.13-3.11	0.014*	36	30.8	36	47.4	2.02	1.11-3.68	0.020*
Back	No	113	73.9	35	30.2	1.00	Reference		72	61.5	31	40.8	1.00	Reference	
	Yes	40	26.1	81	69.8	6.53	3.82-11.17	<0.0001*	45	38.5	45	59.2	2.32	1.28-4.18	0.005*
Chest	No	133	86.9	65	56.0	1.00	Reference		92	78.6	46	60.5	1.00	Reference	
	Yes	20	13.1	51	44.0	5.21	2.87-9.47	<0.0001*	25	21.4	30	39.5	2.40	1.26-4.54	0.007*
Postlesional hyperpigmentation	No	64	41.8	42	36.2	1.00	Reference		49	41.9	21	27.6	1.00	Reference	
	Yes	89	58.2	74	63.8	1.26	0.77-2.08	0.350	68	58.1	55	72.4	1.88	1.01-3.51	0.045*

Table 2 continues

Table 2. Univariable Analysis of Factors Associated with Acne Severity and Acne Scar Severity (N=269). *(continued)*

		GAGS (≤25) (n = 153)		GAGS>25 (n = 116)		Acne Severity			Acne scarring (Grade 1-2) (n = 117)		Acne scarring (Grade 3-4) (n = 76)		Acne Scar Severity		
		N	%	N	%	uOR	95% CI	p-value	N	%	N	%	uOR	95% CI	p-value
Erythema	No	41	26.8	24	20.7	1.00	Reference		32	27.4	11	14.5	1.00	Reference	
	Yes	112	73.2	92	79.3	1.40	0.79-2.49	0.247	85	72.6	65	85.5	2.22	1.04-4.74	0.038*
Smoking	No	122	79.7	99	85.3	1.00	Reference		92	78.6	63	82.9	1.00	Reference	
	Yes	31	20.3	17	14.7	0.67	0.35-1.29	0.235	25	21.4	13	17.1	0.75	0.36-1.59	0.467
Alcohol	No	148	96.7	110	94.8	1.00	Reference		112	95.7	74	97.4	1.00	Reference	
	Yes	5	3.3	6	5.2	1.61	0.48-5.42	0.435	5	4.3	2	2.6	0.60	0.11-3.20	0.554
Regular use of cosmetics	No	58	37.9	38	32.8	1.00	Reference		40	34.2	33	43.4	1.00	Reference	
	Yes	95	62.1	78	67.2	1.25	0.75-2.08	0.383	77	65.8	43	56.6	0.67	0.37-1.22	0.197
Triggering medication	No	132	86.3	94	81.0	1.00	Reference		100	85.5	64	84.2	1.00	Reference	
	Yes	21	13.7	22	19.0	1.47	0.76-2.82	0.247	17	14.5	12	15.8	1.10	0.49-2.46	0.810
Dairy	No	95	62.1	69	59.5	1.00	Reference		73	62.4	46	60.5	1.00	Reference	
	Yes	58	37.9	47	40.5	1.11	0.68-1.82	0.664	44	37.6	30	39.5	1.08	0.59-1.95	0.794

*Significant difference at <0.05 level according to logistic regression. uOR: univariable odds ratio. CI: confidence interval.

Table 3. Clinical Characteristics and Univariable Analysis of Factors Associated with Acne Scar.

Variables		acne scarring (+) (N=193)		acne scar (-) (N=76)		p-value		
		N	%	N	%	OR	95% CI	p-Value
Gender	Female	115	59.6	60	78.9	1.00	Reference	
	Male	78	40.4	16	21.1	2.54	1.36-4.73	0.003**
Adolescent acne	No	74	38.3	42	55.3	1.00	Reference	
	Yes	119	61.7	34	44.7	1.98	1.16-3.39	0.012**
Skin type	Dry	86	44.6	36	47.4	1.00	Reference	
	Oily	107	55.4	40	52.6	1.12	0.65-1.90	0.677
Family history of acne	No	88	45.6	38	50.0	1.00	Reference	
	Yes	105	54.4	38	50.0	1.19	0.70-2.03	0.515
Family history of acne scar	No	141	73.1	57	75.0	1.00	Reference	
	Yes	52	26.9	19	25.0	1.10	0.60-2.03	0.745
Forehead	No	33	17.1	21	27.6	1.00	Reference	
	Yes	160	82.9	55	72.4	1.85	0.98-3.46	0.054
Cheek	No	11	5.7	8	10.5	1.00	Reference	
	Yes	182	94.3	68	89.5	1.94	0.75-5.04	0.170
Nose	No	149	77.2	56	73.7	1.00	Reference	
	Yes	44	22.8	20	26.3	0.82	0.44-1.52	0.542
Chin	No	54	28.0	39	51.3	1.00	Reference	
	Yes	139	72.0	37	48.7	2.71	1.56-4.69	0.000**
Submandibular area	No	121	62.7	54	71.1	1.00	Reference	
	Yes	72	37.3	22	28.9	1.46	0.82-2.59	0.196
Back	No	103	53.4	45	59.2	1.00	Reference	
	Yes	90	46.6	31	40.8	1.26	0.74-2.17	0.386
Chest	No	138	71.5	60	78.9	1.00	Reference	
	Yes	55	28.5	16	21.1	1.49	0.79-2.81	0.214
Postlesional hyperpigmentation	No	70	36.3	36	47.4	1.00	Reference	
	Yes	123	63.7	40	52.6	1.58	0.92-2.71	0.094
Erythema	No	43	22.3	22	28.9	1.00	Reference	
	Yes	150	77.7	54	71.1	1.42	0.78-2.59	0.251
Previous treatment	No	63	32.6	37	48.7	1.00	Reference	
	Topical	93	48.2	27	35.5	2.02	1.12-3.65	0.019**
	Antibiotic (Oral)	35	18.1	5	6.6	4.11	1.48-11.4	0.006**
	İsotretinoin (Oral)	2	1.0	7	9.2	0.16	0.03-0.85	0.031**
Smoking	No	155	80.3	66	86.8	1.00	Reference	
	Yes	38	19.7	10	13.2	1.61	0.76-3.43	0.210
Alcohol	No	186	96.4	72	94.7	1.00	Reference	
	Yes	7	3.6	4	5.3	0.67	0.19-2.38	0.544
Regular use of cosmetics	No	73	37.8	23	30.3	1.00	Reference	
	Yes	120	62.2	53	69.7	0.71	0.40-1.26	0.245
Triggering medication	No	164	85.0	62	81.6	1.00	Reference	
	Yes	29	15.0	14	18.4	0.78	0.38-1.57	0.494
Dairy consumption	No	119	61.7	45	59.2	1.00	Reference	
	Yes	74	38.3	31	40.8	0.90	0.52-1.55	0.711

*Significant difference at <0.05 level according to logistic regression. uOR: Univariable dds ratio. CI: confidence interval.

Table 4. Summary of Factors Affecting Acne Severity, Scarring, and Scar Severity.

Factor	Associated with	Effect	uOr/ mOR	p-value	Comment
Younger age	Acne severity ↑ Acne Scar ↑	Increased risk	—	0.000/ 0.001	Severe acne is more common in younger individuals
Earlier acne onset	Acne severity ↑ Acne Scar	Increased risk	—	0.001/ 0.003	Early onset is linked to higher severity
History of adolescent acne	Acne Severity ↑ Acne Scar ↑	Increased risk	1.87 / 1.98	0.013 / 0.012	Increases both severity and scarring risk
Stress levels	Acne Scar ↑	Increased risk	1.453	< 0.0001	Strong predictor of scarring
Global acne severity (GAGS)	Acne Scar ↑ / Scar severity ↑	Increased risk	1.079 / 1.195	0.033 / 0.000	Both scar presence and severity increase with acne severity
Postlesional hyperpigmentation	Acne Scar ↑ / Scar severity ↑	Increased risk	2.436 / 4.751	0.031 / 0.001	Strongest marker for scar risk and severity
Topical treatment	Acne Scar ↑	Increased risk	3.158	0.007	May indicate insufficient control in moderate/severe cases
Oral antibiotic	Acne Scar ↑	Increased risk	4.263	0.026	Linked to delayed or inadequate treatment
Oral isotretinoin	Acne Scar ↓	Protective	0.088	0.037	Strongly protective against scarring
Regular cosmetic use	Scar severity ↓	Protective	0.413	0.041	May reduce scar severity
Nasal acne	Scar severity ↓	Less severe	0.302	0.028	Scars on the nose tend to be milder

Significant difference at <0.05 level according to logistic regression., Unadjusted odds ratios (uOR) are reported for acne severity, while adjusted odds ratios (mOR) are reported for acne scarring and acne scarring risk

males [4, 11]; however, we found no sex-based difference in severity. Although a positive family history has been linked to both acne risk and severity in some studies [12–15], others reported no such association [4]. In our study, family history was not related to acne severity or scarring.

Previous studies have associated oily and mixed skin types with increased acne severity [4]; however, in our study, skin type was not linked to acne severity or scarring. Although hormonal factors are known to influence acne in females, Heng et al. reported in a systematic review no association between menstrual history and severe acne [4]. Similarly, we found no relationship between acne severity, scarring, and menstrual irregularity or hyperandrogenism.

Dietary factors, particularly milk consumption, remain a debated topic. While milk has been frequently implicated in acne pathogenesis due to its hormonal and IGF-1 content [10,14,15], some studies have reported protective effects [4,11] A systematic review found this association primarily in Western populations [3], and some studies have linked milk intake to the presence of acne and the severity of acne scars [12,13]. In contrast, our study did not identify any association between milk consumption and acne severity or scarring.

Studies on smoking and alcohol have shown inconsistent results regarding their effects on acne and scarring. While some linked living with a smoker or alcohol use to greater acne severity, others found no association [4,12,13]. In line with Yan et al. [16], our study found no relationship between smoking or alcohol intake and acne severity or scarring.

In our study, 71.3% of patients had acne scarring, consistent with Yan et al.'s finding of 61.3%, and most of the scars were mild, similar to previous reports [5,13,14,16]. Studies have identified male sex, younger age, family or sibling history, and behaviors like squeezing as risk factors for scarring [13,14,16]. While milk consumption appeared protective, butter intake was linked to more severe scars, and smoking showed no clear association [13,14]. In our study, acne scars were more severe in males and in those with earlier acne onset and younger age, consistent with previous findings [5,13–15]. Unlike some reports [13,14,16], we found no link

between family history and scar severity. Scar severity correlated with acne severity [5,15], but showed no association with cosmetic use, medications, acne duration, or stress.

In our study, topical and systemic antibiotic treatments were associated with an increased risk of acne scarring, consistent with Yan et al. [15], while systemic isotretinoin reduced this risk. Previous research supports early low-dose oral isotretinoin as effective for managing and preventing acne scars [17,18]. We also identified postlesional hyperpigmentation and erythema as risk factors for scar severity. Acne scars can significantly impact mental well-being, increasing risks of depression, suicide, and reduced quality of life [6]. Emotional stress was more prevalent among patients with acne scars, underscoring the psychosocial burden of this condition. These findings reinforce the importance of early, aggressive acne management.

Limitations of the Study

This study has several limitations that should be acknowledged. First, the cross-sectional design precludes the establishment of causal relationships. Additionally, there is a potential for recall bias, as participants may not have accurately remembered or reported relevant information, including family history of acne or scarring, cosmetic use, dairy consumption, and the use of acne-triggering medications. Specifically, the consumption of milk and dairy products was assessed through self-reported frequency-based measures, which may introduce reporting bias and represent a limitation of the study. This limitation may have influenced the strength or direction of the associations observed and should be taken into account when interpreting the results. Furthermore, as the study was conducted in a tertiary care setting, the findings may not be generalizable to the broader population. This setting also introduces the possibility of selection bias, as patients with more severe acne and scarring may have been overrepresented. While the sample size was adequate for the study's aims, future research with larger and more diverse populations would help strengthen the generalizability of the findings.

A notable strength of this study is that all participants were evaluated in person by experienced dermatologists, rather than participants' providing self-reported data, thereby enhancing the accuracy and reliability of clinical assessments.

Conclusion

This study demonstrates that acne severity and scarring are influenced by multiple factors, including age, age at onset, stress levels, lesion location, and treatment history. Younger patients with earlier acne onset and higher stress levels were more likely to experience severe acne and scarring. Topical treatments and oral antibiotics increased scarring risk, while oral isotretinoin had a protective effect. Post-inflammatory hyperpigmentation was a key factor in scar severity. These findings underline the importance of early, appropriate treatment and highlight the role of both physical and psychological factors in acne management.

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Dermatology Practical & Conceptual

Supplementary File

Table S1. STROBE Statement—checklist of items that should be included in reports of observational studies.

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1
Objectives	3	State specific objectives, including any prespecified hypotheses	1
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	3
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3

Table S1 continues

Table S1. STROBE Statement—checklist of items that should be included in reports of observational studies. *(continued)*

	Item No.	Recommendation	Page No.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Participants	13*	*(a)* Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	*(a)* Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	4
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	4
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	4
Discussion			
Key results	18	Summarise key results with reference to study objectives	4
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	5
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	5
Generalisability	21	Discuss the generalisability (external validity) of the study results	5
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	7

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Dermatology Practical & Conceptual

Secukinumab Efficacy Predictors in Korean Hidradenitis Suppurativa: A 48-Week Clinical Trial Analysis

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Key message: Faster initial responses to secukinumab in hidradenitis suppurativa patients are observed in those with milder disease, earlier treatment, and no previous biological therapy. Secukinumab also significantly reduced antibiotic usage.

Key words: Hidradenitis Suppurativa, Secukinumab, Korean Patients, Predictive Factors, IHS4-55

Citation: Nguyen NH, Lee SG, Ham S, Lee JH, Lee YI. Secukinumab Efficacy Predictors in Korean Hidradenitis Suppurativa: A 48-Week Clinical Trial Analysis. *Dermatol Pract Concept*. 2025;15(4):5933. DOI: https://doi.org/10.5826/dpc.1504a5933

Accepted: June 2, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Background: Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by painful nodules, abscesses, and draining tunnels commonly occurring in body folds. The IL-17A inhibitor, secukinumab, has shown efficacy in reducing HS lesions in clinical studies, but data on epidemiologic and patient-specific factors influencing response remain limited.

Objectives: To assess how baseline disease severity, treatment initiation delay, and prior biologics exposure influence clinical response to secukinumab and patterns of antibiotic use.

Materials and Methods: This 48-week real-world prospective trial enrolled 10 Korean patients with moderate-to-severe HS. Patients received secukinumab 300 mg subcutaneously at weeks 0, 1, 2, 3, and 4, then every two weeks. Outcomes included Hidradenitis Suppurativa Clinical Response (HiSCR), a 55% reduction in the International HS Severity Score System (IHS4-55), mean change in abscesses and inflammatory nodules, a ≥ 30% reduction in pain score on a numeric rating scale (NRS30), and duration of concomitant antibiotic use.

Results: At week 48, 90% of patients achieved HiSCR, with 90% meeting the IHS4-55 threshold and 60% reaching the NRS30 criteria. Faster responses were recorded in subjects with Hurley stage II, treatment delays of <10 years, or no prior biologics use, although response rates equalized by week

48. All patients, particularly moderate cases, either discontinued or transitioned to monotherapy with systemic antibiotics.

Conclusions: Secukinumab demonstrated efficacy in alleviating HS symptoms in moderate-to-severe cases. Patients with less severe disease, shorter treatment delays, and/or no prior biologic therapy exhibited more rapid initial responses. Additionally, the majority of patients experienced a significant duration of antibiotic cessation, underscoring the importance of early intervention. Future studies with larger populations are required to substantiate these findings.

Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disorder characterized by deep-seated abscesses and nodules that predominantly occur in intertriginous regions such as the axillae, groin, and perineal areas. Over time, the condition often progresses to draining sinus tracts and extensive scarring [1]. The disease significantly impacts patients' quality of life (QoL) owing to the debilitating pain, recurrent lesions, and social distress caused by disfigurement. Conventional treatments for HS primarily aim to control inflammation, secondary infections, and associated symptoms, including systemic antibiotics, triamcinolone acetonide intralesional injections (TA ILI), and surgical interventions such as incision and drainage (I&D) [2]. However, these therapies are often associated with limited efficacy, high recurrence rates, and suboptimal improvements in QoL [3].

The pathogenesis of HS remains incompletely understood, but it is believed to involve a combination of genetic predisposition, immune dysregulation, and pro-inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α) and interleukin-17 (IL-17), at the pilosebaceous unit [4]. To better address this inflammatory nature, targeted biologic therapies have been explored. Adalimumab, a TNF-α inhibitor, received FDA approval for the management of HS in 2015 [5]. While it has provided meaningful clinical benefits, concerns regarding safety, diminishing efficacy over time, and variability in response have limited its utility in some cases [6-8].

Recently, the efficacy and safety of secukinumab, an IL-17A inhibitor, have been demonstrated in two large-scale, multicenter randomized controlled trials (RCTs): SUNSHINE and SUNRISE [9]. These trials reported response rates of 42–45% at 16 weeks, with continued improvement observed at 52 weeks, underscoring the drug's potential for long-term disease control [9]. Subsequent real-world studies have further corroborated the effectiveness of secukinumab [10-16], culminating in its FDA approval for moderate-to-severe HS on 31 October 2023.

Although data from RCTs and real-world studies have established the efficacy and safety profile of secukinumab, the influence of disease-related factors such as severity, treatment delay, and prior biologics use on therapeutic outcomes remains insufficiently explored. Severe HS often presents with extensive scarring and multiple interconnected sinus tracts, which may hinder treatment response compared to less advanced diseases. To address this gap, we conducted a 48-week real-world clinical trial on Korean patients with moderate-to-severe HS.

Objectives

This study aimed to evaluate how baseline disease severity (Hurley stage), treatment delay, and prior biologics exposure affect clinical response to secukinumab in Korean patients with moderate-to-severe HS over a 48-week treatment period in a real-world clinical setting. Additionally, this research sought to examine the impact of secukinumab on systemic antibiotic use.

Materials and Methods

Study Design and Participants

This prospective, non-controlled clinical trial recruited moderate-to-severe HS patients in a real-world setting at the Department of Dermatology, Severance Hospital, Seoul, Republic of Korea from May 2023 to November 2024. To facilitate easier access to adequate therapy, the global Managed Access Program (MAP) by Novartis was established, providing secukinumab treatment to moderate-to-severe HS patients. The requesting physician submitted a supply or resupply request for secukinumab through the Grants, External Requests, and Managed Access System (GEMS), and the request was evaluated based on the eligibility criteria. Our study recruited HS patients from MAP, specifically those over 18 years old, diagnosed with moderate-to-severe HS for over six months (defined as having a total of five inflammatory lesions, namely abscesses and nodules, in two different anatomical areas). Detailed descriptions of inclusion and exclusion criteria are provided in Table S1. Patients were administered 300 mg of secukinumab subcutaneously at weeks

0, 1, 2, 3, and 4, then every two weeks until 48 weeks. Other concurrent treatments, namely systemic antibiotics, TA ILI, and I&D, were permitted for continuation based on clinical guidelines and recommendations.

Baseline Characteristics

At baseline, demographic and clinical data were collected, specifically sex, age, age at onset, body mass index (BMI), smoking habit, family history of HS, treatment delay (defined as the duration from disease onset to the initiation of secukinumab, categorized as <10 years and ≥10 years), comorbidities, and prior treatments of HS.

Assessment of Clinical Endpoints of Secukinumab Treatment

At baseline, clinical symptoms, namely inflammatory nodules, abscesses, and draining tunnels, were assessed and quantified. Abscesses presented as a soft mass larger than 10 mm in diameter, surrounded by a red area, with central purulent material, often associated with inflammation, pain, and tenderness. Inflammatory nodules were raised, deep, three-dimensional round lesions that were tender, red, and infiltrated, potentially forming pyogenic granulomas and measuring over 10 mm in diameter. Draining fistulae were raised sinus tracts, tender with fluctuating tunnels of varying length and depth, connected to the skin surface, and exuding purulent fluid [9].

Subsequently, disease severity was categorized based on the Hurley staging system: stage I (mild), distinguished by single or multiple abscesses without the formation of sinus tracts or scarring; stage II (moderate), involving recurrent abscesses with one or more sinus tracts and scarring that are widely separated by areas of normal skin; stage III (severe), marked by widespread involvement with multiple sinus tracts and no areas of normal skin in between [17]. Moreover, skin pain was reported by the patients via the Patient's Global Assessment of Skin Pain numeric rating scale (NRS) at the worst level within the previous 24 hours, varying from 0 (no skin pain) to 10 (the worst skin pain conceivable). All patients were examined and evaluated for clinical symptoms and skin pain at baseline and at weeks 4, 8, 16, 32, and 48. Our main clinical endpoints include:

- Hidradenitis Suppurativa Clinical Response (HiSCR): a reduction of 50% or more from baseline in the count of abscesses and inflammatory nodules (AN), without any increase in the number of abscesses or draining tunnels [18].
- IHS4-55: a decrease of at least 55% from baseline in the International Hidradenitis Suppurativa Severity Score System (IHS4), calculated using the formula: number of nodules + (number of abscesses x 2) + (number of draining tunnels x 4) [19,20].
- Mean change in AN count from baseline: the average percentage change from baseline in the AN count.
- NRS30: A reduction of 30% or more, along with a decrease of at least two points, from baseline in skin pain assessed on a continuous NRS, applicable for those with a baseline NRS of three or higher [9].

The duration of single and multiple systemic antibiotic medications was quantified from the start to the end of the study, measured in week (s). All patients were asked to report any adverse event during secukinumab treatment.

Ethics

This study was approved by the Institutional Review Board of Yonsei University Hospital (IRB No. 4-2023-0201). All patients provided written informed consent before participation, in accordance with the Declaration of Helsinki.

Statistical Analysis

Means and standard deviation (SD) are used to describe continuous variables. Qualitative variables are displayed as a frequency distribution. Comparisons between continuous variables were conducted by an independent Student t-test or Mann-Whitney test based on normality results via the Shapiro-Wilk test. For nominal variables, the $\chi 2$ test or Fisher's exact test was utilized for comparison, as appropriate, and the relative risk (RR) was calculated with a 95% confidence interval (CI). Logistic regression analysis was conducted to assess any correlation between nominal endpoints (HiSCR, IHS4-55, NRS30) and patients' demographic characteristics. Simple linear regression was used to test possible related factors for the quantitative endpoint (Mean change in AN count from baseline). Statistical significance was set at $P<0.05$. Statistical analyses were performed using the R software (version 4.3.1). The graphing of results was done via the GraphPad Prism software (version 10.2.2).

Results

Ten patients with moderate-to-severe HS were enrolled and monitored over 48 weeks. Baseline demographic and clinical characteristics are summarized in Table 1, while baseline features categorized by Hurley stage, treatment delay, and prior biologics use are presented in Table 2. Notably, 70% of patients (N=7) were classified as Hurley stage II, while the remaining 30% (N=3) were Hurley stage III. All patients had prior treatments with antibiotics and TA ILI, and 40% (N=4) had previously received an anti-TNF-α biologic agent, specifically adalimumab. Patients with Hurley stage II or no

Table 1. Baseline Characteristics of Patients.

Patient number	Sex	Age	Age at onset	Secukinumab treatment delay	Family history	Body mass index (kg/m^2)	Smoking habit	Comorbidities	Prior treatment	Baseline Hurley stage	Baseline IHS4	Baseline NRS
1	M	20	15	5	Yes	24.97	Yes	Acne conglobata	Antibiotics TA ILI I&D	3	46	5
2	F	23	17	7	No	20.37	No	Acne conglobata	Adalimumab Antibiotics TA ILI	3	31	3
3	M	19	17	2	No	23.89	No	Acne conglobata	Antibiotics TA ILI I&D	3	31	4
4	M	31	18	13	No	25.51	Yes	Agent resistant to multiple antibiotics	Adalimumab Antibiotics I&D TA ILI	2	13	5
5	F	28	18	10	No	22.31	No	Acne vulgaris	Adalimumab Antibiotics TA ILI I&D	2	20	6.5
6	F	22	6	17	Yes	25.66	No	Female pattern alopecia	Adalimumab Antibiotics I&D TA ILI	2	8	8
7	M	22	20	2	Yes	25.08	No	Acne conglobata	Antibiotics TA ILI	2	16	1
8	M	23	9	15	No	27.17	Yes		Antibiotics TA ILI	2	11	3
9	F	54	52	3	Yes	32.37	No	Acne conglobata	Antibiotics TA ILI I&D	2	12	3
10	M	31	17	15	Yes	30.79	Yes		Antibiotics TA ILI I&D	2	9	0

Abbreviations: IHS4, International Hidradenitis Suppurativa Severity Score System; NRS, Patient's Global Assessment of Skin Pain on a continuous numeric rating scale; TA ILI, triamcinolone acetonide intralesional injection; I&D, incision & drainage.

Table 2. Summarized Characteristics of Patients, Stratified by Hurley Stage, Treatment Delay, and Prior Biologics Use.

	Overall	Hurley stage		Treatment delay		Prior biologics use	
		II (N=7)	III (N=3)	< 10 years (N=5)	≥ 10 years (N=5)	Biologics-experienced (N=4)	Biologics-naïve (N=6)
Sex, n (%)							
Male	6 (60)	5 (71.43)	1 (33.33)	3 (60)	3 (60)	1 (25)	5 (83.33)
Female	4 (40)	2 (28.57)	2 (66.67)	2 (40)	2 (40)	3 (75)	1 (16.67)
Age, years	27.3 ± 10.31	27.43 ± 12.34	27 ± 4.58	27.6 ± 14.84	27 ± 4.3	26 ± 4.24	28.17 ± 13.35
Age at onset, years	18.9 ± 12.42	21.67 ± 15.31	14.75 ± 5.85	24.2 ± 15.64	13.6 ± 5.68	14.75 ± 5.85	21.67 ± 15.31
Disease duration, years	8.9 ± 5.84	7.00 ± 6.29	11.75 ± 4.27	3.8 ± 2.17	14 ± 2.65	11.75 ± 4.27	7 ± 6.29
Family history, n (%)	5 (50)	4 (57.15)	1 (33.33)	3 (60)	2 (40)	1 (25)	4 (66.7)
Body mass index, kg/m^2	25.81 ± 3.6	26.38 ± 4.12	24.49 ± 1.89	25.33 ± 4.37	26.29 ± 3.08	23.46 ± 2.58	27.38 ± 3.46
Smoking habit, n (%)	4 (40)	3 (42.85)	1 (33.33)	1 (20)	3 (60)	1 (25)	3 (50)
Prior treatments, n (%)							
Adalimumab	4 (40)	1 (14.28)	3 (100)	1 (20)	3 (60)	4 (100)	0 (0)
Antibiotics	10 (100)	7 (100)	3 (100)	5 (100)	5 (100)	4 (100)	6 (100)
TA ILI	10 (100)	7 (100)	3 (100)	5 (100)	5 (100)	4 (100)	6 (100)
I&D	6 (60)	4 (57.14)	2 (66.67)	3 (60)	3 (60)	2 (50)	4 (66.7)

TA ILI, triamcinolone acetonide intralesional injection; I&D, incision & drainage

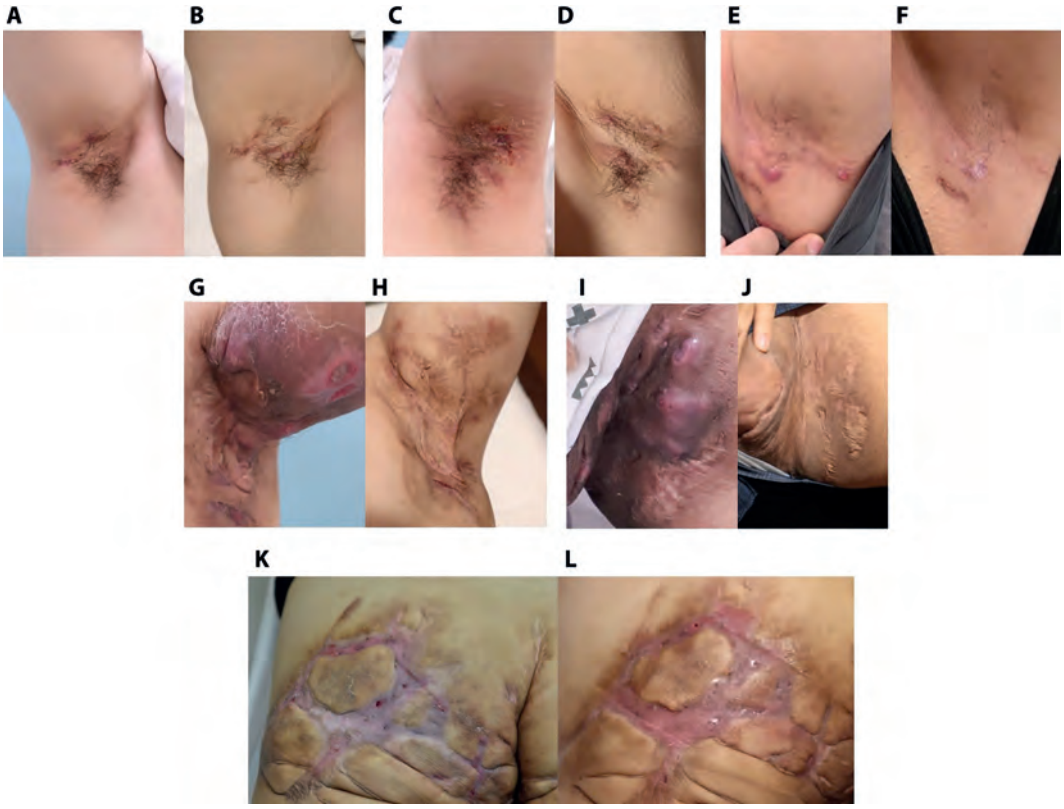


Figure 1. Visual improvements in lesions before and after the use of secukinumab in moderate and severe HS patients. Inflammatory nodules and abscesses before treatment in the right axillae (A) and left axillae (C, E) of Hurley stage II patients and after 48 weeks of secukinumab administration (B, D, F). Inflammatory nodules, abscesses, and draining fistula before treatment in the left axillae (G), inguinal (I), and gluteal area (K) of Hurley stage III patients and after 48 weeks of secukinumab administration (H, J, L).

prior biologics use had shorter disease duration than those with Hurley stage III or prior biologics exposure.

Reductions in inflammatory lesions following treatment are illustrated in Figure 1, with significant diminishment of abscesses and inflammatory nodules across all Hurley stages. However, sinus tract attenuation was less pronounced, particularly in patients with more severe disease.

The overall efficacy of secukinumab is presented in Figure 2. Rapid responses were evident across all endpoints by week 4, with 30% of patients achieving IHS4-55, 70% achieving HiSCR, and 40% achieving NRS30. Mean reductions included a -64.18 ± 27.89% decrease in AN count, IHS4 reduction from 19.4 ± 11.96 to 11.9 ± 12.38, and pain NRS improvement from 4.69 ± 1.83 to 2.59 ± 1.67. By week 16, 70% achieved IHS4-55, and 60% achieved NRS30. Improvements were reflected in a -84.46 ± 10.60% reduction in AN count, an IHS4 decrease to 7.6 ± 8.11, and a pain NRS decrease to 1.7 ± 1.54. However, HiSCR decreased from 100% to 90% from week 8 to week 16 due to the recurrence of an abscess in one male patient. Nonetheless, all endpoints maintained their improvement until week 48, with 90% of patients maintaining HiSCR, 90% achieving IHS4-55, and 60% sustaining NRS30. Moreover, AN count was reduced by -92.93 ± 11.42%, and IHS4 decreased further to 3.7 ± 5.48, but pain NRS increased slightly, to 1.99 ± 1.6, due to the aforementioned relapse.

Univariate analyses were conducted to evaluate the impact of participants' demographic characteristics on their responses to secukinumab administration. No statistically significant correlation was detected between sex, age, age at onset, BMI, smoking habit, and prior I&D and HiSCR, IHS4-55, mean change in AN count from baseline, and NRS30 (P>0.05) (Table S2).

Patients with Hurley stage II (moderate HS) achieved IHS4-55 responses more rapidly and to a greater extent than those with stage III (severe HS), with statistically significant differences at weeks 8 and 16 (RR: 0.00; 95% CI: 0.00–0.71; P=0.033; RR: 0.00; 95% CI: 0.00–0.56; P=0.0083; Figure 3A). Although moderate patients showed higher HiSCR rates at week 4, the difference was not significant (P>0.05; Figure 3B). A relapse in one male patient at week 16 lowered the HiSCR rate in moderate patients to 80%, but both groups maintained efficacy without further significant differences. This relapse also impacted the AN count and NRS30 outcomes. Moderate patients initially showed a greater reduction in AN count up to week 16, after which severe patients showed more improvement, though differences

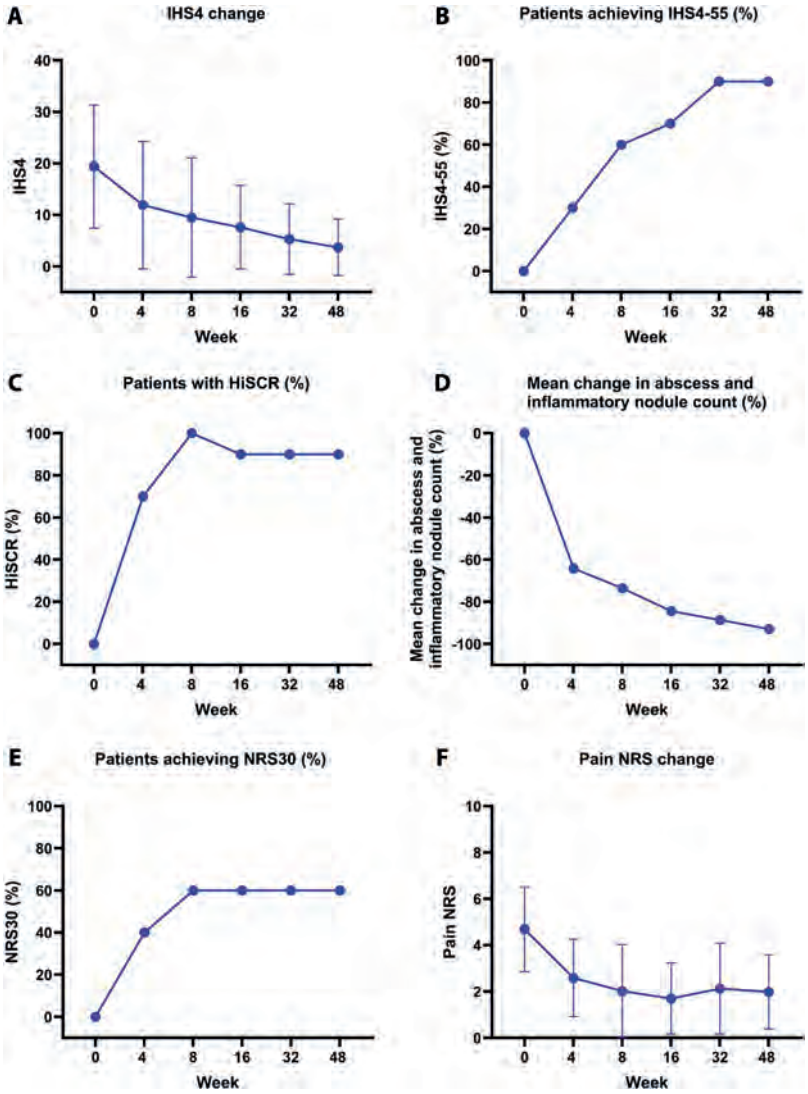


Figure 2. The effect of secukinumab on moderate-to-severe HS patients. Treatment responses are illustrated for HiSCR (A), mean change in abscess and nodule count from baseline (B), IHS4-55 (C), IHS-4 change (D), NRS30 (E), and Pain NRS change (F). HiSCR, Hidradenitis Suppurativa Clinical Response; IHS4-55, a 55% reduction in the International Hidradenitis Suppurativa Severity Score System; NRS30, a 30% or more reduction and reduction of two units or more from baseline in Patient's Global Assessment of Skin Pain on a continuous numeric rating scale.

were not significant (P>0.05; Figure 3C). NRS30 rates were consistently higher in moderate patients across all time points but dropped from 100% to 80% after the relapse, with no statistically significant difference observed (P>0.05; Figure 3D).

Patients with a treatment delay of less than 10 years showed higher IHS4-55 response rates at all time points, with a statistically significant difference at week 8 (RR: 0.2; 95% CI: 0.03622–0.6610; P=0.047; Figure 4A). HiSCR rates were initially higher in this group at week 4 but reversed after a relapse in one patient at week 16 (Figure 4B). AN count changes were comparable between groups throughout the study (P>0.05; Figure 4C). NRS30 rates were consistently higher in patients with shorter treatment delay, though not statistically significant (P>0.05; Figure 4D).

Biologics-naïve patients showed greater improvement in IHS4-55 compared to biologics-experienced ones, with a significant difference at week 16 (RR: 0.25; 95% CI: 0.046–0.70; P=0.033; Figure 5A). HiSCR rates were higher in biologics-naïve patients at week 4 but not significantly (P>0.05; Figure 5B). A relapse after week 16 reduced their HiSCR to 80% and impacted AN count and NRS30 rates, but the efficacy was maintained until the end of the study. AN count declined faster in biologics-naïve patients early on, but the difference was not significant (P>0.05; Figure 5C). NRS30 rates were higher in biologics-naïve patients at weeks 4–8, then equalized by week 16 (Figure 5D). At week 48, relapse lowered the NRS30 rate from 66.67% to 50%.

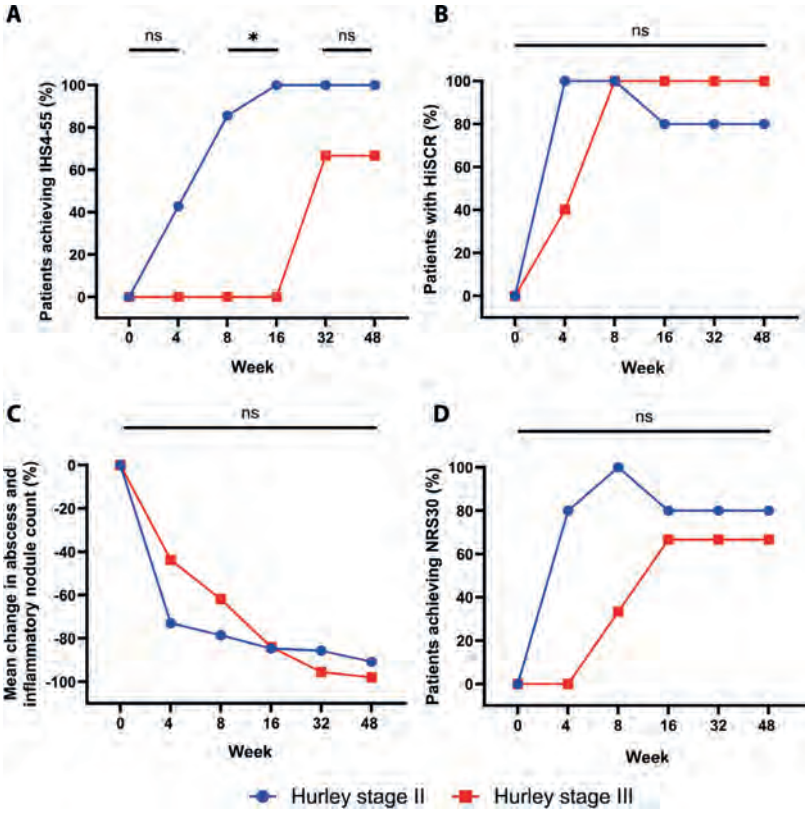


Figure 3. The effect of secukinumab, stratified by Hurley stage, on IHS4-55 (A), HiSCR (B), mean change in abscess and nodule count (C), and NRS30 (D). HiSCR, Hidradenitis Suppurativa Clinical Response; IHS4-55, a 55% reduction in the International Hidradenitis Suppurativa Severity Score System; NRS30, a 30% or more reduction and a reduction of two units or more from baseline in Patient's Global Assessment of Skin Pain on a continuous numeric rating scale; **P*<0.05; ns, no significance.

Moreover, we compared the antibiotic use duration between Hurley stage II and III patients (Figure 6). While the duration of antibiotic monotherapy was similar between the groups (*P*>0.05), patients with severe disease had significantly longer periods of combined antibiotic use than those with moderate disease (*P*<0.05). Notably, moderate patients had a significantly longer duration of antibiotic cessation than did severe cases (*P*<0.05).

Regarding adverse events, secukinumab was well tolerated, and no patient reported any non-serious or serious adverse event that could have led to the discontinuation of participation in the study (Table 3). Additionally, no new adverse event outside of the known safety profile of secukinumab was reported during the 48 weeks of treatment. Notably, the longest duration of treatment maintenance without any adverse event observed during our patient monitoring was 80 weeks.

Discussion

This 48-week prospective study demonstrates the robust efficacy of secukinumab in managing moderate-to-severe HS in a Korean cohort, providing clinically relevant insights into factors influencing treatment response. Our findings affirm the significant therapeutic potential of secukinumab while highlighting the role of disease severity, treatment timing, and prior biologics exposure in shaping patient outcomes.

Secukinumab elicited rapid and sustained clinical responses across key endpoints, including HiSCR, IHS4-55, and pain NRS30, with nearly all patients showing marked improvements by week 48. Patients with Hurley stage II disease, shorter treatment delays (<10 years), and biologics-naïve status exhibited faster initial responses, underscoring the importance of early intervention and patient-specific treatment planning. Notably, despite these early differences, long-term outcomes were favorable across all groups, reinforcing the broad applicability of secukinumab in HS management.

The variation in response based on disease severity emphasizes the inherent challenges in treating advanced HS. Patients with Hurley stage II disease achieved faster reductions in inflammatory nodules and abscesses, as evidenced by higher IHS4-55 rates at weeks 8 and 16, compared to

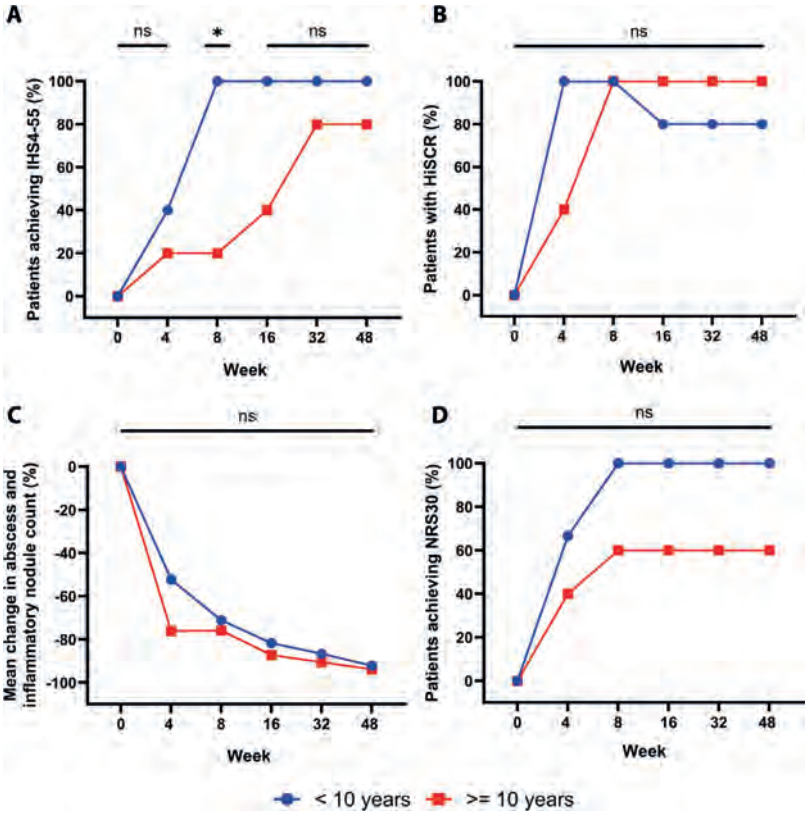


Figure 4. The effect of secukinumab, stratified by treatment delay, on IHS4-55 (A), HiSCR (B), AN count (C), and NRS30 (D). HiSCR, Hidradenitis Suppurativa Clinical Response; IHS4-55, a 55% reduction in the International Hidradenitis Suppurativa Severity Score System; NRS30, a 30% or more reduction and a reduction of two units or more from baseline in Patient's Global Assessment of Skin Pain on a continuous numeric rating scale; *P<0.05; ns, no significance.

those with Hurley stage III disease, who exhibited a slower but steady trajectory of improvement. The limited efficacy of secukinumab in addressing sinus tracts—chronic lesions predominantly observed in severe HS—suggests the involvement of alternative pathogenic pathways beyond IL-17A. These findings highlight the need for adjunctive or combination therapies targeting cytokines such as TNF-α or other profibrotic mediators, including hepatocyte growth factor, to address the complex pathophysiology of severe HS [21].

Treatment delay also emerged as a pivotal determinant of response; patients initiating secukinumab within 10 years of disease onset showed significantly faster and more pronounced improvements in IHS4-55 and pain NRS30 outcomes. These findings align with the concept of a "therapeutic window of opportunity," wherein early biologics intervention may prevent irreversible disease progression characterized by fistula formation and scarring. To illustrate, a retrospective Italian cohort found that longer delays in adalimumab initiation correlated with poorer response, and a recent multicenter study reported that high "therapeutic burden" (many prior treatments) was inversely related to secukinumab response [15,22]. These data support our emphasis that prompt recognition and therapy are crucial to optimizing long-term outcomes.

Prior biologics exposure further influenced treatment efficacy. Biologics-naïve patients achieved superior IHS4-55 rates at week 16 compared to those with prior biologics failure, although response rates between the two groups converged by week 48. This observation suggests that prior biologics failure may indicate more refractory disease phenotypes, potentially necessitating more prolonged or intensified therapeutic regimens. Nevertheless, the comparable long-term efficacy observed in both groups underscores secukinumab's therapeutic versatility in both treatment-naïve and biologics-experienced populations.

An additional strength of secukinumab therapy observed in this study was the significant reduction in systemic antibiotic usage. Nearly all patients discontinued or transitioned to antibiotic monotherapy, with the effect being particularly pronounced in those with moderate disease. This highlights secukinumab's immunomodulatory capabilities in mitigating the inflammatory drivers of HS and in reducing reliance on systemic antibiotics [4]. Given the increasing global concern over antimicrobial resistance, this finding is

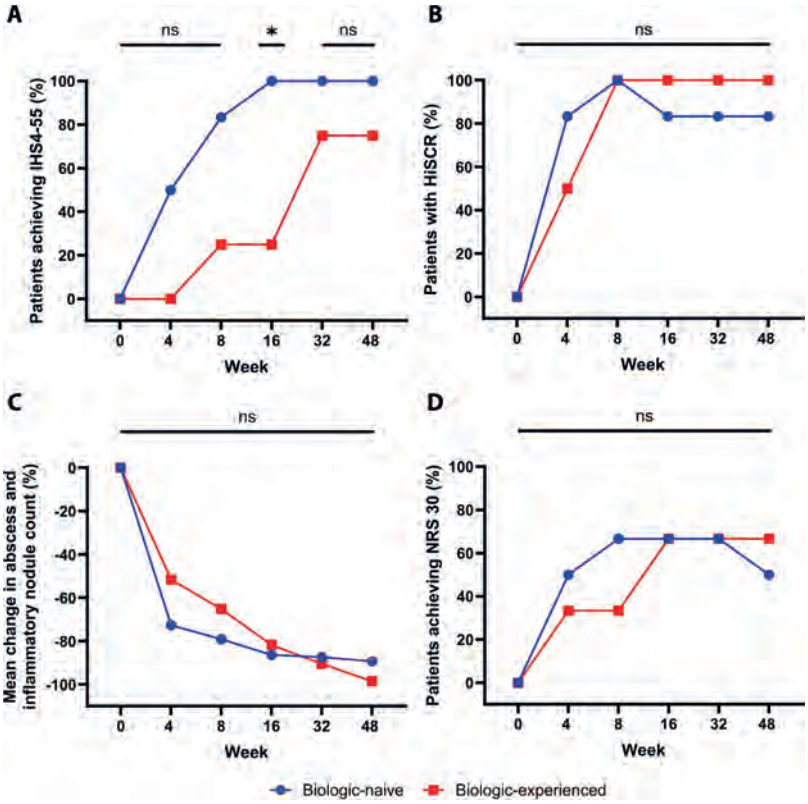


Figure 5. The effect of secukinumab, stratified by prior biologics use, on IHS4-55 (A), HiSCR (B), AN count (C), and NRS30 (D). HiSCR, Hidradenitis Suppurativa Clinical Response; IHS4-55, a 55% reduction in the International Hidradenitis Suppurativa Severity Score System, AN, abscess and nodule count; NRS30, a 30% or more reduction and a reduction of two units or more from baseline in Patient's Global Assessment of Skin Pain on a continuous numeric rating scale; *P<0.05; ns, no significance.

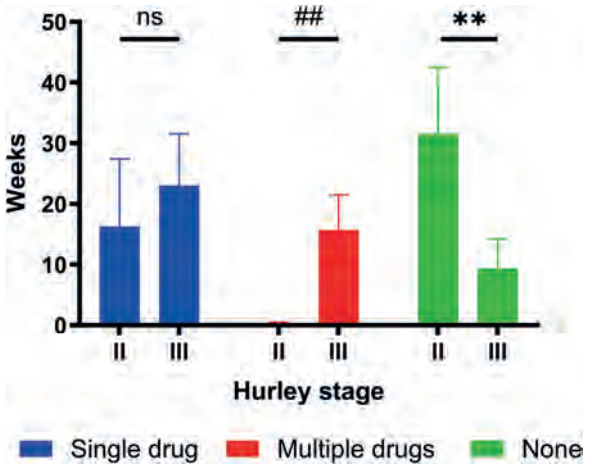


Figure 6. The duration of systemic antibiotic treatment stratified by Hurley stage after the administration of Secukinumab. ## P<0.01, Mann-Whitney test; ** P<0.01, independent t-test; ns, no significance.

clinically significant. However, further studies incorporating direct comparisons between antibiotic usage pre- and post-treatment are warranted to substantiate these observations.

Another novelty stemming from our study is the demonstration of secukinumab efficacy on Korean HS patients, a subgroup with various features distinct from those of the global population. Nationwide data showed that the incidence of HS in Korea rose six-fold between 2003 and 2019 (from 11.7 to 78.8 cases per million person-years), but overall prevalence remained low (0.06%), and the disease was male-predominant (female-to-male ratio of about 1:1.6) [23,24]. In contrast, most North American and European cohorts reported a prevalence of 0.1–1.0% and a female-to-male ratio of roughly 3:1 [25]. These demographic differences underline the importance of region-specific real-world data such as ours when evaluating treatment response.

From a safety perspective, secukinumab was well tolerated, with no serious adverse event or treatment discontinuation reported during the study period. These findings are consistent with data from pivotal RCTs, including the SUNSHINE and SUNRISE trials, which reported favorable safety profiles [9]. Although vigilance remains necessary, particularly in patients with coexisting inflammatory bowel disease [9,26], the safety and tolerability of secukinumab affirm its suitability for long-term management of HS.

In spite of promising results regarding biologic therapy, optimal HS management still requires a multidisciplinary approach. HS patients benefit from comprehensive care

Table 3. Adverse Events during 48 Weeks of Secukinumab Treatment in Moderate-to-Severe HS Patients.

Adverse event	Patients (N=10)
Patients with any adverse event, N (%)	0 (0.0)
Common adverse events, N (%)	
Headache	0 (0.0)
Nasopharyngitis	0 (0.0)
Patients with serious or other significant event, N (%)	
Death	0 (0.0)
Non-fatal serious adverse event	0 (0.0)
Discontinued study treatment due to any adverse event	0 (0.0)
Adverse events of special interest, N (%)	
Infections and infestations by system organ class	0 (0.0)
Upper respiratory tract infection	0 (0.0)
Fungal infectious disorders	0 (0.0)
Candida infection	0 (0.0)
Hypersensitivity	0 (0.0)
Malignant or unspecified tumor	0 (0.0)
Major adverse cardiovascular event	0 (0.0)
Inflammatory bowel disease	0 (0.0)

pathways, including smoking cessation, weight management, metabolic monitoring, and psychosocial support, in addition to targeted medical therapy [27]. Therefore, modern consensus statements emphasize that optimal HS care extends beyond dermatologic therapy and should integrate surgery, wound-care nursing, pain specialists, dieticians, psychologists, and primary care physicians [28]. In practice, a combined medical-surgical strategy may yield better outcomes: perioperative use of adalimumab has been shown to improve HiSCR rates after excisional surgery without increasing complications [29]. Hence, our findings support the paradigm that secukinumab can allow many patients to discontinue long-term antibiotics, facilitating coordination with surgeons for excisional procedures.

Additionally, differences in biologics availability across health systems may constitute an impact on secukinumab utilization. The European Academy of Dermatology and Venereology (EADV) has provided guidelines for biologic therapy as second-line treatment for HS, notably adalimumab and secukinumab [30]. The EADV additionally complemented bimekizumab, further expanding options [30]. The FDA in the United States also approved secukinumab as an authorized treatment for moderate-to-severe HS, along with the already authorized adalimumab [16]. In those settings, adalimumab or secukinumab could be administered first-line; inadequate responders may switch to the remaining option before relying on prolonged antibiotics or surgery. By contrast, Korean patients currently have routine access to mainly adalimumab for HS. Our data, therefore, provide early evidence to support policy discussions on widening biologics availability in Korea and in Asia in general, where the male-predominant, often deeply tunnelling phenotype may particularly benefit from timely escalation [23,24].

However, this study is limited by its small sample size, lack of a control group, and potential confounding factors such as demographic imbalances. These limitations underscore the need for larger multicenter studies with robust control measures to validate these findings and further delineate the optimal use of secukinumab in HS. Future investigations should also explore the integration of complementary therapeutic approaches to enhance outcomes, particularly in patients with advanced disease or refractory lesions. Despite these drawbacks, our small cohort yields useful real-world insights, partially from our extensive period of follow-up (48 weeks). In addition, the overall response rate and safety profile of secukinumab in our patients align with those reported in larger studies, supporting external consistency [14,15,31]. Notably, the phase 3 SUNSHINE/SUNRISE trials in North America and Europe showed that secukinumab achieved HiSCR in 42–45% of patients at 16 weeks, with effectiveness achieved in both TNF-naïve and TNF-experienced groups [9]. Similarly, real-world studies have reported good clinical responses and safety with IL-17–targeted therapy [10-16]. Observed trends in our data, namely higher response likelihood in patients with lower prior therapeutic burden, align with the "window of opportunity" concept and are similar to predictors identified in other analyses [15]. Finally, our study also noted a reduction in antibiotic dependence following secukinumab treatment, which is consistent with evidence that secukinumab is effective regardless of concomitant antibiotic use [32].

Conclusion

Secukinumab showed strong efficacy in Korean patients with moderate-to-severe hidradenitis suppurativa in real-world settings. Patients with Hurley stage III, longer treatment delays, or prior biologics use had slower and less pronounced responses than did those with stage II, shorter delays, or no biologics history. These findings highlight the benefits of early intervention. Continued treatment also significantly reduced the need for systemic antibiotics, suggesting secukinumab's potential to decrease antimicrobial dependence. Overall, secukinumab appears to be an effective option for HS, warranting further large-scale studies to validate these results and explore factors influencing treatment response for more personalized care.

Acknowledgments: The drug (secukinumab) was granted by Novartis under a Managed Access Program (MAP). This work was supported by the Technology Innovation Program (or Industrial Strategic Technology Development Program-Novel microbiome therapy for hidradenitis suppurativa and severe acne based on integrative microbiome-multiomics approach) (20024192) funded by the Ministry of Trade, Industry & Energy (MOTIE, Korea). This study was supported by an MEF Fellowship conducted as part of "Education and Research capacity building project at University of Medicine and Pharmacy at Ho Chi Minh City" implemented by the Korea International Cooperation Agency (KOICA) in 2025. (No. 2021-00020-4).

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Supplementary File

Table S1. Inclusion and exclusion criteria of Managed Access Program (MAP) Cohort Treatment Plan CAIN457M2002M to provide access to Secukinumab for adult patients with Hidradenitis Suppurativa (HS).

Inclusion Criteria
Patients eligible for inclusion in this Treatment Plan have to meet all of the following criteria: 1. Adult male and female patients (≥ 18 years) who are able and willing to provide written informed consent prior to enrolling in the cohort. 2. HS diagnosis for ≥ 6 months (defined as onset of HS with supporting documentation) 3. Patients with moderate to severe HS defined as: • A total of at least 5 inflammatory lesions, i.e., abscesses and/or inflammatory nodules AND • Inflammatory lesions should affect at least 2 distinct anatomic areas 4. Not eligible or able to enroll in a clinical trial or no relevant clinical trials available
Exclusion Criteria
1. Total fistulae count ≥ 20 at baseline. 2. Active ongoing inflammatory diseases other than HS that require treatment with prohibited medications (prohibited medication: the use of live vaccines within 6 weeks prior to drug use until the end of administration). 3. Underlying conditions (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal disorders, including history of inflammatory bowel disease) which in the opinion of the treating physician significantly immunocompromises the patient and/or places the patient at unacceptable risk for receiving an anti-IL-17A immunomodulatory therapy. 4. Current severe progressive or uncontrolled diseases which renders the patient unsuitable for the managed access program or puts the patient at increased risk, including any medical or psychiatric condition which, in the treating physician's opinion, would preclude the participant from adhering to the treatment plan. 5. Use or planned use of live vaccines within 6 weeks prior to drug use until the end of administration). 6. History of hypersensitivity to any of the secukinumab constituents. 7. History of chronic or recurrent systemic infections or active systemic infections during the last two weeks (exception: common cold) prior to the access request. 8. Evidence of tuberculosis infection as defined by a positive QuantiFERON® TB-Gold test (QFT) at the time of requesting access. Patients with a positive or indeterminate QFTtest may get access if a full tuberculosis work-up (according to local practice/guidelines) completed within 12 weeks prior to randomization, establishes conclusively that the patient has no evidence of active tuberculosis. Patients who test positive for latent TB per work-up may get access if sufficient treatment has been initiated according to local routine clinical practice/guidelines and was completed at least four weeks prior to the access request. 9. Medical history of infection with human immunodeficiency virus (HIV), hepatitis B or C prior to access request, except for hepatitis C successfully treated and cured. 10. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system treated or untreated within the past 5 years, regardless of whether there is evidence of local recurrence or metastases (except for skin Bowen's disease, or basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed). 11. History or evidence of ongoing alcohol or drug abuse, which in the opinion of the physician will prevent the patient from adhering to the treatment plan. 12. Pregnant or lactating women.

Table S1 continues

Table S1. Inclusion and exclusion criteria of Managed Access Program (MAP) Cohort Treatment Plan CAIN457M2002M to provide access to Secukinumab for adult patients with Hidradenitis Suppurativa (HS). *(continued)*

13. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using methods of contraception during the entire duration of the treatment or longer if required by locally approved prescribing information (e.g., in European Union (EU) 20 weeks). Contraception methods include:
    - Total abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks prior to the access request. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that patient.
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For United Kingdom: with spermicidal foam/gel/film/cream/vaginal suppository.
    - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS). In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking secukinumab. In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the informed consent template. Note: Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior to enrollment. In the case of oophorectomy alone, only when their productive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of childbearing potential.

Table S2. p values for the univariate analyses between different endpoints and demographic characteristics of patients.

	Week																			
	HiSCR[(a)]					IHS4-55[(a)]					Mean change in AN count from baseline[(b)]					NRS30[(a)]				
	4	8	16	32	48	4	8	16	32	48	4	8	16	32	48	4	8	16	32	48
Sex	0.779	1	1	1	1	1	1	1	1	1	0.70	0.37	0.56	0.25	0.58	1	1	1	1	1
Age	1	1	1	1	1	1	1	1	1	1	0.31	0.11	0.41	0.63	0.11	1	1	1	1	1
Onset	1	1	1	1	1	1	1	1	1	1	0.15	0.12	0.15	0.31	0.51	1	1	1	1	1
Family history	1	1	1	1	1	1	1	1	1	1	0.37	0.21	0.16	0.52	0.13	1	1	1	1	1
BMI	1	1	1	1	1	1	1	1	1	1	0.28	0.16	0.79	0.41	0.08	1	1	1	1	1
Smoking habit	1	1	1	1	1	1	1	1	1	1	0.39	0.95	0.19	0.09	0.12	1	1	1	1	1
Prior I&D	1	1	1	1	1	1	1	1	1	1	0.19	0.93	0.79	0.65	0.07	1	1	1	1	1

BMI, body mass index; HiSCR, Hidradenitis Suppurativa Clinical Response; IHS4-55, a 55% reduction in the International Hidradenitis Suppurativa Severity Score System, AN, abscess and nodule count; NRS30, a 30% or more reduction and reduction of two units or more from baseline in Patient's Global Assessment of Skin Pain on a continuous numeric rating scale; I&D, incision & drainage; [(a)] Logistic regression analysis; [(b)] simple linear regression analysis

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Artificial Intelligence in Patient Education for Androgenetic Alopecia: A Comparative Study of ChatGPT, Gemini, and Deepseek R1

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Key words: Androgenetic alopecia, Artificial intelligence, ChatGPT, Patient education, Large language model

Citation: Yigen İritaş S. Artificial Intelligence in Patient Education for Androgenetic Alopecia: A Comparative Study of ChatGPT, Gemini, and Deepseek R1. *Dermatol Pract Concept*. 2025;15(4):5929. DOI: https://doi.org/10.5826/dpc.1504a5929

Accepted: September 1, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Androgenetic alopecia (AGA) is a common cause of hair loss worldwide. Accurate patient education may improve treatment adherence and outcomes.

Objective: To compare the accuracy, readability, and user experience of ChatGPT 4.0, Gemini 1.5 Flash, and Deepseek R1 in answering common patient questions about AGA.

Methods: In February 2025, a cross-sectional study was conducted using 12 frequently asked patient questions on AGA, sourced from online platforms. The questions were submitted to ChatGPT 4.0, Gemini 1.5 Flash, and Deepseek R1. Two dermatologists independently assessed responses using a validated 4-point accuracy scale. Readability was measured with the Flesch-Kincaid Grade Level and Flesch Reading Ease Score. User experience was evaluated based on response speed, presence of visual aids, citation usage, and overall satisfaction. Inter-rater reliability was analyzed via Cohen's kappa, and statistical comparisons were made between models.

Results: ChatGPT 4.0 and Gemini 1.5 Flash successfully answered all 12 questions, with most responses rated as "satisfactory with minimal corrections." Deepseek R1 answered only five questions and frequently provided inaccurate content, especially when differentiating between AGA and cicatricial alopecia. It also lacked warnings about potential misinformation. Gemini 1.5 Flash included visual aids and citations, improving interpretability. All models generated responses at a high school reading level. In terms of user experience, ChatGPT 4.0 and Gemini 1.5 Flash outperformed Deepseek R1.

Conclusions: ChatGPT 4.0 and Gemini 1.5 Flash provided accurate, readable, and user-friendly responses on AGA-related questions, making them promising tools for patient education under physician guidance. Deepseek R1's limitations highlight the need for cautious implementation.

Introduction

Hair is an important part of a person's perception of beauty and individual image. Hair loss is therefore a significant problem, not only dermatologically but also psychologically [1]. The most common cause of hair loss in both males and females is androgenetic alopecia (AGA), or male pattern baldness. It is more common in the Caucasian race and has a slightly lower prevalence in individuals of Black and Asian ethnicity [2]. Androgenetic alopecia is a type of alopecia characterised by progressive miniaturisation of genetically predisposed hair follicles under the influence of androgens [3]. There are various topical and systemic treatment options available, but due to the progressive nature of the disease, these treatments must be continued over a long period of time. The lack of information about treatment duration and side effects leads to disappointment, which affects compliance and premature discontinuation. It is therefore important that patients are provided with accurate and appropriate information [4]. Patients often use internet tools to learn about diseases and treatments, and artificial intelligence (AI) tools have recently been added. This situation has also led to publications evaluating the role of AI tools in patient education [5].

ChatGPT 4.o, Google's Gemini Flash 1.5, and DeepSeek R1 represent a new generation of large language models (LLM) that leverage advanced artificial intelligence techniques, specifically deep learning methodologies, to generate responses to natural language prompts that exhibit characteristics reminiscent of human interaction. These models are initially pre-trained on extensive textual data, followed by fine-tuning to facilitate conversational responses to a range of user commands [6-9]. Improved patient interaction can be achieved by integrating AI models into the field of dermatology.

In consideration of the aforementioned factors, this study was designed to compare responses from ChatGPT 4.o, Gemini 1.5 Flash, and DeepSeek R1 to a series of patient inquiries concerning androgenic alopecia.

Methods

A search for "patients' questions about androgenetic alopecia" was conducted using Google (www.google.com). The Frequently Asked Questions sections from various clinics were analyzed. From a list of twenty questions, the 12 most frequently asked were selected by a dermatologist with experience in hair-related conditions who evaluates approximately 800-1000 patients annually.

The selected questions were presented to ChatGPT (version 4.o, the latest free version as of 2 February 2025), Gemini 1.5 Flash, and DeepSeek R1 chatbot in a single session without follow-up or repetition. Two dermatologists independently reviewed all responses using an evidence-based framework. The second reviewer is a dermatologist currently working at a Training and Research Hospital, where he manages tertiary-level patients. He has clinical experience in the management of hair disorders and evaluates approximately 700–800 patients annually.

Responses were evaluated using the Mika et al. rating system, previously utilized in AI-related medical research [10]. This system assigns scores on a four-point scale:

1. Excellent (no clarification required): Complete and aligned with the existing literature
2. Satisfactory (minimal clarification required): Lacking minor details but generally accurate
3. Satisfactory (moderate clarification required): Containing outdated or partially irrelevant information
4. Unsatisfactory (substantial clarification required): Including erroneous or overly generalized information that could lead to misinterpretation

To ensure consistency and reliability in scoring, each response was rated independently by two dermatologists, and inter-rater agreement was calculated.

The readability of the responses was assessed using the Flesch-Kincaid Reading Ease Score (FRES) and Grade Level (FKGL), widely used tools for evaluating text readability [11]. The FRES provides a score between 0 and 100, with higher scores indicating easier readability. For instance, a score of 70–80 corresponds to a 7th-grade reading level, whereas a score of 30–50 corresponds to a college-level reading ability. The FKGL represents the minimum educational background required for comprehension.

As this study solely analyzed publicly available online content without involving human subjects, ethical approval was not required.

Statistical Analysis

The data analysis was conducted using the IBM SPSS Statistics version 25 software package (IBM Corporation, Armonk, NY, USA). The normality of the distribution of continuous variables was assessed using the Shapiro-Wilk test, and descriptive statistics are reported as mean ± standard deviation for continuous variables. Categorical data are expressed as frequency (N) and percentage (%). The Flesch-Kincaid Grade Level (FKGL) and Flesch Reading Ease Score (FRES) for the responses provided by each large language model (LLM)-based AI application (i.e., Chat GPT, Gemini Flash 1.5, DeepSeek R1) were calculated using an online Flesch-Kincaid calculator tool available at the Good Calculators website (https://goodcalculators.com/flesch-kincaid-calculator/). The statistical significance of differences in

FKGL and FRES levels across the applications was evaluated by repeated-measures analysis of variance via Wilks' lambda test. As DeepSeek R1 failed to provide responses to four of the directed questions, the subsequent analysis focused on the subset of fully answered questions. The differences in FKGL and FRES levels between ChatGPT 4.o and Gemini were assessed by a paired samples t-test. Finally, the responses to each user experience question were visualized as bar graphs for ChatGPT, Gemini Flash 1.5, and DeepSeek R1, and descriptive statistics were calculated for the scores obtained from each subdomain. To assess the agreement between the dermatology specialists' evaluations, kappa coefficients and their standard errors were calculated. A p-value of less than 0.05 was considered statistically significant.

Results

The questions and answers of ChatGPT 4.o, Gemini 1.5 Flash, and DeepSeek R1 are shown in Table 1. ChatGPT 4.o and Gemini Flash 1.5 were able to respond to all 12 questions in succession without interruption, while DeepSeek R1 was able to answer only five. When it came to the 6th question, DeepSeek R1 replied, "The server is busy. Please try again later." The same question was asked again five minutes later, but the same response was received. After 10 minutes, the same question was asked again, and the same answer was received. Then, when the 7th question was asked again, "The server is busy. Please try again later," and no response was received. DeepSeek R1 was able to respond to each subsequent question after about 15–20 minutes, but the waiting time gradually increased. It was decided that, considering that waiting for more than 20 minutes to get the answer to a question is incompatible with real-life experience, the answers to the other questions would not be included in the study.

One week later, the same questions were presented to DeepSeek R1 again; however, starting from the second question, the response **"Server busy. Please try again later."** was received, resulting in a slower user experience. When the questions were asked for the third time on 25 February 2025, the same issue persisted, with DeepSeek R1 displaying the **"Server busy. Please try again later."** message from the second question onward.

ChatGPT 4.o's eight responses were rated as "excellent" by Reviewer 1, four responses were rated as "satisfactory requiring minimal clarification;" nine responses were rated as "excellent" by Reviewer 2, and three responses were rated as "satisfactory requiring minimal clarification."

Gemini Flash 1.5's nine responses were rated as "excellent" by Reviewer 1, and three responses were rated as "satisfactory requiring minimal clarification;" nine responses were rated as "excellent" by Reviewer 2, and three response was rated as "satisfactory requiring minimal clarification."

Deepseek R1 could only answer eight questions in total. DeepSeek R1's six responses were rated as "excellent" by Reviewer 1 and Reviewer 2, one response was rated as "satisfactory requiring minimal clarification," and one response was rated as " Unsatisfactory, substantial clarification required" (Table 2).

The ratings given by both evaluators regarding the consistency of ChatGPT 4. o's responses were found to be highly concordant (κ=0.800±0.188, P=0.0001). Similarly, the ratings given by both evaluators regarding the consistency of responses from Gemini Flash 1.5 and DeepSeek R1 were found to be perfectly concordant (κ=1.000±0.000, P=0.000).

The average FKGL levels for the first eight responses between ChatGPT 4.o, Gemini Flash 1.5, and DeepSeek R1 were found to be statistically similar (P=0.666). While no statistically significant difference was observed in terms of average FRES levels between ChatGPT 4.o, Gemini Flash 1.5, and DeepSeek R1 (P=0.053), the Bonferroni-corrected multiple comparison test showed that the average FRES value of ChatGPT 4.o was slightly higher than that of DeepSeek R1 (P=0.047). (Table 3)

The average FKGL levels for twelve responses between ChatGPT 4.o and Gemini Flash 1.5 were found to be statistically similar, corresponding to a $10t^{h}$–11th grade level (P=0.674). Although the average FRES value of ChatGPT 4.o was slightly higher than that of Gemini Flash 1.5, no statistically significant difference was observed in terms of average FRES levels between ChatGPT 4.o and Gemini Flash 1.5 (P=0.059) (Table 4). All of the documents were found to be in a format that was difficult to read.

Figure 1 displays the average responses given by the evaluators for each question that constitutes the user experience of ChatGPT 4.o, Gemini Flash 1.5, and DeepSeek R1, respectively, in bar chart form. It can be seen that ChatGPT 4.o and Gemini Flash 1.5 are in a very good position in terms of user experience. On the other hand, it was found that DeepSeek R1 had a relatively poor user experience, especially in the subcomponents of effectiveness and attractiveness.

Discussion

In the case of chronic dermatological diseases such as AGA, the most common alopecia in the community, providing accurate information and effective patient education is of great importance for the success of treatment processes [12]. With patients increasingly using artificial intelligence to inform themselves about their diseases, the evaluation of both the accuracy of content generated by artificial intelligence and its usability and readability is becoming imperative.

A salient finding of the present study is that while ChatGPT 4.o and Gemini Flash 1.5 were able to respond to all 12 questions quickly and without interruption, DeepSeek

Table 1. Questions and Answers to ChatGPT, Gemini Flash 1.5, and DeepSeek R1.

QUESTIONS	ChatGPT 4.o's answers	Gemini's answers	DeepSeek R1'S answers
1. Why does hair fall out?	Hair loss can happen for a variety of reasons. Here are some common causes: 1. **Genetics (Androgenetic Alopecia):** This is the most common cause of hair loss and is often referred to as male or female pattern baldness. It typically starts gradually and follows a predictable pattern. In men, this may result in a receding hairline or bald spots, while women may notice thinning along the part line. 2. **Hormonal Changes:** Hormonal fluctuations, such as those occurring during pregnancy, childbirth, menopause, or thyroid imbalances, can lead to temporary or permanent hair loss. 3. **Medical Conditions:** Conditions like alopecia areata (an autoimmune disorder where the body attacks hair follicles), scalp infections (e.g., ringworm), or diseases like lupus and diabetes can cause hair loss. 4. **Nutritional Deficiencies:** Lack of essential nutrients, such as iron, vitamin D, zinc, and proteins, can result in hair shedding or thinning. 5. **Stress:** High levels of stress or trauma can trigger a type of hair loss known as telogen effluvium, where hair prematurely enters the shedding phase. This usually resolves once the stress is managed. 6. **Medications and Treatments:** Some medications, such as those used for cancer (chemotherapy), arthritis, depression, or high blood pressure, can cause hair loss as a side effect. 7. **Physical Trauma or Injury:** Hair can fall out as a result of physical stress to the hair follicles, such as from tight hairstyles (e.g., ponytails or braids) or excessive combing and brushing. 8. **Age:** As people age, hair growth slows down, and hair may become thinner or fall out more easily. If you're experiencing significant hair loss, it may be helpful to consult a healthcare provider or dermatologist to determine the underlying cause and appropriate treatment.	This is for informational purposes only. For medical advice or diagnosis, consult a professional. Hair loss, also known as alopecia, can have various causes. Here are some of the most common reasons why hair might fall out: • **Genetics:** Androgenetic alopecia, often referred to as male or female pattern baldness, is a common cause of hair loss due to genetic. * (An image taken from tuniohairtransplant.com) • **Hormonal changes:** Fluctuations in hormones, such as during pregnancy, childbirth, menopause, or thyroid disorders, can affect the hair growth cycle. *(An image taken from www.zrtlab.com Hormonal changes hair loss • **Medical conditions:** Certain medical conditions like autoimmune diseases (alopecia areata), thyroid problems, and iron deficiency can lead to hair loss. *(An image taken from insparya.es Thyroid problems hair loss) • **Medications and treatments:** Some medications, such as chemotherapy drugs, can cause temporary hair loss as a side effect. • **Stress:** Physical or emotional stress can disrupt the hair growth cycle and lead to increased shedding. *(An image taken from traya.health Stress hair loss) • **Hairstyles and treatments:** Tight hairstyles, excessive heat styling, and harsh chemical treatments can damage hair and cause breakage. • **Nutritional deficiencies:** Lack of essential nutrients like iron, protein, and vitamins can weaken hair follicles. If you're experiencing hair loss, it's important to consult a doctor to determine the underlying cause and discuss treatment options.	Hair loss, or alopecia, can result from a variety of factors, often interacting in complex ways. Here's a structured overview of the primary causes: 1. **Genetic Factors (Androgenetic Alopecia):** • The most common cause, affecting both men (male pattern baldness) and women (female pattern hair loss). It involves sensitivity to dihydrotestosterone (DHT), which shrinks hair follicles over time. 2. **Hormonal Changes:** • **Life Events:** Pregnancy, menopause, or discontinuation of birth control pills can disrupt hormone levels (e.g., estrogen, progesterone), triggering temporary shedding (telogen effluvium). • **Thyroid Disorders:** Both hypothyroidism and hyperthyroidism can lead to hair thinning. 3. **Aging:** • Hair growth slows with age, and follicles may produce thinner, shorter hairs, eventually ceasing production. 4. **Medical Conditions:** • **Autoimmune Diseases:** Alopecia areata (patchy hair loss), lupus, or lichen planus. • **Infections:** Scalp fungal infections (e.g., tinea capitis) or bacterial folliculitis. • **Chronic Illnesses:** Diabetes, lupus, or iron-deficiency anemia. 5. **Nutritional Deficiencies:** • Low levels of iron, zinc, vitamin D, B vitamins (especially biotin), or protein can weaken hair. Rapid weight loss or extreme diets often exacerbate this. 6. **Medications/Treatments:** • Chemotherapy, radiation, antidepressants, blood thinners, and beta-blockers may cause temporary or prolonged shedding. 7. **Physical/Traumatic Stressors:** • **Telogen Effluvium:** Triggered by surgery, illness, or severe stress, pushing hair follicles into a resting phase, followed by shedding months later. • **Traction Alopecia:** Tight hairstyles (e.g., braids, ponytails) that pull on hair roots. • **Damage from Styling:** Heat tools, chemical treatments, or harsh products leading to breakage. 8. **Psychological Factors:** • Trichotillomania, a compulsive urge to pull out hair, often due to stress or anxiety. 9. **Environmental Factors:** • Pollution, toxins, or seasonal changes may contribute to shedding in some individuals. **Key Notes:** • **Temporary vs. Permanent:** Stress-related loss (telogen effluvium) often reverses, while genetic balding is typically permanent without intervention. • **Diagnosis:** A dermatologist can assess via blood tests, scalp biopsies, or trichoscopy. Treatments range from topical minoxidil and oral finasteride to dietary adjustments or stress management. • **When to Seek Help:** Sudden, patchy, or symptomatic hair loss (e.g., itching, pain) warrants medical evaluation. Understanding the hair growth cycle (anagen [growth], catagen [transition], telogen [resting]) helps explain how disruptions lead to shedding. Addressing the root cause is essential for effective management.

2. At what age does androgenetic alopecia begin?	Androgenetic alopecia (AGA), or male pattern hair loss, can begin as early as the late teens to early 20s. On average, many men start noticing signs of hair loss in their 20s or 30s, but it can vary widely depending on genetics. Some men may not experience noticeable hair loss until their 40s or even later. The onset and progression of AGA are influenced by several factors: 1. **Genetics**: If a man has close relatives who experienced early hair loss, he is more likely to start losing hair at a younger age. Family history plays a significant role in determining when and how severely hair loss will occur. 2. **Hormones**: Androgenetic alopecia is linked to the body's sensitivity to androgens, which are male hormones such as testosterone. The conversion of testosterone to dihydrotestosterone (DHT) in the scalp contributes to hair follicle shrinkage and hair loss. Individuals who have higher DHT levels or a genetic predisposition to hair follicles sensitive to DHT are more prone to early hair loss. 3. **Stage of Hair Loss**: AGA often starts with a receding hairline at the temples and/or thinning at the crown of the head. This pattern is usually seen as early as the late teens to 20s. Over time, the hair loss can progress, leading to more extensive bald spots and potential baldness on the top of the head. **Age Ranges for Onset of AGA:** • **Late Teens to Early 20s**: Some men may start noticing hair loss during this time, especially if they have a family history of early hair loss. • **30s**: This is a common age range for the initial stages of male pattern baldness to become more noticeable. • **40s and Beyond**: Hair loss becomes more apparent, and the pattern may become more severe, affecting a larger area of the scalp. Overall, while AGA can start in the late teens to early 20s, the exact age of onset depends on a combination of genetic and hormonal factors.	This is for informational purposes only. For medical advice or diagnosis, consult a professional. Androgenetic alopecia, also known as male or female pattern baldness, can begin at different ages for men and women. • **Men:** It often starts in their late teens or early 20s, but some men may notice signs as early as their late teens. • **Women:** Hair loss is most likely after menopause. The risk of androgenetic alopecia increases with age for both men and women.	Androgenetic alopecia, commonly known as male or female pattern baldness, can begin at different ages depending on genetic predisposition, hormonal factors, and overall health. Here's a breakdown: **Male Pattern Baldness** • **Onset**: Typically begins in the late teens to early 20s, but it can start at any age after puberty. • **Progression**: By age 35, about 66% of men experience some degree of hair loss. By age 50, approximately 85% of men have significantly thinning hair. • **Pattern**: Often starts with a receding hairline or thinning at the crown and progresses over time. **Female Pattern Baldness** • **Onset**: Usually begins later than in men, often after menopause (around age 50 or older), but it can start as early as the 20s or 30s. • **Progression**: Hair thinning is more diffuse, with widening of the part line and overall reduction in hair density. • **Pattern**: Unlike men, women rarely experience a receding hairline but may notice their scalp becoming more visible. **Key Factors Influencing Onset** 1. **Genetics**: A family history of androgenetic alopecia increases the likelihood of early onset. 2. **Hormonal Changes**: Androgens (like dihydrotestosterone or DHT) play a significant role in triggering hair loss. 3. **Lifestyle and Health**: Poor diet, stress, and certain medical conditions can accelerate hair loss. **Early Signs to Watch For** • **Men**: Receding hairline, thinning at the crown, or a change in hair texture. • **Women**: Widening part line, increased hair shedding, or reduced hair volume. **What You Can Do** If you notice early signs of androgenetic alopecia, consult a dermatologist. Early intervention with treatments like minoxidil, finasteride (for men), or hormone therapy (for women) can slow progression and improve outcomes. Lifestyle changes, such as a balanced diet and stress management, can also help maintain hair health.

Table 1 (*Continued*)

Table 1. Questions and Answers to ChatGPT, Gemini Flash 1.5, and DeepSeek R1. *(continued)*

QUESTIONS	ChatGPT 4.o's answers	Gemini's answers	DeepSeek R1'S answers
3. What causes androgenetic alopecia?	Androgenetic alopecia (AGA), also known as male pattern hair loss or female pattern hair loss, is primarily caused by a combination of **genetic predisposition** and **hormonal influences**, particularly the hormone **dihydrotestosterone (DHT)**. Here's a closer look at the key factors involved: 1. **Genetics:** • **Hereditary Factors**: AGA is highly influenced by genetic inheritance. If your parents or grandparents had male or female pattern baldness, you are more likely to develop it yourself. The genes responsible for AGA can come from either side of the family, though the influence of genes from the mother's side has often been emphasized. • **Specific Genes**: Research has identified several genes related to androgen sensitivity, particularly those affecting the androgen receptor (AR) gene on the X chromosome. This receptor plays a role in how hair follicles respond to androgens like DHT. 2. **Hormones (Androgens):** • **Dihydrotestosterone (DHT)**: The main hormone implicated in AGA is DHT, which is derived from testosterone through the action of an enzyme called **5-alpha reductase**. DHT binds to androgen receptors in hair follicles, leading to their shrinkage (miniaturization). Over time, this miniaturization causes the affected follicles to produce thinner, shorter hairs, and eventually, hair production may stop completely. • **Androgen Sensitivity**: The extent to which DHT affects hair follicles depends on how sensitive they are to the hormone. Men with more sensitive hair follicles may experience more rapid and severe hair loss. 3. **Hair Follicle Sensitivity and Miniaturization:** • Hair follicles on certain parts of the scalp, like the temples and crown, are more susceptible to the effects of DHT. This selective sensitivity leads to the characteristic pattern of AGA, which typically starts with a receding hairline and/or thinning at the crown, progressing to bald spots and potentially complete baldness on the top of the head. • Miniaturized follicles produce hairs that are finer and weaker. Over time, these hairs may become almost invisible, contributing to the appearance of baldness.	This is for informational purposes only. For medical advice or diagnosis, consult a professional. Androgenetic alopecia is caused by a combination of genetic and hormonal factors. • **Genetics:** A family history of hair loss is a strong predictor of developing androgenetic alopecia. • **Hormones:** The male hormone dihydrotestosterone (DHT) plays a key role. DHT shrinks hair follicles, leading to thinner, shorter hairs that eventually stop growing. In women, androgenetic alopecia is also influenced by hormones, but the exact mechanisms are not fully understood.	Androgenetic alopecia, also known as male or female pattern baldness, is primarily caused by a combination of genetic, hormonal, and environmental factors. Here's a detailed breakdown of the key causes: 1. **Genetic Predisposition** • **Inherited Traits**: Androgenetic alopecia is strongly linked to genetics. If you have a family history of hair loss (especially on either parent's side), you are more likely to develop it. • **Gene Variants**: Specific genes, such as those related to androgen receptors on hair follicles, can make follicles more sensitive to androgens (male hormones). 2. **Hormonal Factors** • **Dihydrotestosterone (DHT)**: This is the primary hormone responsible for androgenetic alopecia. DHT is derived from testosterone through the action of an enzyme called **5-alpha reductase**. • In genetically susceptible individuals, DHT binds to receptors in hair follicles, particularly in the scalp's frontal and crown areas. • Over time, DHT shrinks (miniaturizes) the hair follicles, leading to shorter, thinner hairs and eventually preventing new hair growth. • **Androgen Sensitivity**: Some people have hair follicles that are more sensitive to androgens, even at normal levels, which accelerates hair loss. 3. **Aging** • As people age, hair follicles become more susceptible to the effects of DHT, leading to progressive thinning and hair loss. • The hair growth cycle shortens, and the resting phase (telogen) becomes longer, resulting in fewer active hair follicles. 4. **Gender Differences** • **Men**: Male pattern baldness is driven by high levels of DHT and typically follows a predictable pattern (receding hairline and thinning at the crown). • **Women**: Female pattern baldness is often related to hormonal changes, such as those during menopause, and results in diffuse thinning across the scalp rather than a receding hairline. 5. **Environmental and Lifestyle Factors** While genetics and hormones are the primary drivers, certain factors can exacerbate androgenetic alopecia: • **Stress**: Chronic stress can worsen hair loss by disrupting the hair growth cycle. • **Poor Nutrition**: Deficiencies in vitamins and minerals (e.g., iron, zinc, vitamin D) can weaken hair follicles. • **Smoking**: Reduces blood flow to the scalp, impairing hair follicle health. • **Scalp Health**: Conditions like dandruff or seborrheic dermatitis can worsen hair loss. 6. **Underlying Medical Conditions** • **Polycystic Ovary Syndrome (PCOS)**: In women, PCOS can cause elevated androgen levels, leading to hair loss. • **Thyroid Disorders**: Both hypothyroidism and hyperthyroidism can disrupt the hair growth cycle. • **Insulin Resistance**: Linked to hormonal imbalances that may contribute to hair loss.

	4. **Age:** • AGA typically starts to show signs in the late teens to early 20s and progresses with age. As men age, the levels of DHT can fluctuate, and the density of hair may decrease due to accumulated follicular miniaturization. 5. **Other Contributing Factors:** • **Lifestyle and Stress**: While not direct causes of AGA, stress and an unhealthy lifestyle can potentially accelerate the hair loss process or exacerbate the condition. • **Underlying Medical Conditions**: Some medical issues, such as hormonal imbalances or conditions affecting the scalp (e.g., seborrheic dermatitis), can make hair loss more noticeable or contribute to hair loss, although they are not the primary causes of AGA.		7. **Medications** Certain medications, such as anabolic steroids or hormone therapies, can increase androgen levels and accelerate hair loss in genetically predisposed individuals. **Summary** Androgenetic alopecia is primarily caused by a combination of genetic susceptibility and the effects of DHT on hair follicles. While it cannot be completely prevented, treatments like **minoxidil**, **finasteride** (for men), **spironolactone** (for women), and lifestyle changes can help slow its progression and manage symptoms. Early intervention is key to preserving hair density. Consulting a dermatologist or healthcare provider is recommended for personalized treatment options.
4. Is androgenetic alopecia contagious?	No, androgenetic alopecia (AGA) is not contagious. It cannot be spread from person to person through direct contact or any other means. AGA is a **genetic and hormonal condition**, and its primary causes are related to inherited genes and the body's response to hormones, particularly **dihydrotestosterone** (**DHT**). **Why AGA Is Not Contagious:** 1. **Genetic Basis**: AGA is linked to your genetic makeup. If you have a family history of male or female pattern baldness, you may be more predisposed to developing it, but it is not something that can be caught from others. 2. **Hormonal Influence**: The process involves hormonal changes in the body, specifically how the hormone DHT affects hair follicles. This interaction is internal to the individual and does not involve external transmission. 3. **Non-Communicable Nature**: Unlike certain infections or skin conditions that can be transmitted through contact, AGA is not spread by sharing personal items, close physical contact, or any environmental factors.	This is for informational purposes only. For medical advice or diagnosis, consult a professional. No, androgenetic alopecia is not contagious. [1] **It's not caused by an infection:** It's a genetic condition influenced by hormones, not a disease that can be spread from person to person. You cannot "catch" androgenetic alopecia from someone else.	No, **androgenetic alopecia (male or female pattern baldness) is not contagious**. It is a genetic and hormonal condition that results from a combination of inherited traits and the effects of hormones like dihydrotestosterone (DHT) on hair follicles. It cannot be spread from person to person through physical contact, sharing personal items, or any other means. **Key Points:** 1. **Genetic Basis**: Androgenetic alopecia is caused by inherited genes that make hair follicles more sensitive to DHT. 2. **Hormonal Influence**: DHT, a derivative of testosterone, shrinks hair follicles over time, leading to thinning and hair loss. 3. **Non-Communicable**: Since it is not caused by bacteria, viruses, or fungi, it cannot be transmitted to others. If you are experiencing hair loss, it is important to consult a dermatologist or healthcare provider to confirm the diagnosis and explore treatment options.

Table 1 (*Continued*)

Table 1. Questions and Answers to ChatGPT, Gemini Flash 1.5, and DeepSeek R1. *(continued)*

QUESTIONS	ChatGPT 4.o's answers	Gemini's answers	DeepSeek R1'S answers
5. What are the symptoms of androgenetic alopecia?	The symptoms of androgenetic alopecia (AGA) vary depending on whether it affects men or women, but they generally involve progressive hair thinning and loss that follows specific patterns. Here's a breakdown of the typical symptoms for each gender: 1. **In Men (Male Pattern Baldness):** • **Receding Hairline**: The first noticeable symptom is a gradual receding of the hairline, often starting at the temples and moving backward. This can create an "M" shape as the hairline retreats. • **Thinning at the Crown**: Hair loss often continues with thinning or balding at the crown of the head. Over time, this area may become more prominent, leading to a bald spot. • **Progression to Bald Spots**: The hair thinning at the crown and receding hairline can merge, forming larger bald areas on the top of the head. • **Preserved Hair on the Sides and Back**: Typically, hair loss in AGA does not affect the sides and back of the scalp, which often retain full hair growth even as the top becomes bald. • **Miniaturization of Hair Follicles**: The hair shafts produced by the follicles become thinner and weaker as AGA progresses, resulting in finer and shorter hair. 2. **In Women (Female Pattern Hair Loss):** • **Diffuse Thinning**: Women often experience more diffuse thinning of hair rather than bald patches. The hair generally thins evenly over the top of the scalp while the hairline usually remains intact. • **Widening Part**: One of the early signs in women is a widening part, where the scalp becomes more visible. • **Thinning at the Crown**: Women may notice thinning at the crown, which can become more noticeable over time but typically does not progress to complete baldness as it does in men. • **Retention of Hairline**: Unlike men, women with AGA often retain their natural hairline, with thinning occurring more throughout the top and crown areas.	This is for informational purposes only. For medical advice or diagnosis, consult a professional. Androgenetic alopecia, also known as male or female pattern baldness, is the most common cause of hair loss. It results in a gradual thinning of hair on the scalp. **Here are some common symptoms:** • **Gradual thinning of hair:** This is the most noticeable symptom. The hair may become thinner and finer over time. • **Receding hairline:** In men, the hairline often recedes in an "M" shape. • **Hair loss on the crown:** In both men and women, hair loss can occur on the top of the head (crown). • **Widening part:** In women, the part in the hair may become wider. **It's important to note:** • **The severity of hair loss varies:** Some people may experience only mild thinning, while others may experience significant hair loss. • **The rate of hair loss also varies:** Hair loss can occur gradually over many years. If you are concerned about hair loss, it is important to see a doctor to rule out any underlying medical conditions.	Androgenetic alopecia, also known as male or female pattern baldness, has distinct symptoms that vary between men and women. Here's a detailed breakdown of the symptoms: **Symptoms in Men (Male Pattern Baldness)** 1. **Receding Hairline:** • Hair loss typically begins at the temples, creating an "M-shaped" hairline. 2. **Thinning at the Crown:** • Hair thinning or bald spots develop at the top (vertex) of the scalp. 3. **Progressive Hair Loss:** • Over time, the receding hairline and crown thinning may meet, leaving a horseshoe-shaped ring of hair around the sides and back of the head. 4. **Miniaturization of Hair:** • Affected hairs become finer, shorter, and lighter in color before eventually stopping growth. **Symptoms in Women (Female Pattern Baldness)** 1. **Diffuse Thinning:** • Hair thinning occurs across the entire scalp, but it is most noticeable at the part line. 2. **Widening Part Line:** • The part line becomes wider as hair density decreases. 3. **Preserved Hairline:** • Unlike men, women usually retain their frontal hairline but may experience overall thinning. 4. **Reduced Hair Volume:** • Hair may feel thinner and less dense, especially on the top of the scalp. 5. **Miniaturization of Hair:** • Similar to men, affected hairs become finer and shorter over time. **Common Symptoms in Both Men and Women** 1. **Increased Hair Shedding:** • More hair than usual may fall out during brushing, washing, or styling. 2. **Slower Hair Growth:** • Hair may take longer to grow back after shedding. 3. **Scalp Visibility:** • The scalp may become more visible as hair thins. 4. **Itching or Tenderness:** • Some individuals may experience mild scalp discomfort, though this is less common. **Stages of Androgenetic Alopecia** • **Men**: The progression is often measured using the **Norwood-Hamilton Scale**, which categorizes the stages of male pattern baldness. • **Women**: The progression is measured using the **Ludwig Scale**, which describes the stages of female pattern thinning.

	• **Gradual Progression**: The hair loss in women tends to be more gradual compared to men, and it may take many years before it becomes severe. **General Symptoms of AGA:** • **Reduced Hair Density**: Both men and women will notice that their hair density decreases as AGA progresses. • **Miniaturized Hairs**: Hair follicles produce thinner, softer hairs, which are often less noticeable and may not grow long. • **Slower Hair Growth**: Hair may grow more slowly as follicles become less effective. • **No Other Health Issues**: AGA is usually not associated with pain, itching, or other scalp issues, making it distinct from other types of hair loss that may be related to medical conditions (e.g., alopecia areata, scalp psoriasis).		**When to See a Doctor** If you notice sudden or excessive hair loss, or if the pattern of hair loss is unusual, consult a dermatologist or healthcare provider. They can confirm whether it is androgenetic alopecia or another type of hair loss (e.g., alopecia areata, telogen effluvium) and recommend appropriate treatments. **Key Takeaway** Androgenetic alopecia is a gradual process, and early intervention can help slow its progression. Treatments like **minoxidil**, **finasteride** (for men), **spironolactone** (for women), and lifestyle changes can be effective in managing symptoms.
6. Can androgenetic alopecia be confused with other hair loss conditions?	Yes, androgenetic alopecia (AGA) can sometimes be confused with other types of hair loss conditions because several conditions cause similar symptoms, such as thinning, shedding, or balding. However, the underlying causes and patterns of hair loss typically differ. Here's a look at some conditions that can be mistaken for AGA: 1. **Telogen Effluvium:** • **What It Is:** Telogen effluvium is a temporary form of hair loss triggered by factors like stress, illness, nutritional deficiencies, or medications. It occurs when a large number of hair follicles enter the shedding phase (telogen) prematurely. • **How It Differs from AGA:** Unlike AGA, which is a progressive condition and typically follows a pattern of thinning (e.g., along the crown or temples), telogen effluvium causes diffuse shedding throughout the scalp. The hair loss in telogen effluvium usually resolves once the underlying trigger is addressed, whereas AGA tends to worsen over time if untreated. 2. **Alopecia Areata:** • **What It Is:** Alopecia areata is an autoimmune disorder where the body's immune system attacks the hair follicles, leading to patchy hair loss. It can affect any area of the scalp or body. • **How It Differs from AGA:** While both cause hair loss, alopecia areata results in round, smooth patches of hair loss, not the gradual thinning seen in AGA. AGA typically results in diffuse thinning in specific areas (e.g., crown and temples), while alopecia areata can cause sudden, localized hair loss.	This is for informational purposes only. For medical advice or diagnosis, consult a professional. Yes, androgenetic alopecia can sometimes be confused with other hair loss conditions. This is because the symptoms can overlap, making it difficult to distinguish between them based on appearance alone. **Here are some conditions that androgenetic alopecia can be confused with:** • **Alopecia areata:** This autoimmune condition causes patchy hair loss on the scalp, and sometimes other parts of the body. While it can sometimes mimic the appearance of androgenetic alopecia, especially in its diffuse form, the pattern of hair loss is often different. • **Telogen effluvium:** This is a type of temporary hair loss triggered by stress, illness, or certain medications. It often presents as diffuse thinning all over the scalp, which can resemble female pattern hair loss. • **Anagen effluvium:** This type of hair loss is caused by certain medications, such as chemotherapy drugs. It results in rapid hair shedding and can cause significant hair loss within weeks.	(The server is busy. Please try again later.) Yes, **androgenetic alopecia** can sometimes be confused with other hair loss conditions because the symptoms of hair thinning or shedding may overlap. However, each type of hair loss has distinct characteristics, causes, and patterns. Here are some conditions that can be mistaken for androgenetic alopecia and how to differentiate them: 1. **Telogen Effluvium** • **Cause**: Temporary hair shedding triggered by stress, illness, surgery, hormonal changes, or nutritional deficiencies. • **Symptoms**: • Diffuse thinning across the scalp. • Increased hair shedding (e.g., more hair on pillows, brushes, or in the shower). • **Key Difference**: Telogen effluvium is usually temporary and reversible once the underlying cause is addressed, whereas androgenetic alopecia is progressive and permanent without treatment. 2. **Alopecia Areata** • **Cause**: An autoimmune condition where the immune system attacks hair follicles. • **Symptoms**: • Sudden, patchy hair loss on the scalp or other body areas. • Smooth, round bald patches. • **Key Difference**: Alopecia areata causes patchy hair loss rather than the patterned thinning seen in androgenetic alopecia.

Table 1 (*Continued*)

Table 1. Questions and Answers to ChatGPT, Gemini Flash 1.5, and DeepSeek R1. *(continued)*

QUESTIONS	ChatGPT 4.o's answers	Gemini's answers	DeepSeek R1'S answers
	3. **Traction Alopecia:** • **What It Is:** Traction alopecia is caused by prolonged tension or pulling on the hair, often due to tight hairstyles like braids, ponytails, or buns. • **How It Differs from AGA:** This type of hair loss is usually localized to areas where tension is applied (e.g., along the hairline or nape of the neck) and is reversible if the damaging hairstyles are stopped. AGA, on the other hand, is more diffuse and progressive, often affecting the crown or temples and generally not related to hair styling habits. 4. **Hormonal Imbalances (e.g., Polycystic Ovary Syndrome - PCOS):** • **What It Is:** Hormonal imbalances, such as those seen in conditions like PCOS, can lead to hair thinning, particularly in women. High levels of androgens (male hormones) can cause thinning of hair on the scalp while promoting excessive hair growth on other parts of the body (hirsutism). • **How It Differs from AGA:** While both conditions can cause thinning hair, PCOS-related hair loss may also present with other symptoms such as acne, irregular periods, or excessive body hair. AGA tends to be more gradual and is usually seen in a characteristic pattern, especially in men (receding hairline, crown thinning) and women (diffuse thinning on the top and crown of the scalp). 5. **Scalp Infections or Dermatologic Conditions:** • **What It Is:** Fungal infections (like ringworm) or skin conditions (such as psoriasis or seborrheic dermatitis) can lead to hair loss due to inflammation or infection of the scalp. • **How It Differs from AGA:** These conditions often present with additional symptoms, such as redness, flaking, or scaling on the scalp. The hair loss in these cases may be more patchy or sudden and is typically associated with inflammation or visible scalp irritation, whereas AGA causes gradual thinning with no such visible signs of infection.	• **Hormonal imbalances:** Conditions like hypothyroidism, hyperthyroidism, and polycystic ovary syndrome (PCOS) can cause hair loss. These conditions can sometimes be associated with androgenetic alopecia, but the underlying cause is different. • **Nutritional deficiencies:** Deficiencies in iron, protein, zinc, and biotin can lead to hair loss. These deficiencies can sometimes be mistaken for androgenetic alopecia, especially if they cause diffuse thinning. • **Medications:** Certain medications, such as blood thinners and beta-blockers, can cause hair loss as a side effect. This type of hair loss can sometimes be confused with androgenetic alopecia. • **Traction alopecia:** This type of hair loss is caused by tight hairstyles, such as braids and ponytails, that put excessive tension on the hair follicles. It can cause hair loss in specific areas, such as the hairline or the crown, which can sometimes resemble the pattern of hair loss in androgenetic alopecia. • **Trichotillomania:** This is a mental health condition that causes people to compulsively pull out their hair. It can lead to patchy hair loss in various areas of the scalp, which can sometimes be confused with alopecia areata. If you are experiencing hair loss, it is important to see a doctor to determine the underlying cause. They can perform a physical examination and order any necessary tests to rule out other conditions. Once the cause of hair loss is identified, the appropriate treatment can be started.	3. **Traction Alopecia** • **Cause**: Hair loss due to prolonged tension on the hair from tight hairstyles (e.g., braids, ponytails, or extensions). • **Symptoms**: • Hair loss at the hairline or areas where tension is applied. • Broken hairs or redness and irritation on the scalp. • **Key Difference**: Traction alopecia is localized to areas where hair is pulled, whereas androgenetic alopecia follows a genetic pattern. 4. **Scarring Alopecia (Cicatricial Alopecia)** • **Cause**: Inflammation or damage to hair follicles, leading to permanent hair loss and scarring. • **Symptoms**: • Patchy hair loss with visible scarring or redness on the scalp. • Itching, burning, or pain in affected areas. • **Key Difference**: Scarring alopecia involves visible damage to the scalp and is not patterned like androgenetic alopecia. 5. **Nutritional Deficiencies** • **Cause**: Lack of essential nutrients like iron, zinc, vitamin D, or protein. • **Symptoms**: • Diffuse thinning or increased shedding. • Brittle, dry, or dull hair. • **Key Difference**: Hair loss due to nutritional deficiencies often improves with dietary changes or supplements, unlike androgenetic alopecia. 6. **Thyroid Disorders** • **Cause**: Hypothyroidism (underactive thyroid) or hyperthyroidism (overactive thyroid). • **Symptoms**: • Diffuse thinning or shedding. • Other symptoms like fatigue, weight changes, or skin dryness. • **Key Difference**: Thyroid-related hair loss is accompanied by other systemic symptoms and can be reversed with proper thyroid treatment. 7. **Trichotillomania** • **Cause**: A psychological condition where individuals compulsively pull out their hair. • **Symptoms**: • Irregular patches of hair loss. • Broken hairs of varying lengths. • **Key Difference**: Trichotillomania is behavioral and not patterned like androgenetic alopecia. 8. **Fungal Infections (e.g., Tinea Capitis)** • **Cause**: Fungal infection of the scalp. • **Symptoms**: • Patchy hair loss with scaling, redness, or itching. • Broken hairs or black dots on the scalp.

	6. **Anagen Effluvium (Chemotherapy-Induced Hair Loss):** • **What It Is:** Anagen effluvium occurs when hair loss happens during the active growth phase (anagen) of the hair cycle, often as a result of chemotherapy or radiation therapy. • **How It Differs from AGA:** This type of hair loss is typically rapid and occurs all over the scalp. In contrast, AGA is progressive and tends to start slowly in specific areas of the scalp, such as the crown or temples. **How to Differentiate AGA from Other Conditions:** • **Pattern of Hair Loss:** AGA usually follows a predictable pattern, starting at the temples or crown. In women, it may begin with overall thinning at the crown. • **Progression:** AGA is gradual and progressive. If hair loss is sudden or patchy, other conditions like alopecia areata or telogen effluvium are more likely. • **Associated Symptoms:** Conditions like PCOS, scalp infections, or hormonal imbalances may have other visible symptoms, such as acne, irregular periods, or scalp irritation. **Conclusion:** While androgenetic alopecia is one of the most common causes of hair loss, other conditions can present with similar symptoms. A healthcare provider or dermatologist can perform a thorough examination and possibly run tests (like blood tests or scalp biopsies) to differentiate AGA from other hair loss conditions and determine the most appropriate treatment.		• **Key Difference**: Fungal infections often cause inflammation and scaling, which are not seen in androgenetic alopecia. **How to Differentiate Androgenetic Alopecia** • **Pattern**: Androgenetic alopecia follows a specific pattern (receding hairline and crown thinning in men, diffuse thinning in women). • **Progression**: It is gradual and progressive over time. • **Family History**: A family history of pattern baldness is a strong indicator. • **Diagnostic Tools**: A dermatologist may use tools like a **trichoscope** (scalp magnifier) or perform a **hair pull test** or **biopsy** to confirm the diagnosis. **When to See a Doctor** If you're unsure about the cause of your hair loss, consult a dermatologist. They can accurately diagnose the condition and recommend appropriate treatments. Early intervention is key to managing androgenetic alopecia and other types of hair loss effectively.

Table 1 (*Continued*)

Table 1. Questions and Answers to ChatGPT, Gemini Flash 1.5, and DeepSeek R1. *(continued)*

QUESTIONS	ChatGPT 4.o's answers	Gemini's answers	DeepSeek R1'S answers
7. How is androgenetic alopecia recognized?	Androgenetic alopecia (AGA) is usually recognized through a combination of **medical history**, **physical examination**, and, in some cases, **diagnostic tests**. Here's how healthcare professionals typically diagnose AGA: 1. **Clinical Evaluation:** • **Medical History**: The doctor will first take a detailed medical history, including questions about family history of hair loss (to assess genetic predisposition), age of onset, progression of hair loss, and any related symptoms or health issues. • **Physical Examination**: The healthcare provider will examine the scalp and hair pattern to identify signs of AGA. For men, this includes checking the hairline and crown. For women, it involves observing the top of the scalp for thinning and widening parts. • **Assessment of Hair Loss Pattern**: The classic pattern of AGA is used to help identify it. In men, this typically involves a receding hairline and thinning crown. In women, it usually involves diffuse thinning with a widening part, but the hairline is often preserved. 2. **Norwood-Hamilton Scale (for Men):** • This scale is used to classify the severity of male pattern baldness. It helps doctors determine the stage of hair loss, ranging from Type I (minimal hair loss) to Type VII (severe hair loss). The scale is essential for evaluating progression and planning treatment. 3. **Ludwig Scale (for Women):** • For women, the Ludwig scale is used to assess the extent of hair loss. It categorizes the severity from Type I (mild thinning) to Type III (advanced thinning). 4. **Pull Test:** • A doctor may perform a pull test, which involves gently pulling a small section of hair to determine how easily hairs come out. This helps differentiate AGA from other types of hair loss, such as telogen effluvium, where hair falls out more readily.	This is for informational purposes only. For medical advice or diagnosis, consult a professional. Androgenetic alopecia is usually diagnosed based on a physical examination and a review of your medical history. A doctor may also use tools like a magnifying lamp or dermoscopy to look at your scalp more closely. Here are some of the common signs of androgenetic alopecia: • **Gradual thinning of hair:** This is the most common symptom, especially in the crown area for women and the temples and crown for men. • **Widening part:** The part in your hair may become wider over time. • **Receding hairline:** In men, the hairline often recedes in a characteristic "M" shape. • **Increased hair shedding:** You may notice more hair in your brush or on your pillow than usual. If you're concerned about hair loss, it's important to see a doctor to rule out any underlying medical conditions.	Androgenetic alopecia (AGA), also known as male or female pattern baldness, is recognized through a combination of clinical evaluation, medical history, and sometimes diagnostic tests. Here's how it is typically identified: 1. **Clinical Evaluation** • **Pattern of Hair Loss:** • **Men**: Receding hairline (temporal areas) and thinning at the crown (vertex), often following the **Norwood-Hamilton Scale**. • **Women**: Diffuse thinning over the top of the scalp with a widening part line, often following the **Ludwig Scale**. • **Hair Miniaturization:** • Affected hairs become finer, shorter, and lighter in color over time. • **Scalp Visibility:** • The scalp becomes more visible as hair density decreases. 2. **Medical History** • **Family History:** • A family history of androgenetic alopecia (in parents or siblings) is a strong indicator, as the condition is highly genetic. • **Onset and Progression:** • Gradual hair loss over years, rather than sudden shedding. • **Associated Symptoms:** • In women, symptoms like irregular periods or hirsutism (excessive hair growth in male-pattern areas) may suggest hormonal imbalances (e.g., PCOS). 3. **Physical Examination** • **Hair Pull Test:** • Gently pulling on a small section of hair to check for excessive shedding. In androgenetic alopecia, the hair pull test is usually negative (few hairs come out). • **Scalp Inspection:** • The scalp typically appears normal without redness, scaling, or scarring, which helps rule out other conditions like fungal infections or scarring alopecia. 4. **Diagnostic Tools** • **Trichoscopy:** • A dermatoscope is used to magnify the scalp and hair follicles. In androgenetic alopecia, trichoscopy may show: • Hair shaft variability (thick and thin hairs). • Perifollicular discoloration (brownish halos around follicles). • **Scalp Biopsy:** • Rarely needed, but a biopsy can confirm the diagnosis by showing miniaturized hair follicles and a higher ratio of vellus (fine) hairs to terminal (thick) hairs.

	5. **Dermatoscopy or Scalp Examination:** • A dermatoscope may be used to inspect the scalp and hair follicles more closely. This device can reveal miniaturized hair follicles and other subtle changes that indicate AGA, such as the presence of short, thin hairs. 6. **Hair Density and Count:** • In some cases, a more detailed analysis might be conducted to count hair density and assess the proportion of terminal (thicker) to vellus (finer) hairs. AGA is characterized by an increased proportion of miniaturized vellus hairs compared to terminal hairs. 7. **Blood Tests and Hormonal Assessments:** • While AGA itself doesn't require blood tests for diagnosis, doctors might conduct hormonal assessments to rule out other conditions, particularly in women. Elevated androgens or other hormonal imbalances might be tested to differentiate AGA from conditions like polycystic ovary syndrome (PCOS) or other endocrine disorders. • **Thyroid function tests** may also be ordered to exclude thyroid dysfunction as a contributing factor. 8. **Biopsy (Rarely Used):** • A scalp biopsy is not typically needed for diagnosing AGA but may be used if the diagnosis is unclear or if the doctor suspects another type of hair loss. A small sample of the scalp is taken and examined under a microscope to analyze hair follicle size, density, and the presence of miniaturized hairs. 9. **Family History and Risk Assessment:** • A thorough family history helps establish whether there is a genetic component to the hair loss. This is particularly significant since AGA is often hereditary.		• **Blood Tests:** • Blood tests may be ordered to rule out other causes of hair loss, such as: • Thyroid function tests (to check for hypothyroidism or hyperthyroidism). • Hormone levels (e.g., testosterone, DHEA-S, prolactin) in women. • Iron studies (to check for anemia or iron deficiency). 5. **Differential Diagnosis** The doctor will rule out other conditions that can mimic androgenetic alopecia, such as: • **Telogen Effluvium**: Diffuse shedding without a specific pattern. • **Alopecia Areata**: Patchy hair loss with smooth, bald areas. • **Scarring Alopecia**: Hair loss with visible scarring or inflammation. • **Nutritional Deficiencies**: Hair loss due to low iron, zinc, or vitamin D. 6. **Staging and Classification** • **Men**: The **Norwood-Hamilton Scale** is used to classify the stages of male pattern baldness. • **Women**: The **Ludwig Scale** is used to describe the progression of female pattern hair loss. **Key Takeaways** • Androgenetic alopecia is recognized by its characteristic pattern of hair loss, family history, and gradual progression. • A dermatologist or healthcare provider can confirm the diagnosis through clinical evaluation, trichoscopy, and sometimes blood tests or a biopsy. • Early diagnosis and treatment are crucial to slow progression and improve outcomes. If you suspect androgenetic alopecia, consult a dermatologist for a proper evaluation and personalized treatment plan.

Table 1 (*Continued*)

Table 1. Questions and Answers to ChatGPT, Gemini Flash 1.5, and DeepSeek R1. *(continued)*

QUESTIONS	ChatGPT 4.o's answers	Gemini's answers	DeepSeek R1'S answers
8. How is androgenetic alopecia treated?	Treating androgenetic alopecia (AGA) involves a variety of approaches aimed at slowing hair loss and, in some cases, promoting hair regrowth. The treatment options range from **medications** and **topical treatments** to **surgical procedures** and **lifestyle changes**. The appropriate treatment depends on the severity of the condition, the patient's goals, and any underlying health conditions. Here's a comprehensive overview of the most common treatments for AGA: 1. **Medications**: a. **Minoxidil (Rogaine):** • **How it Works**: Minoxidil is a topical treatment that helps stimulate hair growth and slow hair loss. It is thought to widen blood vessels in the scalp, which may improve blood circulation and nourish hair follicles. • **Usage**: Applied directly to the scalp, usually twice a day. • **Effectiveness**: It can be effective for both men and women, though it may not be as effective in advanced cases. It can promote new hair growth and slow hair loss but does not cure AGA. • **Side Effects**: Potential side effects include scalp irritation, dryness, and unwanted facial hair growth in women. b. **Finasteride (Propecia):** • **How it Works**: Finasteride is an oral medication that inhibits the enzyme **5-alpha reductase**, which converts testosterone into dihydrotestosterone (DHT). Since DHT contributes to hair follicle miniaturization, reducing its levels can slow hair loss and even stimulate new growth. • **Usage**: Taken as a daily pill. • **Effectiveness**: Effective in slowing hair loss and promoting hair regrowth in men. It may also prevent further hair loss, but it is generally not recommended for women, especially those who are pregnant or may become pregnant, due to potential birth defects. • **Side Effects**: Possible side effects include decreased libido, erectile dysfunction, and a slight risk of depression.	This is for informational purposes only. For medical advice or diagnosis, consult a professional. There are several treatments available for androgenetic alopecia, but none can completely stop hair loss or regrow all lost hair. Some common options include: • **Medications:** • **Minoxidil (Rogaine):** This over-the-counter topical medication can slow hair loss and promote some regrowth in both men and women. • **Finasteride (Propecia):** This prescription oral medication is effective for men in slowing hair loss and promoting regrowth. It's generally not recommended for women. • **Other treatments:** • **Low-level laser therapy (LLLT):** This involves using a device that emits low-level lasers to stimulate hair growth. • **Hair transplant surgery:** This is a surgical option that involves transplanting hair follicles from a hair-bearing area of the scalp to a balding area. The best treatment for you will depend on several factors, including your age, sex, the severity of your hair loss, and your personal preferences. It's important to talk to a doctor to discuss your options and determine the	Androgenetic alopecia (AGA), or male/female pattern baldness, can be managed with a variety of treatments aimed at slowing hair loss, promoting regrowth, and improving hair density. The choice of treatment depends on the severity of hair loss, gender, and individual preferences. Here are the most common and effective treatments: 1. **Medications** **For Men and Women:** • **Minoxidil (Rogaine):** • A topical solution or foam applied directly to the scalp. • Stimulates hair growth and slows hair loss by prolonging the growth phase of hair follicles. • Available over-the-counter in 2% and 5% strengths (5% is more effective for men, while women typically use 2% or 5%). • Results take 4–6 months to become noticeable. **For Men Only:** • **Finasteride (Propecia):** • An oral medication that inhibits the enzyme **5-alpha reductase**, reducing the production of dihydrotestosterone (DHT), the hormone responsible for shrinking hair follicles. • Effective at slowing hair loss and promoting regrowth in men. • Requires a prescription and must be taken continuously to maintain results. • Results may take 3–6 months to appear. **For Women Only:** • **Spironolactone:** • An oral anti-androgen medication that blocks the effects of androgens (male hormones) on hair follicles. • Often prescribed for women with androgenetic alopecia, especially those with hormonal imbalances (e.g., PCOS). • Requires a prescription and regular monitoring by a doctor. 2. **Low-Level Laser Therapy (LLLT)** • **How It Works:** Uses red light lasers or LED devices to stimulate hair follicles and improve blood flow to the scalp. • **Devices:** Available as combs, caps, or helmets for home use. • **Effectiveness:** May help slow hair loss and improve hair density, especially when used in combination with other treatments. • **FDA-Approved:** Devices like the **HairMax LaserComb** are FDA-cleared for treating androgenetic alopecia.

	c. **Other Hormonal Treatments:** • For women, especially those with elevated androgens or conditions like polycystic ovary syndrome (PCOS), hormonal treatments such as **birth control pills** or **spironolactone** may be prescribed. These help reduce androgens, potentially slowing hair loss and promoting hair growth. 2. **Low-Level Laser Therapy (LLLT):** • **How it Works**: This therapy uses red light to stimulate hair follicles and promote hair growth. The treatment can be done at home with laser combs, helmets, or caps. • **Effectiveness**: It can be effective in improving hair density and slowing hair loss, although results vary among individuals. • **Safety**: Generally considered safe with minimal side effects like scalp irritation. 3. **Hair Transplant Surgery:** • **How it Works**: Hair transplant procedures involve moving hair follicles from areas of the scalp that are resistant to hair loss (usually the back or sides) to areas experiencing thinning or baldness. • **Techniques:** • **FUT (Follicular Unit Transplantation)**: Involves removing a strip of skin with hair and dissecting it into individual grafts. • **FUE (Follicular Unit Extraction)**: Involves extracting individual hair follicles directly from the scalp and transplanting them to the desired area. • **Effectiveness**: Effective for those with significant hair loss and a good donor area. Results are permanent as long as the transplanted follicles are healthy. • **Side Effects**: Includes scarring (with FUT) and potential for infection, pain, or uneven hair growth. 4. **Lifestyle and Hair Care:** • **Diet and Nutrition**: A well-balanced diet rich in vitamins and minerals, especially **iron**, **zinc**, **biotin**, and **protein**, can support overall hair health. While diet alone won't prevent or treat AGA, maintaining healthy hair and scalp conditions is important. • **Reducing Stress**: Stress can exacerbate hair loss, so stress management techniques such as meditation, exercise, and adequate sleep can be beneficial. • **Avoiding Hair Damage**: Using gentle hair care products and avoiding harsh chemicals, heat styling, or tight hairstyles can help minimize hair breakage.		3. **Platelet-Rich Plasma (PRP) Therapy** • **How It Works**: A concentrated solution of the patient's own platelets is injected into the scalp to stimulate hair growth and improve follicle health. • **Procedure**: Blood is drawn, processed to isolate platelets, and injected into thinning areas. • **Effectiveness**: Studies show PRP can improve hair density and thickness, especially when combined with other treatments. • **Frequency**: Requires multiple sessions (e.g., 3–4 initial treatments, followed by maintenance sessions). 4. **Hair Transplant Surgery** • **How It Works**: Hair follicles are taken from areas of the scalp with healthy hair growth (usually the back or sides) and transplanted to thinning or bald areas. • **Techniques**: • **Follicular Unit Transplantation (FUT)**: A strip of scalp is removed, and follicles are transplanted. • **Follicular Unit Extraction (FUE)**: Individual follicles are extracted and transplanted. • **Effectiveness**: Provides permanent, natural-looking results. • **Considerations**: Expensive and requires a skilled surgeon. Best for individuals with significant hair loss who have sufficient donor hair. 5. **Lifestyle and Nutritional Support** • **Diet**: A balanced diet rich in vitamins and minerals (e.g., iron, zinc, vitamin D, biotin) supports hair health. • **Supplements**: Biotin, collagen, or specialized hair growth supplements may help, especially if nutritional deficiencies are present. • **Stress Management**: Reducing stress through exercise, meditation, or therapy can improve overall hair health. 6. **Cosmetic Solutions** • **Hair Fibers**: Products like Toppik or Caboki use keratin fibers to cover thinning areas and create the appearance of thicker hair. • **Wigs or Hairpieces**: High-quality wigs or hair systems can provide a non-invasive solution for significant hair loss. • **Styling Techniques**: Hairstyles that add volume or cover thinning areas can help camouflage hair loss. 7. **Emerging Treatments** • **Dutasteride**: A stronger 5-alpha reductase inhibitor than finasteride, sometimes used off-label for men with severe hair loss. • **Clascoterone (Breezula)**: A topical anti-androgen currently under investigation for treating androgenetic alopecia. • **Stem Cell Therapy**: Experimental treatments using stem cells to regenerate hair follicles are being studied but are not yet widely available. **Key Considerations** • **Consistency**: Most treatments require consistent, long-term use to maintain results. • **Early Intervention**: Starting treatment early yields the best outcomes. • **Combination Therapy**: Using multiple treatments (e.g., minoxidil + finasteride) often provides better results than a single treatment alone. **When to See a Doctor** If you're experiencing hair loss, consult a dermatologist or healthcare provider to confirm the diagnosis and develop a personalized treatment plan. They can recommend the most appropriate therapies based on your specific needs and medical history.

Table 1 (*Continued*)

Table 1. Questions and Answers to ChatGPT, Gemini Flash 1.5, and DeepSeek R1. *(continued)*

QUESTIONS	ChatGPT 4.o's answers	Gemini's answers	DeepSeek R1'S answers
	5. **Emerging Treatments:** • **Platelet-Rich Plasma (PRP) Therapy**: This involves injecting a concentration of the patient's own platelets into the scalp to potentially promote hair growth and improve hair follicle health. • **Stem Cell Therapy**: Still largely experimental, this approach aims to use stem cells to regenerate hair follicles and promote hair growth. • **New Medications**: Research is ongoing for new drugs and treatments that may target hair loss pathways more effectively and with fewer side effects. 6. **Consulting a Specialist:** • If you're experiencing hair loss and suspect it might be androgenetic alopecia, it's crucial to consult with a dermatologist or a trichologist (a specialist in hair and scalp disorders). They can assess the severity, discuss potential treatment options, and guide you toward the most effective approach based on your individual needs. **Important Notes:** • **Consistency**: Many treatments require long-term commitment to be effective. For example, minoxidil and finasteride often need to be used continuously to maintain results. • **Side Effects**: Always discuss potential side effects and benefits with a healthcare professional before starting a treatment. • **Effectiveness Varies**: Individual responses to treatment vary, and while some people may see significant improvements, others may not respond as well. In summary, while there is no cure for androgenetic alopecia, various treatments can help manage and slow down the progression of hair loss and promote regrowth in some cases.		

9. Can androgenetic type alopecia be prevented?	Androgenetic alopecia (AGA), also known as male or female pattern baldness, is a genetic condition, which means it can't be completely prevented. However, there are measures that can be taken to **slow down its progression** and potentially **preserve hair** for as long as possible. Here are some ways to manage and possibly delay the onset or progression of AGA: 1. **Early Detection and Treatment:** • **Start Treatment Early**: The sooner you start treatment after noticing hair loss, the better the outcome. Treatments like **minoxidil** (topical) and **finasteride** (oral) can help slow hair loss and, in some cases, promote new hair growth. • **Regular Check-Ups**: Periodic visits to a dermatologist or trichologist can help monitor the condition and adjust treatments as necessary. 2. **Medications and Topical Treatments:** • **Minoxidil (Rogaine)**: This topical solution or foam can be applied to the scalp to stimulate hair growth and slow hair loss. It's effective in men and women and is available over-the-counter. • **Finasteride (Propecia)**: An oral medication that reduces the levels of dihydrotestosterone (DHT), a hormone linked to hair follicle shrinkage. This medication can help slow or even reverse hair loss, especially in men. • **Other Medications**: For women, **spironolactone** or **birth control pills** can be prescribed to reduce androgen levels and slow hair loss. 3. **Lifestyle Adjustments:** • **Healthy Diet**: Ensure you get sufficient nutrients that support hair health, such as **protein, iron, zinc, biotin**, and **vitamins A, C, D, and E**. While diet alone can't prevent AGA, good nutrition can help maintain overall hair health. • **Manage Stress**: Chronic stress can contribute to hair loss, so practices like meditation, yoga, or regular exercise can help manage stress levels and promote overall well-being. • **Avoid Hair Damage**: Limit the use of harsh hair products, reduce heat styling, and avoid hairstyles that pull tightly on the hair, which can lead to breakage and worsen hair loss.	This is for informational purposes only. For medical advice or diagnosis, consult a professional. Unfortunately, androgenetic alopecia (male or female pattern baldness) **cannot be prevented**. • **Genetic Predisposition:** Androgenetic alopecia is primarily caused by a combination of genetic factors and sensitivity to androgens (male hormones). If you have a family history of hair loss, you are more likely to experience it yourself. **However, there are things you can do to potentially slow down hair loss or minimize its impact:** • **Early Treatment:** If you notice signs of hair loss, consulting a doctor early on can help. There are medications available (like minoxidil and finasteride) that can slow down hair loss and potentially regrow some hair. • **Healthy Lifestyle:** While not a guaranteed prevention, maintaining a healthy lifestyle can support overall hair health. This includes: • **Balanced Diet:** Ensure you're getting enough protein, vitamins, and minerals essential for hair growth. • **Stress Management:** Chronic stress can contribute to hair loss. Find healthy ways to manage stress, such as exercise, yoga, or meditation. • **Gentle Hair Care:** Avoid harsh hairstyles, excessive heat styling, and chemical treatments that can damage hair. **It's important to remember:** • **Individual Results Vary:** The effectiveness of treatments and lifestyle changes can vary from person to person. • **Consult a Professional:** A dermatologist can provide personalized advice and recommend the most suitable treatment options for your specific situation.	

Table 1 (*Continued*)

Table 1. Questions and Answers to ChatGPT, Gemini Flash 1.5, and DeepSeek R1. *(continued)*

QUESTIONS	ChatGPT 4.o's answers	Gemini's answers	DeepSeek R1'S answers
	1. **Avoid Hormonal Triggers:** • **Monitor Hormonal Changes**: Hormones, especially androgens like testosterone and DHT, play a significant role in AGA. For individuals predisposed to AGA, avoiding hormone imbalances (e.g., those caused by certain medications or medical conditions) may help slow the progression. • **Consult a Healthcare Provider**: If you're taking medications that affect hormone levels, speak with your doctor about potential impacts on hair health. 2. **Low-Level Laser Therapy (LLLT):** • **Laser Treatments**: Devices such as laser combs, helmets, or caps use low-level laser light to stimulate hair follicles, potentially improving hair growth and slowing hair loss. • **Effectiveness**: This treatment is considered safe and non-invasive, though results can vary, and it may need to be used consistently over time. 3. **Scalp Care:** • **Keep Your Scalp Healthy**: Proper scalp hygiene and massage can help promote circulation and create a better environment for hair growth. Use gentle shampoos and conditioners to avoid irritating the scalp or stripping the hair of natural oils. • **Avoid Harsh Chemicals**: Stay away from shampoos and hair products with harsh chemicals that can damage hair and scalp health. 4. **Medical Procedures:** • **Hair Transplant Surgery**: While not a preventive measure, if hair loss has progressed to a significant stage, a hair transplant can be an option to restore hair in balding areas. This procedure moves hair from areas resistant to hair loss (usually the back or sides of the scalp) to the thinning or bald areas. **Important Considerations:** • **Genetics and Irreversibility**: AGA is largely determined by genetics, and once hair loss begins, it is difficult to reverse completely. Treatments can help slow or stop the progression but typically won't prevent it entirely.	While you can't completely prevent androgenetic alopecia, taking proactive steps and consulting with a healthcare professional can help you manage hair loss and maintain the healthiest hair possible.	

	• **Commitment to Treatment**: Many of the treatments require ongoing use to maintain results. If you stop treatment, hair loss may resume or progress as it would have without the intervention. • **Consultation with Specialists**: For the most effective management, work with a dermatologist or a hair specialist to create a tailored treatment plan based on your specific needs. **Conclusion:** While androgenetic alopecia cannot be completely prevented due to its genetic nature, taking proactive steps like starting early treatment, making lifestyle adjustments, and using medications and therapies can significantly slow the progression and help maintain hair for as long as possible. Consulting with a specialist can help you find the best approach for managing hair loss and potentially delaying or reducing its impact.		
10. Will hair continue to fall out if treatment is stopped?	Yes, if treatment for androgenetic alopecia (AGA) is stopped, hair loss is likely to continue and progress as it would have if no treatment had been started. Here's what typically happens when treatment is discontinued: 1. **Minoxidil (Topical Treatment):** • **Immediate Effects**: Minoxidil can help slow hair loss and even promote new hair growth in some cases. If you stop using minoxidil, the benefits it provided will start to diminish. • **Regrowth Loss**: Any new hair growth achieved during treatment will likely be lost within a few months after discontinuation. The hair follicles will revert to their pre-treatment state, which often means continued thinning or shedding. • **Timeline**: Hair loss may resume within a few weeks to a few months after stopping minoxidil. It generally takes 3-6 months for the hair to return to the state it would have been in if treatment had never been started. 2. **Finasteride (Oral Treatment):** • **Mechanism of Action**: Finasteride works by reducing the levels of dihydrotestosterone (DHT), a hormone linked to hair follicle shrinkage. It helps prevent hair loss and can promote regrowth in men. • **Stopping Treatment**: If finasteride is stopped, DHT levels will return to normal, and hair loss will continue. The process of hair loss will resume as it would have without the medication.	This is for informational purposes only. For medical advice or diagnosis, consult a professional. Yes, if you stop treatment for androgenetic alopecia (male or female pattern baldness), hair loss will likely resume. • **Medications:** Medications like minoxidil and finasteride work to slow down hair loss and potentially regrow some hair. However, these effects are usually temporary. Once you stop taking them, the hair loss will likely return to its previous rate. **Here's what typically happens:** • **Minoxidil**: • Regrown hair may start to fall out within a few months of stopping treatment. • The amount of hair loss can vary from person to person. • **Finasteride:** • Hair loss may gradually resume over time, but the rate may be slower than before treatment.	

Table 1 (*Continued*)

Table 1. Questions and Answers to ChatGPT, Gemini Flash 1.5, and DeepSeek R1. *(continued)*

QUESTIONS	ChatGPT 4.o's answers	Gemini's answers	DeepSeek R1'S answers
	• **Timeline**: Hair loss may start within a few months after discontinuing finasteride, and within 12 months, most men who stop treatment will experience a return to their baseline level of hair loss or even a worsening of the condition. 1. **Other Treatments:** • **Spironolactone (for Women)**: If used to manage hair loss due to hormonal imbalances, stopping spironolactone can lead to the return of hair loss, especially if androgens (male hormones) are a contributing factor. • **Low-Level Laser Therapy (LLLT)**: Stopping laser therapy will mean that any positive effects on hair growth may gradually decline, and hair loss could resume over time. • **Platelet-Rich Plasma (PRP) Therapy**: While PRP can improve hair density and stimulate hair growth, its effects will diminish if treatments are stopped, and the hair loss process will continue as it would have without treatment. **Key Points to Remember:** • **Hair Regrowth Loss**: Any hair that was regrown due to treatment is usually lost after discontinuation. Hair typically reverts to its pre-treatment state within 3-6 months. • **Treatment Maintenance**: Treatments for AGA require ongoing use to maintain results. If you stop using them, the benefits are lost, and hair loss will continue according to your natural pattern. • **Consult a Specialist**: If you are considering stopping treatment, consult with a dermatologist or hair specialist. They can discuss potential outcomes and may offer alternative options or suggest a gradual transition. **Conclusion:** Stopping treatment for androgenetic alopecia can lead to a return to the natural progression of hair loss. The hair that was maintained or regrown with treatment will likely be lost, and thinning will resume. Consistency is key for most AGA treatments, and if you want to preserve your results, it's important to continue the treatment as recommended by your doctor.	**Important Considerations:** • **Individual Results Vary:** The exact effects of stopping treatment can vary depending on factors like the type of medication used, the severity of hair loss, and individual response. • **Underlying Condition:** Androgenetic alopecia is a progressive condition. Even without treatment, hair loss will likely continue, but potentially at a slower rate. **If you're considering stopping treatment for androgenetic alopecia, it's important to discuss this with your doctor.** They can help you understand the potential risks and benefits and advise you on the best course of action for your individual situation.	

11.Do women with androgenetic alopecia have more male hormones?	Women with androgenetic alopecia (AGA), also known as female pattern hair loss, do not necessarily have more male hormones, but the condition is influenced by the balance of hormones, including androgens (male hormones like testosterone). In women, androgens are produced in smaller amounts than in men, but they still play a role in hair growth. Androgenetic alopecia in women is typically associated with an increased sensitivity of hair follicles to these androgens, rather than an overall excess of male hormones. Several factors contribute to this sensitivity: 1. **Hormonal Changes:** Women may experience fluctuations in androgens due to menopause, polycystic ovary syndrome (PCOS), or other hormonal imbalances, which can make hair follicles more sensitive to these hormones. 2. **Genetics:** A genetic predisposition to androgenetic alopecia can make hair follicles more prone to shrinking in response to androgens, leading to hair thinning and shedding. In summary, while women with androgenetic alopecia may have normal or even slightly elevated androgen levels, the primary issue is often the sensitivity of hair follicles to these hormones, rather than an overall excess of male hormones. Treatment for this condition can sometimes include medications that block the effects of androgens, such as spironolactone, or topical treatments like minoxidil to help stimulate hair growth.	This is for informational purposes only. For medical advice or diagnosis, consult a professional. It's a common misconception that women with androgenetic alopecia (female pattern hair loss) necessarily have higher levels of male hormones (androgens). **Here's the truth:** • **Androgens Play a Role:** Androgens, like testosterone, do play a role in female pattern hair loss. However, most women with this condition have normal androgen levels. • **Sensitivity to Androgens:** The key factor is often not the level of androgens, but rather an increased sensitivity to these hormones in the hair follicles. • **Genetic Predisposition:** Androgenetic alopecia is primarily a genetic condition. Women with a family history of hair loss are more likely to experience it, even with normal hormone levels. **When Androgens Might Be a Factor:** • **In some cases,** women with androgenetic alopecia may have slightly elevated androgen levels. • **Certain conditions,** such as polycystic ovary syndrome (PCOS), can cause an imbalance in hormones and contribute to hair loss. **It's important to note:** • **Individual Variation:** The cause of androgenetic alopecia can vary from woman to woman. • **Hormone Testing:** If your doctor suspects a hormonal imbalance, they may recommend hormone tests to investigate further. **If you're concerned about hair loss, it's best to consult a doctor or dermatologist.** They can help determine the underlying cause and recommend the most appropriate treatment option	

Table 1 (*Continued*)

Table 1. Questions and Answers to ChatGPT, Gemini Flash 1.5, and DeepSeek R1. *(continued)*

QUESTIONS	ChatGPT 4.o's answers	Gemini's answers	DeepSeek R1'S answers
12.In androgenetic alopecia, does the hereditary character come from the mother's or father's side?	In androgenetic alopecia (AGA), the hereditary factors that contribute to the condition can come from both the mother's and father's sides of the family, though the genetic inheritance pattern is more complex than being solely from one side. **Key points about inheritance:** 1. **X-Chromosome Influence:** The most significant genetic influence for androgenetic alopecia is thought to be related to a gene on the **X chromosome**. Since women have two X chromosomes (one from each parent) and men only have one (from their mother), the condition is often more strongly inherited through the maternal side in men. If a man's mother carries the gene for AGA, he is more likely to develop the condition, even though his father might not have it. 2. **Polygenic Inheritance:** The inheritance of AGA is **polygenic**, meaning it involves multiple genes. These genes can come from both sides of the family. While the X-chromosome influence is particularly important, other genes on both the X and non-sex chromosomes contribute to the condition as well. 3. **Both Parents Can Contribute:** While the maternal side plays a large role due to the X chromosome, the father's genes can also contribute. For example, if the father has androgenetic alopecia, his children (both sons and daughters) may inherit a genetic predisposition from him as well. **Conclusion:** In general, the condition is often inherited through the **mother's side**, particularly in men, because of the X-chromosome connection. However, the genetics are multifactorial, so both the mother's and father's genes can influence the development of androgenetic alopecia.	This is for informational purposes only. For medical advice or diagnosis, consult a professional. Androgenetic alopecia, often referred to as male or female pattern baldness, is a complex genetic condition. It's a common misconception that it's solely inherited from the mother's side. **The Reality:** • **Both Parents Contribute:** The genetic predisposition for androgenetic alopecia comes from both parents. • **X Chromosome Influence:** A key gene involved in hair loss, the androgen receptor (AR) gene, is located on the X chromosome. Since males inherit their only X chromosome from their mothers, this has led to the "mother's side" myth. • **Multiple Genes:** However, multiple genes on different chromosomes also play a role. These genes can be inherited from either parent. **Key Points:** • **Family History Matters:** A family history of hair loss on either side increases the risk, but doesn't guarantee it. • **Individual Variation:** The severity and pattern of hair loss can vary greatly, even within the same family. **If you're concerned about hair loss, it's best to consult a doctor or dermatologist for personalized advice.** They can help you understand your specific situation and recommend appropriate treatment options.	

* In the interest of copyright compliance and intellectual property protection, the incorporation of relevant photographs has been withheld from this document.

Table 2. The Accuracy of Responses Provided by ChatGPT 4.o, Gemini Flash 1.5, and DeepSeek R1.

Question Number	*ChatGPT 4.o*	*Gemini Flash 1.5*	*DeepSeek R1*
	Answer Accuracy Score	***Answer Accuracy Scores***	***Answer Accuracy Score***
1	2-2	2-2	2-2
2	2-2	1-1	1-1
3	1-1	1-1	1-1
4	1-1	1-1	1-1
5	1-1	1-1	1-1
6	2-2	2-2	4-4
7	2-1	1-1	1-1
8	1-1	2-2	1-1
9	1-1	1-1	
10	1-1	1-1	
11	1-1	1-1	
12	1-1	1-1	

Table 3. Comparisons among Large Language Model-Based Artificial Intelligent Applications in terms of FKGL ve FRES levels (N=8).

	FKGL	FRES
Chat GPT	10.5±1.18	44.1±9.1
Gemini Flash 1.5	10.8±1.94	39.7±13.8
DeepSeek R1	10.6±1.49	35.6±9.6
p-value[A]	0.666	0.053

Data were shown as mean ± SD. [A]Repeated measures of ANOVA via Wilks' Lambda test.

Table 4. Comparisons between ChatGPT 4.o and Gemini Flash 1.5 in terms of FKGL vs FRES levels (N=12).

	FKGL	FRES
Chat GPT	11.0±1.61	42.0±9.3
Gemini	11.2±1.62	37.5±11.5
p-value [A]	0.674	0.059

Data are shown as mean ± SD. [A] Paired samples t-test.

R1 experienced considerable delays in the response process commencing from the sixth question and could only respond to eight questions due to augmented response times. This delay resulted in DeepSeek R1 receiving the lowest score for speed and practicality in the user experience survey. Conversely, ChatGPT 4.o and Gemini Flash 1.5 demonstrated high levels of speed and practicality. In a similar vein, a study by Heather C. Lent et al. evaluated the responses of ChatGPT 4.o to questions regarding actinic keratosis, and ChatGPT 4.o received high scores in terms of speed and practicality.

Another notable finding of the user survey is that DeepSeek R1 received very low scores in the "friendly," "enjoyable," and "boring" categories. In contrast, ChatGPT 4.o and Gemini Flash 1.5 scored high in these categories. As a result, ChatGPT 4.o and Gemini Flash 1.5 met user expectations, while DeepSeek R1 did not. Although LLMs have been around for a few years, one reason for the widespread interest in this technology is the emergence of user-friendly interfaces. Our findings suggest that language model-based AI tools should be evaluated not only for their technical accuracy but also for their interface and interaction features that improve the user experience. Especially in terms of patient education, it is inevitable to prefer AI tools that provide fast accessible information. Accordingly, in order for DeepSeek R1 to be more effective in patient education processes, it is necessary to make the responses fast and uninterrupted and to make interface improvements to improve the user experience.

When ChatGPT 4.o and Gemini Flash 1.5 were compared, although both met the expectations in user experience and received valid answers for all questions, Gemini Flash 1.5 was found to be easier and more practical to use than was ChatGPT 4.o, and the former was seen as more understandable; it was thus considered more valuable and better by the users. This resulted in a higher score in terms of meeting expectations. In the light of these findings, Gemini Flash 1.5 is more prominent in terms of user experience compared to ChatGPT 4.o.

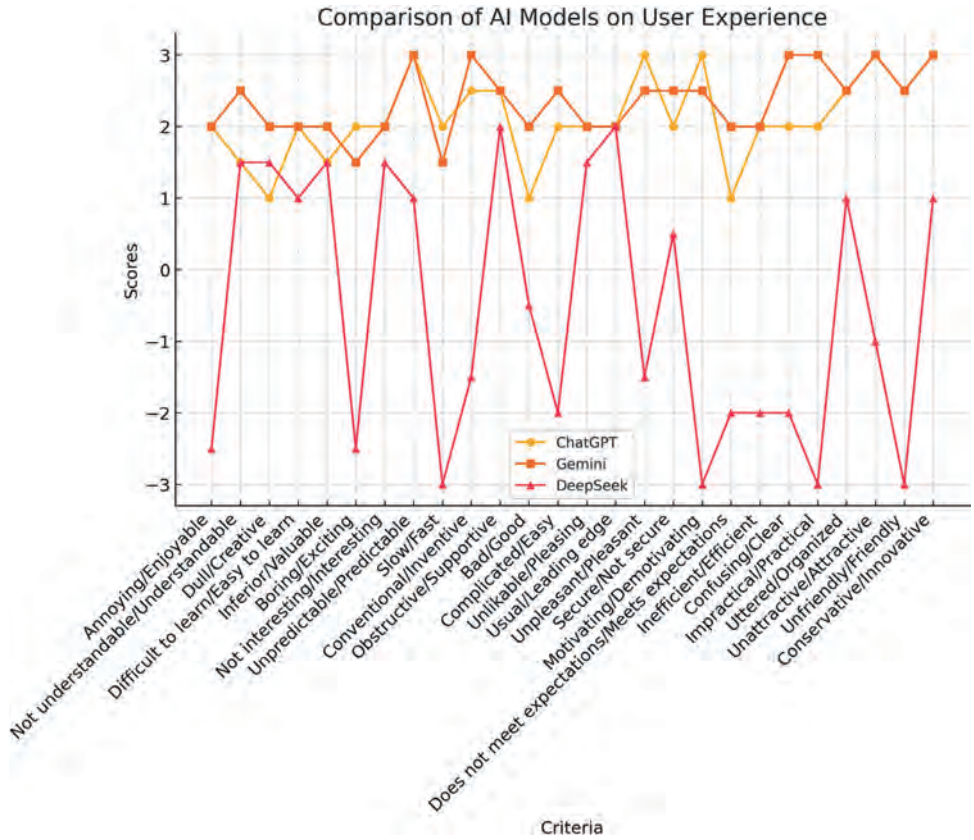


Figure 1. Mean user experience ratings for ChatGPT-4.o, Gemini Flash 1.5, and DeepSeek R1, derived from the feedback of dermatology specialists who completed a user experience questionnaire on AI-assisted analysis. Scores range from –3 to +3, where values between –0.8 and +0.8 denote a neutral evaluation, values above +0.8 indicate a positive evaluation, and values below –0.8 indicate a negative evaluation.

It is interesting to note that Gemini 1.5 Flash provided visual materials with its answers to some questions, in contrast to ChatGPT 4.o and DeepSeek R1, which did not. While visual aids can enhance comprehension, they may pose a risk for individuals with limited visual health literacy, potentially leading to misinterpretation of medical information. Further studies are needed to assess the impact of AI-generated visuals on patient education.

The phenomenon of AI hallucinations emerges when machine learning models such as Gemini 1.5, Flash, ChatGPT-4.o, and DeepSeek R1 endeavour to generate content that extends beyond the boundaries of their training data. AI hallucinations can be delineated as content that is not grounded in reality and is not derived from authentic data. Instead, it is the product of extrapolation or creative interpretation of a machine learning model's training data [13]. Therefore, users of ChatGPT 4.o are notified with the warning "ChatGPT 4.o may make errors. Check important information," while Gemini 1.5 Flash provides users with a warning that says, "Verify the answers given by Gemini Flash 1.5 as it can make mistakes." In contrast, DeepSeek R1 does not provide any information to users in this regard. Since Deepsek R1 does not provide any warnings about potential errors, users may perceive the information it provides as entirely accurate. In cases where the model disseminates incorrect or misleading information, this could lead to delays in seeking medical assistance and the misuse of over-the-counter products, resulting in inappropriate treatment approaches.

In the present study, references were appended to the responses of Gemini 1.5 Flash to a number of questions. In contrast, ChatGPT 4.o did not provide references in any of the responses analyzed in this study, although it is capable of including references under the conditions specified by the algorithm. Similarly, DeepSeek R1 did not include any references in its responses. This distinction enables the evaluation of Gemini 1.5 Flash's responses as either verifiable information or AI hallucinations, while the reliability of ChatGPT 4.o's and DeepSeek R1's responses becomes more uncertain. Additionally, DeepSeek R1's failure to notify users of potential inaccuracies due to AI hallucinations may lead to misleading and potentially damaging consequences, as users may not realize that inaccurate or incomplete information is presented.

The response of ChatGPT 4.o, Gemini Flash 1.5, and DeepSeek R1 to the question "Why does hair fall out?" was deemed to be "Satisfactory with minimal explanation required" by both evaluators. This assessment was made on the basis that cicatricial alopecia was not identified as a cause of

hair loss [14]. Although DeepSeek R1 discusses lichen planus and lupus under autoimmune diseases, it does not sufficiently address or provide examples of scarring alopecias.

ChatGPT 4.o's response to the query regarding the onset of androgenetic alopecia was evaluated by both assessors as "Satisfactory with minimal clarification required." Androgenetic alopecia, also known as male pattern baldness, affects both males and females, yet ChatGPT 4. o's response exclusively addressed the topic to men [2].

In their response to the question "Can androgenetic alopecia be confused with other hair loss conditions," both ChatGPT 4.o and Gemini Flash 1.5 were deemed by Reviewer 1 to provide a satisfactory answer that requires minimal clarification. This is because it does not mention fibrosing alopecia in pattern distribution, which is often confused with AGA-related seborrhoeic dermatitis [15].

The response provided by DeepSeek R1 to this question was evaluated by both reviewers as "Unsatisfactory, requiring substantial clarification." The statement given to distinguish androgenetic alopecia from scarring alopecia, "Scarring alopecia involves visible damage to the scalp and is not patterned like androgenetic alopecia," is incorrect. Fibrosing alopecia with pattern distribution was described approximately 30 years ago in a group of Australian women as a subtype of lichen planopilaris [16]. Over time, it has been reported in an increasing number of patients of both sexes [17,18]. Contrary to DeepSeek R1's response, there is a type of scarring alopecia that exhibits a pattern distribution resembling androgenetic alopecia. The provision of incorrect information by DeepSeek R1 could lead to negative consequences for patients. This may cause delays in seeking consultation with a dermatologist and significant time loss. It should be noted that time is a critical factor in the treatment of scarring alopecia. Delayed treatment can result in permanent damage to more hair follicles. Furthermore, patients may incur financial losses by spending money on shampoos or hair cosmetics that have no effect on the treatment of scarring alopecia. These findings underscore the necessity for the information provided by artificial intelligence tools to undergo expert supervision before being applied in clinical settings.

ChatGPT 4. o's response to the question "How is androgenetic alopecia recognised?" was described by both assessors as "Satisfactory requiring minimal clarification required." The response indicated that the pull test can be used to differentiate androgenetic alopecia (AGA) from telogen effluvium. However, it should be noted that the pull test may also be positive in AGA [19].

Gemini Flash 1.5's response to the query regarding the treatment of androgenetic alopecia was evaluated by both assessors as "Satisfactory with minimal clarification." Gemini Flash 1.5 did not mention platelet-rich plasma treatment and was therefore assessed as such [20].

Artificial intelligence models, thanks to their free versions, provide accessible sources of information for a wide range of users. However, the readability level of the information they provide may be above the level that the general public can understand. The answers produced by ChatGPT 4.o, Gemini Flash 1.5, and DeepSeek R1, which we examined in our study, were found to be at the 10th–11th grade FKGL (Flesch-Kincaid Grade Level) and were evaluated as difficult to read in terms of FRES (Flesch Reading Ease Score). However, the American Medical Association (AMA) and the National Institutes of Health (NIH) recommend that patient education materials be written at the 6th and the 8th grade level, respectively [21].

Previous studies have also shown that medical questions posed to AI models for patient education are above the recommended readability level and generally produce answers at the 10th–11th grade and university level [22-23]. These findings suggest that AI-based information resources in the field of healthcare may be insufficient in terms of comprehensibility for patients. Therefore, it is emphasised that the readability level of the information provided by artificial intelligence models be improved and made more suitable for public health needs.

Limitations

This study is not without limitations. Firstly, the questions used in this study were selected based on clinical experience without the application of a standardized selection protocol, which may have limited its reproducibility and introduced selection bias. Additionally, although the accuracy of the questions was evaluated using an evidence-based approach and demonstrated high inter-reviewer reliability, subjectivity remains. Additionally, user experience is entirely subjective and based on individual evaluation.

Second, each question was asked only once and in a literary style. Since the quality of the input presented to the AI tools directly affects the accuracy of the responses, different answers may be generated for the same question. Furthermore, as the free version of ChatGPT 4.o has question limitations, the system may switch to an older version (ChatGPT 3.5) during the conversation, potentially leading to different responses. Moreover, all AI tools may be updated based on new training data. Given these factors, the results obtained may differ from those of a real conversation.

Third, while the rating system we used has been successfully employed in similar studies, it is a relatively new and evolving scoring system

Finally, all questions in our study were presented in English. As AI-based tools may generate responses that are influenced by linguistic and cultural factors, the generalizability of the findings to other languages and cultural contexts may be limited.

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Dermatology Practical & Conceptual

GRWD1 Drives Melanoma Growth Through NF-κB Signaling Pathway

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Key words: Melanoma, GRWD1, NF-κB, Tumor progression, Signaling pathway

Citation: Turkmen D, Ozbey R, Ozdem B, Alan S, Kilincli Cetin A, Baran FB, Dogan B, Altunisik N, Kanat Z, Sener S, Tekedereli I. GRWD1 Drives Melanoma Growth Through NF-κB Signaling Pathway. *Dermatol Pract Concept*. 2025;15(4):5918.
DOI: https://doi.org/10.5826/dpc.1504a5918

Accepted: July 30, 2025; **Published:** October 2025

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Funding: The study was supported by the Scientific Research Projects Coordination Unit of Inonu University with the project code TCD-2019-2018. This study was approved by Clinical Research Ethics Committee of Inonu University Medical Faculty (2022/121).

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Melanoma is an aggressive skin cancer with high metastatic potential. The oncogenic protein GRWD1 has been implicated in various cancer types, but its role in melanoma remains unclear.

Objectives: To examine the effects of GRWD1 knockdown on melanoma cell proliferation, apoptosis, and migration and to evaluate its prognostic significance in melanoma patients.

Methods: A combination of in vitro and clinical analyses was performed. A2058 melanoma cells were treated with GRWD1-specific siRNA, and cell proliferation, apoptosis, and migration assays were conducted. Western blotting was used to assess alterations in key oncogenic pathways. Additionally, clinical tissue samples from melanoma patients were analyzed for GRWD1 expression, and Kaplan-Meier survival analysis was performed to determine its prognostic value.

Results: GRWD1 was highly expressed in melanoma cells. GRWD1 knockdown significantly reduced cell proliferation (by 63%), impaired colony formation, and induced apoptosis (cleaved caspase-3 levels

increased by 17.3%). Migration capacity decreased by 70%, and NF-κB pathway activity was suppressed, leading to reduced expression of Bcl-2, Src, and MDM2, while stabilizing p53. TCGA-based analyses revealed that high GRWD1 expression was significantly associated with shorter survival in metastatic melanoma cases (P=0.00029) but showed no correlation with melanoma subtypes. However, in immunohistochemical analysis of clinical samples, no statistically significant correlation was found between GRWD1 staining intensity and survival.

Conclusions: GRWD1 plays a crucial role in melanoma progression by enhancing NF-κB activity, promoting proliferation, and suppressing apoptosis. While high GRWD1 expression is associated with poor prognosis in public datasets, further clinical validation with larger patient cohorts is needed to confirm its utility as a prognostic biomarker and therapeutic target.

Introduction

Melanomas are malignant skin tumors originating from melanocytes [1,2]. These tumors can arise in any tissue containing melanocytes, including the skin, mucosa, conjunctiva, uvea, and meninges, with the skin being the most commonly affected site [2]. Although melanomas constitute only 4% of all skin cancers, they account for 75% of skin cancer-related deaths [3]. Since the 1960s, the incidence of malignant melanoma has been increasing globally in both males and females, posing a significant socioeconomic burden [4,5].

In the United States, melanoma ranks as the fifth most common cancer among males and the sixth most common among females [4]. Unlike other solid tumors, it frequently affects younger and middle-aged individuals, with a median age at diagnosis of 57 years [4]. Melanoma pathogenesis is a multifactorial process integrating genetic and environmental factors [3]. Ultraviolet radiation (UVR) from natural or artificial sources is the most significant environmental risk factor. Individuals with lighter skin tones, characterized by lower melanin levels, are more susceptible to sunburns, thus increasing their risk of malignant melanoma. Additionally, a higher number of nevi correlates with an elevated risk of developing melanoma. A family history of malignant melanoma further amplifies this risk, potentially due to shared sun exposure habits or hereditary genetic mutations [3].

Early-stage primary amelanotic melanoma (AM) or melanotic melanoma (MM) is generally associated with a favorable prognosis [6]. However, due to challenging anatomical locations, most AM and MM cases are diagnosed at advanced or metastatic stages, leading to poor prognosis and necessitating systemic therapies, including chemotherapy, targeted therapies, or immunotherapy [6]. The five-year survival rate for stage 4 cases is reported to be between 15 and 20% [7]. This underscores the critical need for novel treatment strategies, particularly for advanced-stage melanoma. A thorough understanding of the molecular underpinnings of the disease is imperative for the development of effective therapeutic interventions.

Ribosomal/nucleolar proteins constitute a diverse family with various biological functions. While some members of this protein family exert tumor-suppressive effects, others promote tumorigenesis by inhibiting the activity of tumor-suppressive ribosomal/nucleolar proteins [8]. The glutamate-rich WD40 repeat-containing 1 (GRWD1) protein, a member of this family, interacts with RPL11, disrupting its association with MDM2, thereby facilitating p53 degradation via ubiquitination [8,9]. This mechanism significantly contributes to cancer progression. These findings suggest that GRWD1 is a multifunctional protein involved in multiple cellular regulatory pathways associated with cell growth control [9].

Recent studies have demonstrated that GRWD1 directly interacts with p53, suppressing its transcriptional activity. Additionally, elevated GRWD1 expression has been correlated with poor prognosis in patients with certain cancer types [9]. These findings support the oncogenic role of GRWD1, suggesting that its suppression may inhibit tumor progression. Nevertheless, further investigations are required to elucidate the precise oncogenic mechanisms of GRWD1 [10].

Objectives

The present study examined the effects of GRWD1 on cellular processes, including proliferation, cell cycle regulation, invasion, and apoptosis, in melanoma cancer cell line. Furthermore, GRWD1 expression was analyzed in melanoma tumor samples obtained from patients, and its association with survival rates, histological subtypes, tumor depth, and disease stage was assessed. Our findings suggest that GRWD1 is a promising therapeutic target and prognostic biomarker in melanoma.

Methods

Cell Line and Reagents

The human melanoma cancer cell line A2058 was commercially acquired from the American Type Culture Collection

(ATCC, USA). GRWD1 siRNA was purchased from Qiagen. The culture medium Dulbecco's Minimal Essential Medium (DMEM high glucose), fetal bovine serum (FBS), antibiotics (penicillin and streptomycin), and L-glutamine (Cat. No: 25030-081, Gibco) were obtained from Gibco (USA) with the following catalog numbers: DMEM (11965084, ThermoFisher, Waltham, MA, USA) and FBS (P2442, Sigma). The MTS Assay Kit for cell proliferation was obtained from Promega (Cat. No. G3582). BCA Protein Assay Kit (Abcam, Cambridge, UK, Cat. No: ab287853) were used.

Cell Culture

A2058 cells were cultured in DMEM high glucose supplemented with 10% FBS, 1% penicillin-streptomycin, and 1% L-glutamine in T25 flasks at 37° C in a humidified environment with 5% CO_2. The culture medium was replaced every 48 hours, and cells were subcultured upon reaching 80% confluency.

Cell Proliferation Assay

GRWD1 knockdown was performed via transient siRNA transfection, and efficiency was confirmed 72 hours post-transfection by Western blotting. The effect of GRWD1 siRNA on tumor cell proliferation was evaluated using the MTS assay (3-(4,5-Dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium). Cells were initially seeded in 25 cm² cell culture flasks and treated with GRWD1 siRNA (75 nM) or control siRNA. After 24 hours of incubation, the cells were harvested and plated into 96-well plates with equal cell distribution per well in 100 µL of growth media. For proliferation assessment, CellTiter 96 Aqueous One Solution Cell Proliferation Assay (Promega kit) was used. 25 µL of MTS labeling reagent was added to each well and incubated in a humidified environment at 37° C for two hours. Absorbance was measured at 490 nm using a microplate reader (E-Max Plus, Molecular Devices, USA).

Colony Formation Assay

To evaluate long-term proliferative capacity, cells were seeded in 6-well plates at a density of 3,000 cells per well. The following day, siRNA transfection was performed. The medium was replaced after 24 hours, and the cells were maintained for seven days. A second siRNA treatment was administered, followed by an additional 7-day incubation period. On day 15, colonies were fixed with methanol (5 min) and stained with 0.5% crystal violet (Sigma-Aldrich) for 10 minutes. Colonies were quantified using ImageJ software.

Flow Cytometric Analysis

Annexin V-PI Apoptosis Analysis

Cells were seeded in 6-well plates at a density of 2×10^5 cells per well and treated with GRWD1 siRNA. After 24 hours, fresh growth media was added to the wells. Following an additional 48 hours of incubation (total 72 hours), cells were collected via trypsinization and centrifugation (1500 rpm, 5 min). Apoptosis was assessed using the Annexin V-PI Apoptosis Detection Kit (BD Biosciences, Cat. No: 556547). Samples were analyzed using a Beckman Coulter CytoFLEX Flow Cytometer (Beckman Coulter, USA) [11].

Cell Cycle Analysis via Propidium Iodide (PI) Staining

To determine the effect of GRWD1 knockdown on the cell cycle, A2058 cells (200,000 per 25 cm² flask) were transfected with GRWD1 siRNA. After 24 hours, fresh growth media was added, and cells were further incubated for an additional 48 hours (total 72 hours). Cells were then harvested and fixed in 70% ethanol at -20° C overnight. The following day, cells were stained with propidium iodide (PI, BioLegend, Cat. No: 421301) and RNase A (100 µg/mL) for 30 minutes at 37° C. The cell cycle phase distribution was analyzed using a Beckman Coulter CytoFLEX Flow Cytometer (Beckman Coulter, USA).

Caspase-3 Activation Assay

Cells were seeded in 6-well plates and transfected with GRWD1 siRNA. After 24 hours, fresh growth media was added, and cells were further incubated for an additional 48 hours (total 72 hours). Cells were then collected via centrifugation (500 × g, 5 min), fixed, and permeabilized using BD Cytofix/Cytoperm buffer at 4° C for 20 minutes. Apoptosis was assessed using the FITC Active Caspase-3 Apoptosis Kit (BD Biosciences, Cat. No: 550480). For caspase-3 detection, cells were stained with FITC-conjugated active caspase-3 antibody in the dark for 30 minutes. Data acquisition was performed using a Beckman Coulter CytoFLEX Flow Cytometer (Beckman Coulter, USA), and 10,000 events per sample were analyzed.

Western Blotting

Western blotting was performed to analyze GRWD1 expression and signaling pathway alterations. This method was carried out as described elsewhere [12]. To confirm knockdown efficiency, GRWD1 band intensities were quantified via densitometric analysis using ImageJ software and normalized to β-actin levels. The relative expression was used to verify the silencing efficiency at the 72-hour post-transfection point. After protein extraction and quantification, samples were separated via SDS-PAGE and transferred onto PVDF membranes. Membranes were incubated overnight at 4°C with primary antibodies against GRWD1 (Biolegend, Cat. No: 645702), Bcl-2 (Elabscience, Cat. No: E-AB-22004), cleaved PARP (Cell Signaling, Cat. No: D214, 19F4), P53 (Biolegend, Cat. No: 645702), p21 (BT LAB, Cat. No: BT-AP12602), MDM2 (Biogend, Cat. No: E-AB-60076), NF-κB p65 (St John's Laboratory, Cat. No: STJ903553-100),

Src (Cell Signaling, Cat. No: 2108S), and β-Actin (Santa Cruz, Cat. No: sc-47778) as a loading control. After washing, membranes were incubated with HRP-conjugated secondary antibodies, including goat anti-rabbit HRP (Cell Signaling Technology, Cat. No: 7074S) and goat anti-mouse HRP (Cell Signaling Technology, Cat. No: 7076S). Protein bands were detected using the ChemiDoc Imaging System, and densitometric analysis was conducted using ImageJ software.

Histopathological Examination

The slides and blocks of the patients included in the histopathological study were evaluated. Appropriate samples were selected, and tissues were re-blocked after being taken from the blocks using the microarray method. Routine H&E staining and immunohistochemical staining with the GRWD1 antibody were applied to the sections obtained from the new blocks. Based on GRWD1 staining intensity, nuclear and cytoplasmic staining intensity was graded as strong (+3), moderate (+2), weak (+1), or negative (0). The medical records of the patients included in the study were thoroughly reviewed. Demographic, clinical, and biopsy data such as age, sex, melanoma type, Breslow score, lesion size, ulceration, localization, mitotic rate, and metastasis were recorded. The relationship between staining intensity and sex, melanoma type, Breslow score, lesion size, ulceration, localization, and metastasis was investigated. Numerical data such as Breslow score, mitotic rate, lesion size, and survival were compared among different groups. Correlation analysis was performed between age, Breslow score, mitotic rate, lesion size, survival, and staining intensity.

Statistical Analysis

In Vitro Analysis

For in vitro experiments (including MTS proliferation assay, Annexin V/PI apoptosis analysis, caspase-3 activation, cell cycle distribution, invasion assay, and Western blot quantifications), data were collected from three independent biological replicates (N=3), each performed under identical conditions. Results are presented as mean ± standard deviation (SD). Comparisons among the three groups (untreated control, non-targeting siRNA, and GRWD1 siRNA) were performed using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison post hoc test to determine statistical significance between specific pairs of groups. A p-value <0.05 was considered statistically significant. Student's t-test was used for colony formation ability. Western blot band intensities were quantified using ImageJ software and normalized to β-actin prior to statistical comparison. Flow cytometry data (Annexin V, Caspase-3, and cell cycle analyses) were collected from at least 10,000 events per sample, and gating strategies were consistently applied across replicates. All statistical analyses were conducted using GraphPad Prism v9.0 (GraphPad Software, San Diego, CA, USA).

Clinical Analysis

Correlations between GRWD1 expression and clinical parameters were analyzed. Qualitative data are summarized as counts and percentages, while quantitative data are presented as minimum and maximum values along with mean ± standard deviation (SD). For the comparison of categorical variables, Pearson's chi-square test and Yates' corrected chi-square test were used. Since the data did not follow a normal distribution, Spearman's correlation test was applied for correlation analysis. A p-value <0.05 was considered statistically significant. Nonparametric tests (Mann Whitney-U test) were used to compare Breslow score, mitotic rate, and lesion size between different groups. Experiments were performed in triplicate (N=3) unless otherwise specified.

This study was approved by Clinical Research Ethics Committee of Inonu University Medical Faculty (2022/121).

The study was supported by the Scientific Research Projects Coordination Unit of Inonu University with the project code TCD-2019-2018.

Results

High GRWD1 Expression is Associated with Reduced Survival Time

Although the relationship between GRWD1 expression and survival is reported to be complex and cancer-type specific, in general, high GRWD1 expression has been linked to poor prognosis and decreased survival time in various cancer types [13]. To determine the relationship between GRWD1 expression and patient survival in melanoma cases, data from The Cancer Genome Atlas (TCGA) database were analyzed. However, TCGA data did not provide datasets that allowed a direct comparison of GRWD1 expression between normal skin and melanoma tumor tissues. Additionally, no significant difference in GRWD1 expression was observed between primary and metastatic tumors (Figure 1A). Nevertheless, survival analysis revealed that high GRWD1 expression in melanoma was significantly associated with reduced patient survival (Figure 1B). When examining primary and metastatic tumors separately, high GRWD1 expression in primary tumors was associated with decreased survival, although this finding was not statistically significant (Figure 1C). In contrast, in metastatic tumors, high GRWD1 expression was significantly correlated with markedly reduced survival (Figure 1D). These findings suggest that GRWD1 expression is associated with aggressive tumor characteristics and poor prognosis in melanoma.

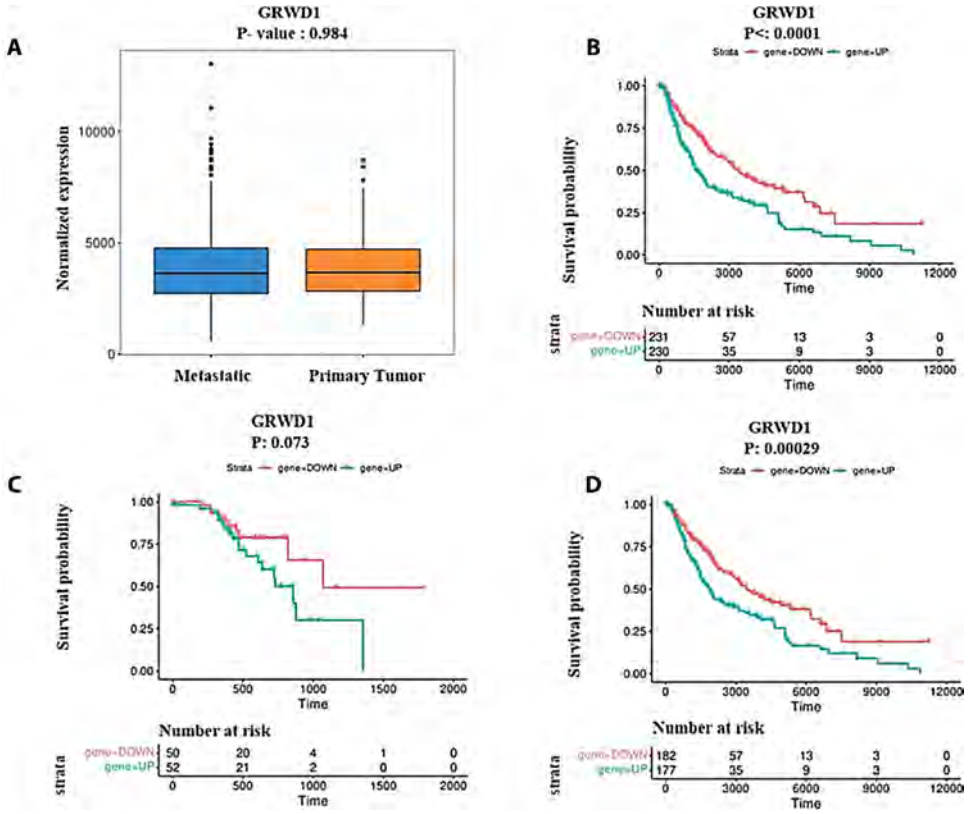


Figure 1. GRWD1 expression and survival analysis in melanoma patients. (A) GRWD1 expression levels in metastatic and primary melanoma tumors based on TCGA data. No significant difference was observed (P=0.984). (B) Kaplan-Meier survival analysis of melanoma patients stratified by GRWD1 expression. High GRWD1 expression correlates with significantly reduced survival (P<0.001). (C) Survival probability analysis for primary melanoma cases based on GRWD1 expression. A trend toward poorer survival in high-GRWD1 cases was observed despite the statistical insignificance (P=0.073). (D) Survival analysis of metastatic melanoma cases. High GRWD1 expression is significantly associated with decreased survival (P<0.001).

GRWD1 is Expressed in Melanoma Cells and Plays a Role in Cell Proliferation

GRWD1 is expressed at higher levels in many cancer cells compared to normal tissues. In breast cancer cells, GRWD1 mRNA and protein levels have been found to be elevated compared to normal human breast epithelial cells [14]. Wang et al. reported that GRWD1 is overexpressed in non-small cell lung cancer (NSCLC) [13]. Since there was no prior study demonstrating GRWD1 expression in melanoma cells, we first confirmed GRWD1 expression in A2058 cells, a highly invasive melanoma cell line (Figure 2A). To test our hypothesis that suppression of GRWD1 expression would reduce melanoma cell proliferation, we used GRWD1-specific siRNA to inhibit GRWD1 expression by 95%. Suppression of GRWD1 expression led to a noticeable decrease in cell viability (Figure 2B). After 72 hours of knockdown, a proliferation assay showed a 63% reduction in cell proliferation in the GRWD1 siRNA-treated group (Figure 2C). This reduction in proliferative capacity was further emphasized by a colony formation assay. Cells treated with 75 nM GRWD1 siRNA were stained after two weeks, and the number of colonies was quantified. The results showed a 74.4% decrease in colony formation ability in treated cells (Figure 2D). Our findings support the conclusion that GRWD1 overexpression promotes cell proliferation.

GRWD1 Knockdown Leads to an Increase in Cell Death

In a study, GRWD1 was found to support cell colony formation by affecting the expression of Cyclin B1, CDK1, and p27 and inducing the G2/M transition [13]. Additionally, research on gastric cancer (GC) demonstrated that GRWD1 overexpression promotes the proliferation, migration, and invasion of gastric cancer cells in vitro [15]. To determine whether the reduction in cell proliferation due to GRWD1 suppression was caused by slowed cell division or increased cell death, cell cycle analysis was first performed using flow cytometry. Cells treated with GRWD1-specific siRNA and control siRNA for 72 hours were stained with PI and analyzed by

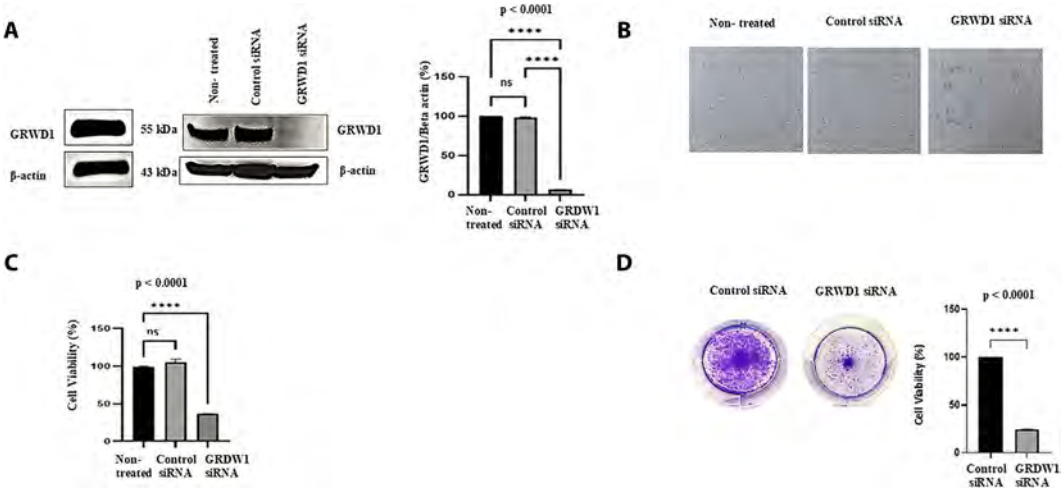


Figure 2. GRWD1 knockdown reduces melanoma cell proliferation and colony formation. (A) Western blot analysis confirming GRWD1 knockdown in A2058 melanoma cells treated with GRWD1 siRNA. (B) Phase-contrast microscopy images showing reduced cell density following GRWD1 knockdown compared to control. (C) MTS assay results demonstrate a significant decrease in cell viability after GRWD1 knockdown (*****P*<0.001). (D) Colony formation assay shows a reduction in the number of colonies formed by GRWD1 siRNA-treated cells. Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test (N=3). Data are shown as mean ± SD.

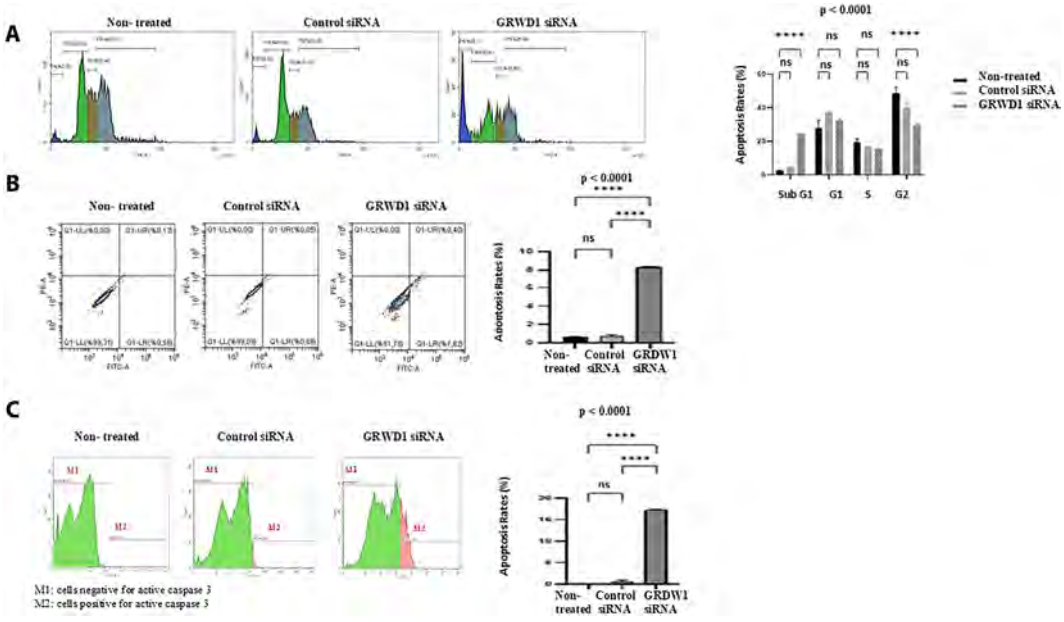


Figure 3. GRWD1 knockdown induces apoptosis in melanoma cells. (A) Flow cytometric analysis of cell cycle distribution. GRWD1 knockdown significantly increases the sub-G1 population, indicating apoptotic cell death (*****P*<0.001). (B) Annexin V-PI staining showing a significant increase in apoptotic cell population following GRWD1 knockdown (*****P*<0.001). (C) Caspase-3 activation assay confirming apoptosis induction in GRWD1 siRNA-treated cells Flow cytometry data represent mean ± SD from three independent experiments. Statistical comparisons were made using one-way ANOVA (Tukey's post hoc test). *****P*<0.0001.

flow cytometry. While no statistically significant change was observed in the number of cells in the G1 and S phases, a decrease in the G2 phase population and a significant increase in the sub-G1 phase cells were detected (Figure 3A). These results suggest that GRWD1 knockdown drives melanoma cells toward apoptosis. This finding was further supported by both Annexin V-PI staining and flow cytometric detection of cleaved caspase-3 levels. In Annexin V-PI staining, the apoptotic cell population increased from 0.91% to 7.82% in the GRWD1 siRNA-treated group (*P*<0.001) (Figure 3B). Additionally, the percentage of cleaved caspase-3-positive cells increased from 0.81% in the control siRNA group

to 17.33% in the GRWD1 siRNA group (P<0.0001) (Figure 3C). These findings indicate that GRWD1 plays a critical role in the survival of melanoma cells. Although these results show that suppression of GRWD1 in vitro stimulated cell death, no significant difference was found in the IHC analyses we performed on pathology samples taken from patients (Figures S1 and S2).

GRWD1 Regulates Cell Migration in Melanoma Cells

A study on non-small cell lung cancer reported that GRWD1 expression enhances the metastatic potential of cells [13]. Another study on triple-negative breast cancer demonstrated that suppression of GRWD1 expression increases apoptosis while reducing cell migration and invasion [14]. GRWD1 overexpression has been shown to be associated with lymph node metastasis in colorectal carcinoma. Suppression of GRWD1 significantly reduced the migration and invasion abilities of colorectal cancer cells in wound healing and transwell assays [16]. A similar study on gastric cancer also obtained comparable results, demonstrating that GRWD1 suppression significantly reduces cell migration and invasion [15]. GRWD1 has been reported to enhance the invasive ability of cancer cells in all these cancer types. To evaluate the invasion capacity of melanoma cells in vitro, we used matrigel-coated Boyden chambers. In A2058 melanoma cells, suppression of GRWD1 expression led to a 70% reduction in invasion capacity (Figure 4A). Our findings indicate that GRWD1 regulates melanoma cell proliferation, apoptosis, and metastasis. As the next step, we performed Western blot analysis to identify the molecular mechanisms underlying these effects. We examined PARP cleavage, a marker of apoptosis, and Bcl-2, a key regulator of apoptosis that is overexpressed in more than half of all cancers. Suppression of GRWD1 expression resulted in an increase in PARP cleavage and a decrease in Bcl-2 expression (Figure 4B). Additionally, we investigated the expression of Src kinase, a key regulator of invasion, and found that its expression was reduced following GRWD1 knockdown (Figure 4C). The relationship between MDM2 and p53 proteins is well known, and previous studies have reported that GRWD1 competes with RPL11 to inhibit MDM2's ability to stabilize p53 [8]. However, in our study, we demonstrate that GRWD1 positively regulates MDM2 expression in melanoma cells. When GRWD1 expression was suppressed via RNA interference (RNAi), MDM2 expression decreased in parallel, and as expected, p53 expression increased (Figure 4C). Furthermore, we analyzed changes in NF-κB expression, a transcription factor known to regulate the expression of Src, Bcl-2, and MDM2 proteins. We show for the first time that GRWD1 knockdown suppresses NF-κB expression (Figure 4C). To determine whether the effects of GRWD1

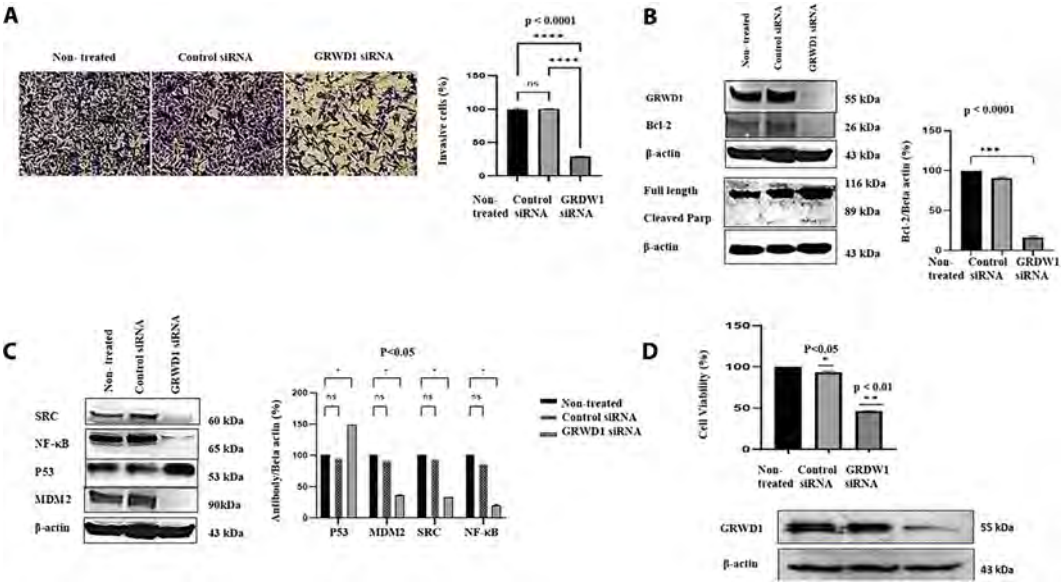


Figure 4. GRWD1 knockdown suppresses invasion and oncogenic signaling in melanoma cells. (A) Matrigel invasion assay shows significantly reduced invasion capacity in GRWD1 siRNA-treated melanoma cells (****P<0.001). (B) Western blot analysis shows reduced Bcl-2 expression and increased cleaved PARP levels in GRWD1 knockdown cells, indicating apoptosis. (C) Western blot analysis of key oncogenic signaling proteins. GRWD1 knockdown leads to decreased NF-κB, Src, and MDM2 expression while increasing p53 levels. (D) Validation of GRWD1 knockdown effects in A2780 ovarian cancer cells. Cell viability is significantly reduced after GRWD1 knockdown (*P<0.05, *P<0.01). Flow cytometry and Western blot data represent mean ± SD from three independent experiments. Statistical comparisons were made using one-way ANOVA (Tukey's post hoc test).

on melanoma cells are cancer-specific, we conducted a proliferation analysis using a second cancer cell line. Suppression of GRWD1 expression in A2780 ovarian cancer cells resulted in a similar inhibitory effect on cell proliferation, demonstrating that GRWD1 plays a critical role in cancer cell growth beyond melanoma (Figure 4D).

No Association was Found between GRWD1 Expression and Melanoma Subtypes

We analyzed the expression of GRWD1 in a cohort of melanoma FFPE tumor samples. Among the 37 patients included in the study, 15 (40.5%) were female, and 22 (59.5%) were male. The mean age was 68.1±14.2 years. Regarding the melanoma subtypes in the examined specimens, 54.1% were nodular melanoma, and 32.4% were acral lentiginous melanoma. Three specimens were from metastatic lesions. The tumor was localized in the extremities in 62.2% of cases, with the second most common localization being the head and neck region (24.3%). Metastasis was observed in 62.2% of the cases. The survival time of deceased patients after diagnosis ranged from one to 39 months, with an average of 13.1±12.7 months. We examined the staining status of melanoma tumor samples with GRWD1 and classified the staining intensity as mild, moderate, or severe (Figure S1). To compare the staining intensity among different subgroups, we divided the staining intensity into two groups as mild/moderate and severe. We could not obtain survival information for some of the patients whose biopsy specimens we examined. Perhaps due to the small sample size, there was no significant difference in survival between the two groups (Figure S2). GRWD1 staining intensity was mild/moderate in 59.5% of patients and severe in 40.5% (Table S1). In the comparison of staining intensity across different groups, severe staining was significantly more frequent in female patients than in male patients (P=0.020). However, no statistically significant difference was observed in staining intensity based on melanoma subtype, lesion size, localization, or metastasis (P>0.05) (Table S2).

Patients with metastasis had a significantly higher mean Breslow score compared to those without metastasis (P=0.029). In nodular melanoma, the mean Breslow score and mitotic rate were significantly higher compared to acral lentiginous melanoma (P=0.034, P=0.012, respectively) (Table S3). Correlation analysis revealed a significant positive relationship between age and Breslow score, mitotic rate, and lesion size. There was also a significant positive correlation between Breslow score and lesion size, while mitotic rate showed a significant negative correlation with both survival and staining intensity (Table S4). We also collected demographic and clinical data of all patients including age, sex, melanoma types, metastasis, localization, and GRWD1 staining intensity in a separate table (Table S5).

Discussion

GRWD1 is a multifunctional protein that has been implicated in various cellular processes, including ribosome biogenesis, DNA damage response, and chromatin remodeling. The regulation of protein expression via the suppression of GRWD1 gene led to a reduction in NF-κB expression. NF-κB, recognized as a transcription factor that orchestrates various cellular functions including immune response, inflammation, and cell viability, is extensively reported in scholarly literature for its role in modulating the expression of numerous proteins such as Bcl-2, Src, and MDM2. GRWD1 has been previously shown to participate in both ribosome biogenesis and chromatin remodeling processes through interactions with RPL11, WDR5, and other regulatory proteins [13,17,18]. In our study, we observed that GRWD1 knockdown led to a reduction in NF-κB protein levels. However, we did not assess NF-κB mRNA expression. Therefore, while our data support a link between GRWD1 and NF-κB activity, the underlying mechanism remains unclear.

Based on the existing literature, we propose that GRWD1 may influence NF-κB at the translational or chromatin remodeling level, although this remains speculative and was not directly tested in our study.

Our data demonstrate that GRWD1 silencing leads to a suppression of NF-κB expression, which likely results in transcriptional downregulation of downstream targets such as Bcl-2, Src, and MDM2. This is supported by the observed decrease in their protein levels (Figure 4C), consistent with NF-κB's known role as a transcriptional activator. Nevertheless, post-transcriptional regulatory mechanisms may also contribute to this downregulation, as GRWD1 is known to regulate ribosome biogenesis and mRNA translation processes. This action is also supported by Kayama et al. [19], who reported that elevated expression levels of GRWD1 were associated with SKCM as well as with certain other malignancies with unfavorable prognosis. The decrease in MDM2 expression upon GRWD1 knockdown, which results in the stabilization of p53, emphasizes the significance of this pathway in melanoma. Earlier studies have indicated that GRWD1 binds with ribosomal proteins to control translational mechanisms and promote protein synthesis in neoplastic cells [13]. These observations are a direct association between GRWD1 and tumor growth via the MDM2-p53 pathway. Deng et al.'s research confirmed that the long non-coding RNA (lncRNA) PiHL forms an interaction with GRWD1 and RPL11 that degrades p53 [20]. The mechanism by which GRWD1 facilitates cancer development through inhibition of the tumor suppressor p53 is further upheld by our data, which demonstrate that repression of GRWD1 caused stabilization of p53 and the activation of apoptotic pathways (Figure 4C).

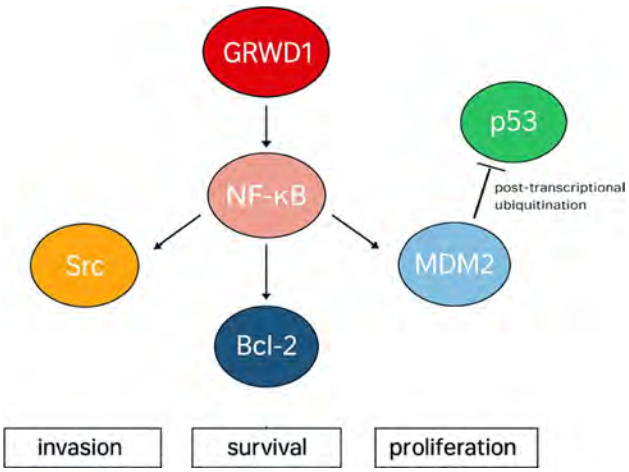


Figure 5. GRWD1 promotes the ability of proliferation, survival and invasion in melanoma cells through the activation of NF-κB pathway. Proposed mechanism underlying GRWD1-mediated melanoma progression. GRWD1 enhances NF-κB signaling, which transcriptionally upregulates Bcl-2 and activates Src. NF-κB also induces MDM2 expression, promoting p53 degradation. The downregulation of p53 relieves transcriptional repression of Bcl-2, further supporting cell survival and proliferation. This GRWD1–NF-κB–MDM2/p53–Bcl-2 axis contributes to melanoma pathogenesis. Arrows represent activation (solid) and inhibition (dashed).

Regarding its role in a variety of malignancies, Zhou and Shang [16] concluded that GRWD1 overexpression is linked to poor clinical outcomes in colorectal cancer. In contrast, in our immunohistochemical analyses conducted with clinical data, the lack of statistical significance in the relationship between GRWD1 expression and survival is likely due to the limited sample size in our local cohort. Therefore, while TCGA data suggest GRWD1 may serve as a potential prognostic marker, further validation in larger, independent patient cohorts is required to confirm its clinical relevance and accuracy. We acknowledge the limitations of our current sample and emphasize the need for future studies with greater statistical power.

Conclusion

Our results suggest that GRWD1 supports melanoma progression through the NF-κB pathway regulating MDM2-p53, Src, Bcl-2 expressions (Figure 5). Therefore, targeting GRWD1 holds promise for melanoma treatment. However, tumor-specific targeting strategies, in vivo studies, and clinical validation are required to confirm its therapeutic potential.

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Supplementary File

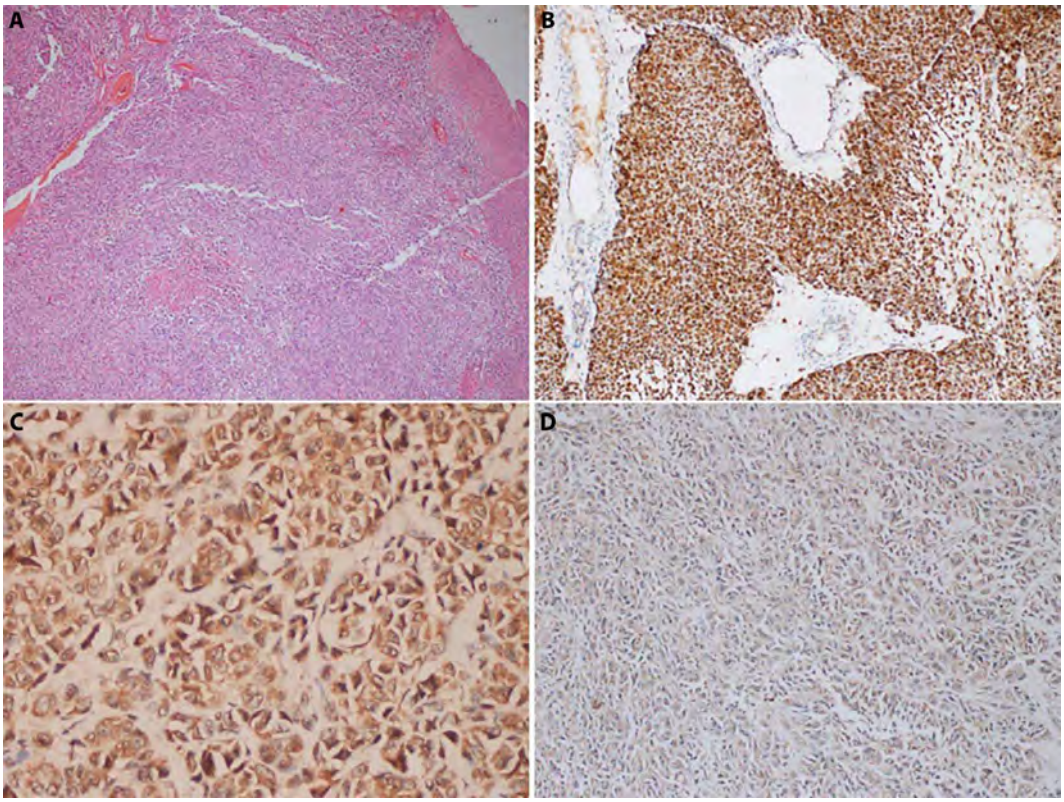


Figure S1. Nodular malignant melanoma. (A) Nodular malignant melanoma, H&Ex40. (B) Strong nuclear-cytoplasmic expression, GRWD1x100. (C) Moderate nuclear-cytoplasmic expression, GRWD1x200. (D) Weak nuclear-cytoplasmic expression, GRWD1x100.

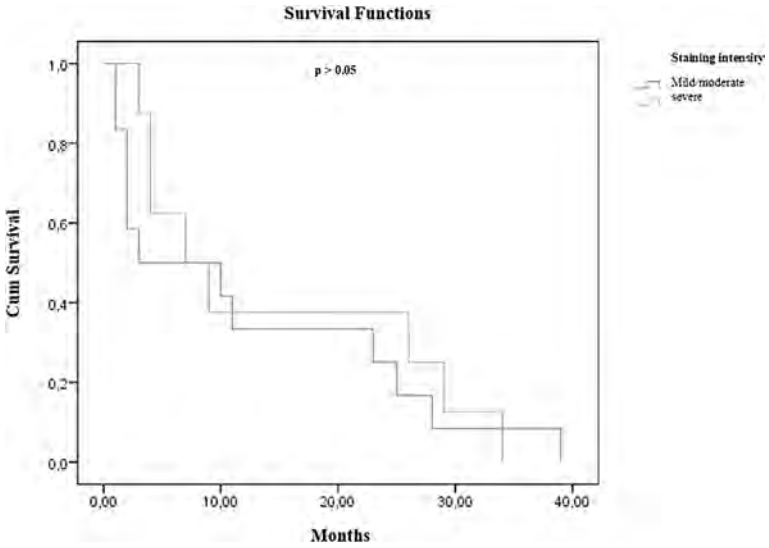


Figure S2. Kaplan-Meier survival curves for patients stratified by GRWD1 staining intensity. Patients were divided into two groups: mild/moderate (blue line) and severe (green line) staining intensity. No statistically significant difference was observed in survival between the two groups (P>0.05).

Table S1. Demographic Data.

	Min-max	Mean ±SD
Age (year)	39-100	68.1±14.2
Breslow score (mm)	0.8-52	11.5±11.4
Mitotic rate (in 1 mm^2)	2-38	9.8±7.7
Lesion size (mm)	5-64	26.1±16.0
Survival (Months)	1-39	13.1±12.7
	Subgroup	**n (%)**
Sex	Female	15 (40.5)
	Male	22 (59.5)
Type	Nodular	20 (54.1)
	Acral lentiginious	12 (32.4)
	Superficial spreading	1 (2.7)
	Lentigo	1 (2.7)
	Metastase	3 (8.1)
Breslow score	≤4 mm	10 (29.7)
	>4 mm	26 (70.3)
Lesion size	≤30 mm	21 (60)
	>30 mm	14 (40)
Ulceration	Yes	21 (56.8)
	No	16 (43.2)
Localization	Head-neck	9 (24.3)
	Trunk	3 (8.1)
	Extremity	23 (62.2)
	Genital	2 (5.4)
Metastasis	N/A	5 (13.5)
	Yes	23 (62.2)
	No	9 (24.3)
Staining intensity	Mild/ Moderate	22 (59.5)
	Severe	15 (40.5)

N/A: data not available; SD. standard deviation.

Table S2. The Relationship between Staining Intensity and Sex, Melanoma Type, Breslow Score, Lesion Size, Ulceration, Localization, and Metastasis.

		Staining		
		Mild/Moderate	Severe	P values
Sex	Female	5 (33.3)	10 (66.7)	**0.020**[a]
	Male	17 (77.3)	5 (22.7)	
Type	Nodular	14 (70)	6 (30)	0.70[b]
	Acral lentiginious	7 (58.3)	5 (41.7)	
Breslow score	≤4 mm	5 (50)	5 (50)	0.70[b]
	>4 mm	16 (61.5)	10 (38.5)	
Lesion size	≤30 mm	13 (61.9)	8 (38.1)	0.72[a]
	>30 mm	7 (50)	7 (50)	
Ulceration	Yes	15 (71.4)	6 (28.6)	0.17[a]
	No	7 (43.7)	9 (56.3)	
Localisation	Head-neck	7 (77.8)	2 (22.2)	0.24[b]
	Extremity	12 (52.2)	11 (47.8)	
Metastasis	Yes	14 (60.9)	9 (39.1)	1.0[b]
	No	5 (55.6)	4 (44.4)	

Note: Bold values are statistically significant values ($P<0.05$).
[a]Chi-squared test.
[b]Fisher's Exact Test.

Table S3. Comparison of Measurable Values by Sex, Localization, Melanoma Type, and Metastasis.

		Breslow score (mm) Mean±SD	Mitotic rate Mean±SD	Lesion size (mm) Mean±SD
Sex	Female	13.4±16.5	9.6±9.1	28.8±19.5
	Male	10.3±6.2	9.9±6.8	24.4±13.4
	P*	0.41	0.54	0.66
Localisation	Head-neck	9.0±6.7	10.5±5.6	23.2±10.8
	Extremity	13.0±13.2	8.8±8.0	26.0±16.5
	P*	0.62	0.19	0.94
Type	Nodular	13.4±10.3	11.5±6.9	27.0±14.6
	Acral lentiginious	6.6±4.3	6.1±3.3	21.9±17.3
	P*	**0.034**	**0.012**	0.21
Metastasis	Yes	14.5±13.2	10.4±8.7	29.3±17.6
	No	5.7±3.6	8.2±5.2	17.7±8.9
	P*	**0.029**	0.70	0.09

Note: Bold values are statistically significant values ($P<0.05$).
*Mann-Whitney U test.

Table S4. Correlation Analysis (Spearman) of Numeric Data.

		Age	Breslow	Mitotic rate	Lesion size	Survival	Staining intensity
Age	Spearman r	1					
	p	.					
	n	37					
Breslow	Spearman r	0.387*	1				
	p	**0.022**	.				
	n	35	35				
Mitotic rate	Spearman r	0.547**	0.330	1			
	p	**<0.001**	0.053	.			
	n	37	35	37			
Lesion size	Spearman r	0.362*	0.674**	0.292	1		
	p	**0.033**	**<0.001**	0.089	.		
	n	35	34	35	35		
Survival	Spearman r	-0.413	-0.206	-0.537*	-0.084	1	
	p	0.071	0.412	**0.015**	0.732	.	
	n	20	18	20	19	20	
Staining intensity	Spearman r	-0.289	0.006	-0.535**	0.103	0.240	1
	p	0.083	0.974	**0.001**	0.556	0.309	.
	n	37	35	37	35	20	37

Note: Bold values are statistically significant values ($P<0.05$).
*$P<0.05$; **$P<0.01$.

Table S5. Patient Demographic and Clinical Data.

Patient numbers	Age	Sex	Melanoma type	Metastasis	Localisation	GRWD1 staining intensity
1	56	M	AL	Yes	Extremity	3
2	55	F	AL	Yes	Extremity	3
3	78	M	Nodular	Yes	Head-neck	2
4	82	M	Nodular	N/A	Extremity	2
5	70	M	AL	Yes	Extremity	2
6	60	M	Nodular	Yes	Extremity	3
7	77	M	Nodular	No	Head-neck	3
8	39	F	AL	No	Extremity	3
9	80	M	Nodular	Yes	Head-neck	1
10	63	M	AL	Yes	Extremity	3
11	58	M	Nodular	Yes	Extremity	1
12	89	M	Nodular	Yes	Trunk	2
13	46	F	Nodular	No	Head-neck	2
14	86	M	Nodular	Yes	Genital	2
15	69	M	Nodular	Yes	Trunk	2
16	84	M	AL	Yes	Extremity	2
17	83	M	AL	Yes	Extremity	2
18	77	F	Nodular	Yes	Extremity	3
19	55	F	AL	Yes	Extremity	2
20	58	F	SS	N/A	Extremity	3
21	48	M	Nodular	N/A	Extremity	2
22	80	M	Nodular	Yes	Extremity	3
23	50	F	AL	No	Extremity	3
24	57	M	AL	No	Extremity	2
25	62	F	Nodular	No	Trunk	3
26	80	M	Nodular	Yes	Extremity	2
27	73	F	Metastasis	Yes	Extremity	3
28	62	M	Metastasis	Yes	Head-neck	1
29	79	F	Nodular	N/A	Head-neck	2
30	72	M	Nodular	No	Extremity	2
31	74	F	Nodular	Yes	Genital	3
32	61	M	Nodular	No	Head-neck	2
33	85	M	AL	No	Extremity	2
34	48	F	AL	Yes	Extremity	2
35	72	F	LMM	N/A	Head-neck	3
36	54	F	Metastasis	Yes	Extremity	3
37	100	F	Nodular	Yes	Head-neck	2

Abbreviations: M, male; F, female; AL, Acral lentiginous; SS, superficial spreading; LMM, lentigo malignant melanoma; N/A, not applicable; GRWD1, glutamate-rich WD40 repeat-containing 1; GRWD1 staining intensity (1: mild, 2: moderate, 3: severe).

Dermatology Practical & Conceptual

Ultraviolet-Induced Fluorescence and Sub-Ultraviolet Reflectance Dermatoscopy of Grover's Disease (Transient Acantholytic Dermatosis): A Retrospective Single-Center Cohort Study

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Key words: Dermoscopy, Skin imaging, Grover's disease, Ultraviolet, Skin cancer

Citation: Pietkiewicz P, Navarrete-Dechent C, Adhikari A, et al. Ultraviolet-Induced Fluorescence and Sub-Ultraviolet Reflectance Dermatoscopy of Grover's Disease (Transient Acantholytic Dermatosis): a Retrospective Single-Center Cohort Study. *Dermatol Pract Concept*. 2025;15(4):5980. DOI: https://doi.org/10.5826/dpc.1504a5980

Accepted: July 30, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Grover's disease (GD) is a rare acantholytic skin disorder typically characterized by pruritic vesicular or keratotic truncal papules, most commonly affecting older Caucasian males. Ultraviolet-induced fluorescence dermatoscopy (UVFD) and sub-ultraviolet reflectance dermatoscopy (sUVRD) are novel imaging techniques with potential diagnostic value in dermatology.

Objectives: The objective of this study was to evaluate the dermatoscopic patterns of GD using UVFD and sUVRD techniques.

Methods: A retrospective observational single-center cohort study was conducted including consecutive adult patients diagnosed with GD. Dermatoscopic images were obtained using a Dermlite DL5 dermatoscope paired with a smartphone for UVFD and a Casio DZ-D100 Dermocamera for sUVRD.

Results: Among the 23 investigated patients (15 females, 8 males; mean age 49.13 years), UVFD images frequently showed central polygonal bright scales with a greenish background. sUVRD images demonstrated hyporeflective polygonal scales, hyperreflective halos, and vascular patterns at the periphery. sUVRD was superior to UVFD and CD in the detection of semi-specific polygonal scales in GD. Eccrine duct involvement was observed in 76.31% of sUVRD images and 57.89% of matching conventional polarized dermatoscopy images. Contrary to the existing literature, female patients represented a higher percentage of the cohort. Twelve GD patients (52.2%) had a personal history of skin cancer.

Conclusion: UVFD and sUVRD effectively characterized the unique features of GD lesions. Our findings suggest that GD may affect younger individuals and females more frequently than previously reported, potentially indicating underdiagnosis in this population. Incorporating dermatoscopy into routine examinations may improve the detection and management of GD.

Introduction

Grover's disease (GD), also known as transient acantholytic dermatosis, was first described by the American dermatologist Ralph Weir Grover in 1970 [1]. This rare acantholytic disorder manifests as moderately pruritic vesicular or keratotic papules [2]. In its classic form, the lesions are distributed over the trunk, mainly the chest, whereas extensive variants affect additional skin sites [3]. Despite being termed "transient", GD may last from weeks to years, with a tendency to seasonal, periodic recurrence. It is more common in males (2.4:1 M/F ratio) of Caucasian origin, and the mean age at onset of GD is 61 years [4]. It has been speculated that GD involves acrosyringia [4] and is related to an increased risk of malignancy [5].

Dermatoscopy is a noninvasive diagnostic method useful in both neoplastic and general dermatology (non-neoplastic diseases) [6], including GD. Dermatoscopy allows for the visualization of structures invisible to the naked eye and improves diagnostic accuracy when compared to the naked eye examination. GD features quasi-specific clues (shared with Darier's disease) seen with conventional non-contact polarized dermatoscopy (CD), namely central, yellow-to-brown polygonal scale (erosion), surrounded by a whitish halo, further outlined with a pinkish area [7,8] (Figure 1A-F). Ultraviolet-induced fluorescence dermatoscopy (UVFD) and sub-ultraviolet reflectance dermatoscopy (sUVRD) are two novel dermatoscopy modes that are commercially available [8]. The former utilizes ultraviolet (365nm)-excited fluorescence of the fluorophores [9,10], whereas the latter is based on reflectance and absorption of purple light (405nm) in the skin [8]. To date, little is known about UVFD and sUVRD features of GD in the literature.

In the present study, we sought to explore the demographic data in GD patients, evaluate the dermatoscopic patterns of GD using UVFD and sUVRD techniques, and compare them to the polarized dermatoscopy findings (Figure 2A-D).

Materials and Methods

In this retrospective single-center cohort study, performed between January 2023 and December 2024 in Poznań, Poland, we explored the patterns of UVFD/sUVRD in consecutive cases of pathology-confirmed GD in adults. Exclusion criteria consisted of other overlapping dermatoses of similar presentation and any treatment or cosmetic application six weeks before the examination. A Dermlite DL5 dermatoscope (Dermlite, San Juan Capistrano, CA, USA) paired with a smartphone camera was used for UVFD image acquisition. A Casio DZ-D100 Dermocamera (Casio, Tokyo, Japan) was used to obtain sUVRD photographs. Both devices were used to collect clinical and CD photographs as a part of routine examinations. For UVFD we assessed the presence of polygonal scales (bright or dark) and greenish background, whereas in sUVRD we assessed the presence of hyporeflective polygonal scale, hyperreflective halo, hyperreflective eccrine microcircles, and vascular pattern at the periphery (dots, lines looped distributed radially, or none). CD evaluation included the presence of central polygonal scale, white intermediate area, peripheral pink area, eccrine microcircles, and vessels (dots, lines looped distributed radially, or none). All images used for the quantitative study remained unprocessed. All evaluations were performed by two investigators; a third investigator served as a referee and resolved discrepancies.

Statistical Analysis

Differences in the visibility of clues between CD, UVFD, and sUVRD were statistically assessed with z-test, whereas comparisons in visibility of acrosyringial involvement between

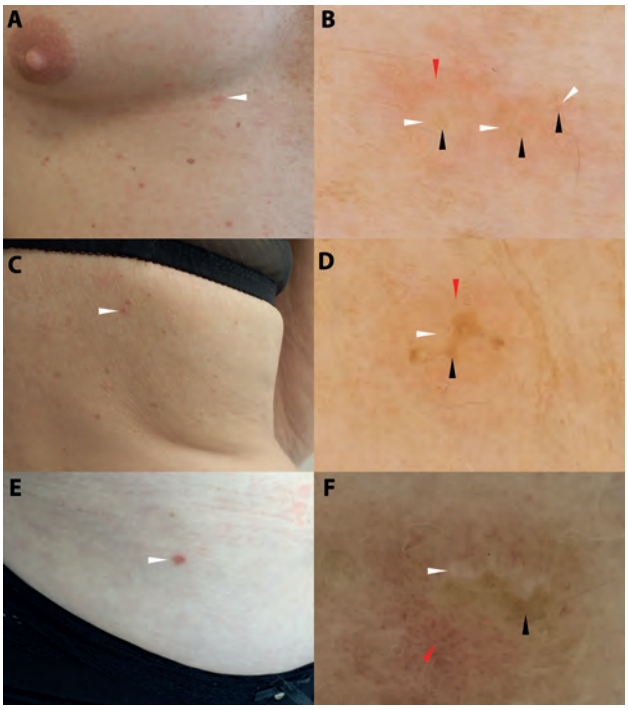


Figure 1. Presentation of Grover's disease in an atypical setting: (A) Grouped papules located on a chest of a 38-year-old male (white arrowhead); (B) Contact polarized dermatoscopy displaying yellow polygonal serous crusts (black arrowheads) surrounded by white outlines (white arrowheads), located over a common pink area (red arrowhead) (Casio DZ-D100 Dermocamera, original magnification 20×); (C) Multiple disseminated papules on a back of a 70-year old female (Casio DZ-D100 Dermocamera, original magnification 20x); (D) Polygonal brown-orange crust (black arrowhead) surrounded by white zone of acanthosis (white arrowhead), located over a pink area (red arrowhead) (Casio DZ-D100 Dermocamera, original magnification 80×); (E) Solitary lesion on abdomen of a 45-year-old female (white arrowhead); (F) Polygonal brownish crust (black arrowhead) surrounded by white outline of acanthosis over a pink area (red arrowhead) (DL5 paired with iPhone 6, original magnification 10×) (Figure © Paweł Pietkiewicz).

matching cases imaged with CD and sUVRD were assessed with McNemar's test. Relations between the number of lesions (≤3 for solitary, >3 for multiple), presence of symptoms, sex (M/F), and age (<60 years, ≥60 years) were assessed with chi-squared tests. Statistical analysis was performed using Python v3.11.4 (SciPy v1.11.4, Seaborn v0.13.2). *P*-values <0.05 were considered statistically significant for all tests.

The study was approved by the Scientific Ethics Committee for Health Sciences of Pontificia Universidad Católica de Chile (Approval #211213001). The informed consent to publication form was signed by the patients whose images were included in this study. The data underlying this article are available at Harvard Dataverse at https://doi.org/10.7910/DVN/S9KOMP. The manuscript was prepared in alignment with the STROBE guidelines.

Results

A total of 2,484 medical records from a single private dermatology clinic were evaluated to identify unique GD patients. There were 980 first-visit patients, 1,400 returning visits, and 104 prescription visits. We included 23 unique patients with GD (fifteen females, eight males; mean age 49.13 years, min. 27, max. 81 years), corresponding to 0.11% first-time visits (Table 1). Multiple lesions (>3) were present in 62.5% of male vs. 46.47% of female patients, yet the differences between sexes were not statistically significant (chi-squared test; *P*=0.775). Although all patients ≥60 years and only 42.11% of patients <60 years had multiple lesions, this trend did not prove to be statistically significant (chi-squared test; *P*=0.12). A total of 60 lesions were photographed as part of the routine examination (mean, 2.68 images per patient;

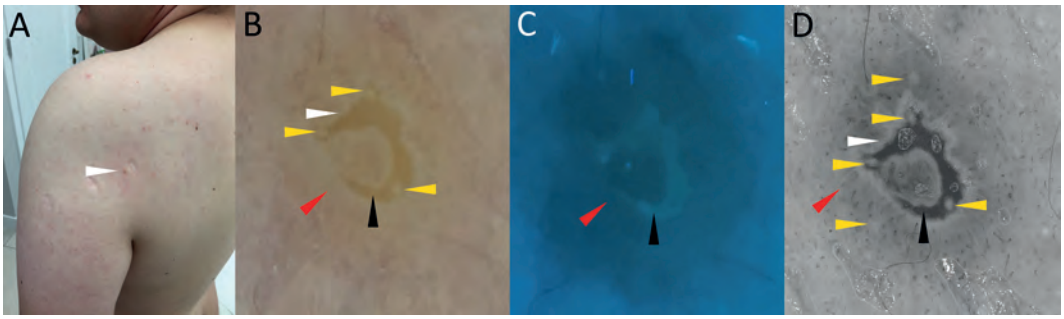


Figure 2. Dermatoscopic presentation of solitary Grover's disease lesion in a renal transplant patient: (A) Clinical presentation of an isolated papule on a left shoulder (white arrowhead); (B) Contact polarized dermatoscopy displaying yellow polygonal serous crust (black arrowhead) surrounded by white outline (red arrowhead) over a pink area (red arrowhead). Note the white clods of eccrine duct ostia (yellow arrowheads) (DL5 paired with iPhone 6, original magnification 10×); (C) Ultraviolet-induced fluorescence dermatoscopy showing central polygonal bright scale (black arrowhead) over greenish background (red arrowhead) (DL5 paired with iPhone 6, original magnification 10×); (D) Sub-ultraviolet reflectance dermatoscopy showing central hyporeflective polygonal scale (black arrowhead) outlined with hyperreflective halo (white arrowhead); Background was marked with red arrowhead (Casio DZ-D100 Dermocamera, original magnification 10×). Radially arranged linear looped vessels and dotted vessels can be seen at the lesion's periphery. Of note, hyperreflective microcircles of eccrine duct openings, both within the erosion and peripheral inflammatory area, remain intact (yellow areas). (Figure © Paweł Pietkiewicz)

Table 1. Demographic and Clinical Data of the Study Group.

Demographics (N=23)	
Parameter	**Value**
Mean Age (years)	49.13
M/F Ratio	0.53
Symptomatic (%)	21.74
Lesion distribution by site (N=60)	n (%)
Chest	40 (66.67)
Abdomen	7 (11.67)
Back	5 (8.33)
Flank	5 (8.33)
Thigh	2 (3.33)
Arm	1 (1.67)

60 non-contact polarized images, 55 UVFD, 40 sUVRD); 21.74% of patients were symptomatic (4/15 females, 1/8 males), yet no statistically significant difference was found between the sexes (chi-squared test; *P*=0.43). Dermatoscopy patterns for all the different light modes are presented in Table 2. sUVRD was superior to UVFD (95.00% vs 76.36%; z-test: *P*=0.0139) and CD (95.00% vs 78.33%; z-test: *P*=0.022) in detecting semi-specific central polygonal scales. There was no significant difference in this aspect when comparing UVFD and CD (z-test: *P*=0.801).

Eccrine duct opening involvement within the central scale or peripheral inflammatory area was detected in 80% sUVRD and 30% of conventional CD dermatoscopy images. When considering only sUVRD images (N=40), pale microcircles of eccrine duct openings were detected in 43.75% matching CD images, making sUVRD superior in this regard (McNemar's test; *P*<0.001).

A total of 12 GD patients (52.2%) had a personal history of concomitant or past skin cancer: basal cell carcinoma (BCC) (30.4%), melanoma (26.1%), and squamous cell carcinoma (SCC) (13.0%). In 13 cases (56.5%), GD was detected during total body dermatoscopy.

Table 2. Ultraviolet-Induced Fluorescence, Sub-Ultraviolet Reflectance, and Conventional Non-Contact Polarized Dermatoscopic Clues of Assessed Lesions of Grover's Disease (N=60).

UVFD (N=55)	
Feature	**N (%)**
Central polygonal bright scale	42 (76.36)
Central polygonal dark scale	1 (1.82)
Greenish background	47 (85.45)
sUVRD (N=40)	
Feature	**N (%)**
Central hyporeflective polygonal scale	38 (95.00)
Hyperreflective halo	33 (82.50)
Hyperreflective eccrine microcircles	32 (80.00)
Vascular pattern (overlap possible)	
Radially distributed linear looped vessels	20 (50.00)
Peripheral dots	14 (35.00)
None	13 (32.50)
Polarized dermoscopy, non-contact (N=60)	
Feature	**N (%)**
Central yellow-to-brown polygonal scale	47 (78.33)
White intermediate area	50 (83.33)
Peripheral pink area	53 (88.33)
Pale eccrine microcircles	18 (30.00)
Vascular pattern (overlap possible)	
Radially distributed linear looped vessels	17 (28.33)
Peripheral dots	22 (36.67)
None	28 (46.67)

Abbreviations: F: female; N: number of cases; M: male; sUVRD: sub-ultraviolet reflectance dermatoscopy; UVFD: ultraviolet-induced flu.

Discussion

GD is an epidermal acantholytic disorder resulting from the loss of cell-cell adhesion due to desmosome instability and aggravated by heat, sweating, or microbial imbalance [11]. Other contributing factors are exposure to ultraviolet radiation, immunosuppression, organ transplantation, HIV, mechanical trauma, hospitalization, prolonged bedrest, renal failure, exposure to honeybee venom, and a number of medications, including cancer therapeutics [3,12-14]. Considered by some to be a rare dermatosis, it typically affects 0.1% of the total population. As the disease can greatly impact the quality of life, a correct and prompt diagnosis is of paramount importance. GD has been reported to predominantly affect males (M/F ratio of 2.4:1), with a peak incidence at 48 to 61 years of age [4,15]. Interestingly, even though the mean age and incidence in our study matched previous reports, females were more commonly affected than males (M/F ratio of 0.53). In the authors' opinion, this discrepancy may be incidental due to a relatively small study group or may originate from the demographic differences between patients attending private and public healthcare, particularly before midday. Female predominance in this particular setting could be explained by the fact that working males are reluctant to seek private health screening [16]. Even though the literature data suggest that the majority of patients with typical presentation are symptomatic [3], only a minority of our patients were aware of the lesions or complained of

pruritus and burning sensation. We speculate that many patients may present with few recurrent oligosymptomatic or asymptomatic lesions, including with extra-truncal involvement, making the disease likely underdiagnosed, neglected, or mistaken for other conditions and thus underreported when based only on naked-eye physical examination. It is also possible that the specific sampling bias–e.g., type of practice (frequent full body checks and using a dermatoscope as a part of routine examination regardless of the cause and higher vigilance)–was responsible for the increased detection of GD. Based on the reported M/F ratio, we speculate that the neglected population may include middle-aged females, and to a lesser extent, middle-aged males. This underrepresentation may result from a mismatch between age group and the male predominance previously reported in the literature, leading clinicians to overlook the disease in these groups. Although future studies are required to investigate these hypotheses, caution concerning oligosymptomatic patients, particularly outside previously reported risk groups, is advised.

Inflammoscopy (dermatoscopy of non-neoplastic dermatoses) is becoming an indispensable part of medical examination in the field of dermatology [17]. There is also greater interest in the description of the dermatoscopic features of non-neoplastic dermatosis. Two novel imaging techniques based on ultraviolet and close-to-ultraviolet light illumination – namely, UVFD and sUVRD – have been introduced over the last five years. Until now, only a single case of GD has been characterized by UVFD. In a review paper on both methods, the authors described a central polygonal bright scale imposed over a darker background seen under UVFD. This finding was confirmed in our study. These structures correspond to serum-induced bluish/greenish excited fluorescence of the serous scale and inflammatory infiltrate, respectively, seen as a yellow-to-brown polygonal scale with a whitish outline and pink background visualized with CD (Figure 1) [8].

On the other hand, sUVRD in the assessed GD cases showed a hyporeflective polygonal scale (likely due to the trace of hemoglobin with a peak absorption at 405 nm) surrounded by a hyperreflective outline of acanthosis and mildly hyperreflective area of inflammation, frequently with a vascular pattern of looped and/or dotted vessels (Figure 1).

There are four main histopathologic patterns of GD: Darier-like (with focal acantholytic dyskeratosis, Figure 3), pemphigus vulgaris-like, or pemphigus foliaceus-like (featuring few acantholytic keratinocytes over suprabasilar clefts), Hailey–Hailey-like (displaying numerous acantholytic keratinocytes over suprabasilar clefts), and spongiotic pattern (with acantholytic keratinocytes within the spongiotic foci) [18]. Other, less common patterns include lentiginous patterns (presenting with papillomatosis with some solar lentigo-like or Dowling-Degos-like basal hyperpigmentation) [19-21], porokeratotic (oblique parakeratotic columns located over areas of agranulosis, occasional dyskeratotic cells in the upper epidermis, and basal vacuolar degeneration) [21,22], epidermolytic hyperkeratosis [21,23-25], vesicular (intraepidermal vesicles with minimal spongiosis or acantholysis on their sides) [23], lichenoid (vacuolar degeneration and scarce interface dermatitis, with occasional dyskeratotic keratinocytes and barely recognizable acantholysis) [23], and dysmaturative (dysmaturated keratinocytes with polymorphic nuclei and slight hyperchromasia) [21,26]. Some authors have previously suggested that GD may begin at or involve acrosyringia [4,14,27–29]. Eccrine duct ostia can be visualized under dermatoscopy and play a role in several skin disorders [30–34]. In our study, pale microcircles of eccrine duct openings were detected either within the central scale or peripheral inflammatory area in the minority of CD images but in the majority of sUVRD images (Figure 1 and Table 2), which could support their role in disease etiopathogenesis. Our observations require further verification in larger studies.

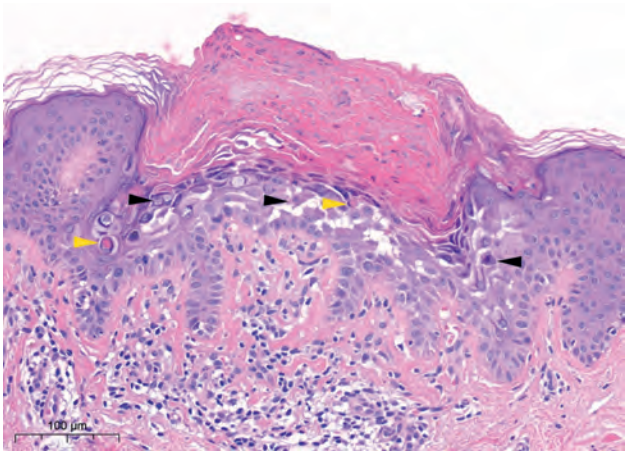


Figure 3. Pathology of Darier-like Grover's disease exhibits suprabasal acantholysis with apoptotic (yellow arrowheads) and dyskeratotic cells (black arrowheads) (H+E routine stain, original magnification 200×).

The relationship between GD and malignancy, including skin cancer, has recently been suggested by some authors [5,15]. In a study on 72 GD patients, 16.67% had a history of skin neoplasm, not otherwise specified [15]. On the other hand, GD may mimic keratinocytic cancers, particularly actinic keratosis/intraepithelial SCC, with actinic keratosis-like morphology (epithelial buds with atypia), nuclear pleomorphism, keratinocyte dysmaturation, and granular layer alteration (large and prominent cells) [26,35] or BCC (trichoblastic proliferation-like areas) [26]. A number of cases and case series describing the link with skin neoplasms have been published to date [36-38]. There are no national registry-based estimations of the skin cancer incidence

among targeted treatment-naive skin cancer GD patients. Among nine such patients reported in the literature, all nine had a history of BCC, three of SCC, and one of melanoma [5,15,37,39]. Cumulative sun damage and immunosuppression may be the main contributing factors to the link between GD and skin cancer.

It is also important to differentiate between "primary" GD developing in skin cancer patients and GD-like reaction caused by skin cancer-targeting drugs, including recombinant human IL-4, immune checkpoint inhibitors, BRAF inhibitors, Hedgehog inhibitors, EGFR inhibitors, or other chemotherapeutics [38,40-49]. Interestingly, a recent national registry-based study from Sweden reported an increased risk of keratinocyte carcinoma (BCCs and SCCs combined, and BCC only) in Darier's disease, which belongs to the same spectrum of acantholytic dermatoses [50]. Although clinically distinct from GD, both entities may feature overlapping dermatoscopic and histopathologic features and share common mechanisms of pathogenesis, including overexpression of yes-associated protein (YAP) [51], which is involved in development of keratinocytic tumors [52,53]. Moreover, gene sequencing of GD lesions identified an acquired mutation of *ATP2A2* [54], a defective gene responsible for Darier's disease [55,56]. In our dataset, 52.2% of GD patients had a history of skin cancer. On the other hand, over a half of our GD cases were detected during total body dermatoscopy, making the results hard to extrapolate to a wider population. Nonetheless, we believe that these findings necessitate further research to better understand the interplay between GD and skin cancer.

The exact mechanism by which keratinocytes detach from each other in GD is probably multifactorial, involving hyperactivated ERK pathway and claudin family of proteins [5,11]. Even though GD is not considered to be an autoimmune blistering dermatosis, desmosome disruption may result in epitope spreading. This mechanism is likely responsible for concomitance of GD and pemphigus foliaceus [57] and of GD and bullous pemphigoid [58]. Desmosomal proteins are involved not only in maintaining cell-cell adhesion but also participate in signal transduction, regulation of expression of proteins, and cell behavior [59-61].

Limitations

Our study has some limitations. For socioeconomic reasons, the results obtained in a setting of Caucasian patients from a single private Central European dermatology practice focusing mainly on skin cancer screening may not be representative of the general population. Fair skin types, higher sun damage, previous history of skin cancer, and/or history of other malignancies may be responsible for increased skin cancer risk in this group. All these factors may have biased the incidence, age at onset, and particularly the M/F ratio in our study group. Despite the high prevalence of skin cancer in our cohort, the study was not designed for this objective and may represent referral bias. No control group was included. Future studies should utilize central registries for the assessment of skin cancer risk in GD patients.

Conclusions

We present CD, UVFD, and sUVRD features in a series of consecutive GD patients. Our findings indicate that GD commonly involves acrosyringia. In some populations, the disease may affect more females and younger patients than previously reported in the literature. Along with the oligo- or asymptomatic course of the disease, these factors may contribute to a lower detection rate. We have demonstrated that sUVRD, but not UVFD, was superior to CD in detecting semi-specific polygonal scales in GD. Including dermatoscopy in general dermatology practice may contribute to optimizing the diagnosis and management of GD patients.

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Dermatology Practical & Conceptual

Clinicopathological Factors Predicting Melanoma Recurrence: A Study From South East Ireland

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Key words: Melanoma, Clinicopathological Predictors ,Recurrence ,Clark Level, Lymphovascular invasion

Citation: Razzaq A, Shahad M, Ditta AA. Clinicopathological factors Predicting Melanoma Recurrence: A Study from South East Ireland. *Dermatol Pract Concept.* 2025;15(4):6006. DOI: https://doi.org/10.5826/dpc.1504a6006

Accepted: October 6, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Cutaneous malignant melanoma is a neoplastic transformation of melanocytes and a major cause of skin cancer–related mortality. Ireland, with its fair-skinned population, continues to see rising incidence rates, highlighting the importance of identifying clinicopathological predictors of recurrence.

Objectives: To assess the relationship between excision margins and melanoma recurrence, with emphasis on anatomical distribution and clinicopathological features.

Methods: This retrospective observational study analyzed 565 patient records from University Hospital Waterford, Ireland, meeting predefined criteria. Data collected included age, sex, primary tumor site, disease stage, Breslow thickness, Clark level, mitotic figures, ulceration, lymphovascular invasion, sentinel lymph node involvement, and adequacy of excision margins. Statistical analysis was conducted using SPSS 26.0.

Results: Significant predictors of recurrence included age ≥65 years, Breslow thickness >4.0 mm, Clark level IV–V, ulceration, lymphovascular invasion (P<0.001), and positive sentinel lymph node biopsy (P=0.004). Inadequate excision margins were also linked to increased recurrence. Conversely, early-stage disease, thin Breslow lesions (≤1.0 mm), and Clark level II were associated with lower recurrence risk.

Conclusions: This study demonstrates a significant association between narrow excision margins and melanoma recurrence, particularly in anatomically complex areas like the head and neck. The findings underscore the importance of individualized surgical planning to ensure oncological safety while preserving function and appearance. Adherence to excision margin guidelines and long-term follow-up are essential, especially in patients with high-risk histological features.

Introduction

Malignant melanomas represent a neoplastic conversion of the neural crest-derived melanocyte [1]. The year 2018 saw malignant melanoma afflicting approximately a third of a million people globally, while 57,000 died as consequence of the disease, with both these numbers expected to double by 2040 [2]. The disease is known to be more common in fair-skinned individuals, and Ireland is no exception. Malignant melanoma is reported to be the fifth most frequently occurring invasive malignancy in the country, with a steadily increasing incidence [3]. This surge is attributed to an increased exposure to ultraviolet radiation whether through the sun or tanning salon exposure [4]. However, other factors have also been implicated and include variables such as immunosuppressive states (drugs, virus, genetic conditions, and neoplastic disease), history of combination therapy with psoralen and ultraviolet A light (PUVA), and a history of the neoplasm in a first-degree relative [5].

Evaluation includes not only establishing the diagnosis but also staging the disease. Using a combination of history/examination, biopsies, and imaging, the managing team has to establish the presence of melanoma and its subtype, the site of the disease, presence of ulceration, the degree of tumor thickness, spread to regional lymph nodes, number of lymph nodes involved, and the presence of distant metastasis, all of which have a direct impact on prognosis [6,7]. The five-year survival rate for stage 1 disease is over 90%, but rapidly drops to 45%–77% and to 27%–70% in those suffering from stage 2 and 3 disease, respectively, while patients with stage 4 disease have a five-year survival rate of below 20% [8].

Management of malignant melanomas centers around wide local excision, with sentinel lymph node biopsy (SLNB) and/or lymph node dissection when the disease is diagnosed at an early stage, while more advanced disease is managed with a combination of surgery and adjuvant treatment or even radiotherapy [9,10]. An essential requirement from successful surgery is the need for margins clear of neoplastic cells on excision [9,10]. We conducted this study with the express purpose of determining the outcomes of management for malignant melanoma in our setup, recurrence, and clinicopathological markers associated with its increased risk.

Methods

We conducted a retrospective study of patients reporting to University Hospital Waterford, Ireland, with melanomas from January 2016 to February 2023. The study sample was based on 565 records extracted from the hospital's database. Data were coded in the Statistical Package for Social Sciences (SPSS) version 26 (Armonk, NY: IBM Corp) and analyzed for accuracy. Partial records were completed using the hospital medical records database. Records that could not be completed were excluded from statistical analysis. An audit team re-verified all histopathology reports for the biopsy of the primary lesion as well as the SLNB, and the data pertaining to total margins with operation notes. Ethical approval was sought and received. Data were analyzed using Statistical Package for the Social Sciences version 26.0. Mean and standard deviation (SD) were calculated for quantitative variables, specifically age, Breslow thickness, and number of mitotic figures per high-power field. Melanoma in situ cases were under-represented in this dataset because the hospital registry records them under dermatopathology follow-up and minor procedure categories. Our study extracted only surgically managed melanomas from the oncology surgery department, so most in situ cases were not captured. Recurrence was defined as any reappearance of melanoma after primary treatment, including local recurrence, regional lymph node recurrence, or distant recurrence.

Qualitative variables like year of diagnosis, sex, site of primary disease, stage of the disease at the time of presentation, degree of Breslow thickness, Clark stage, ulceration, lympho-vascular invasion, whether sentinel lymph node biopsy was done and its results, and whether the melanoma was excised with adequate margins as per the British Association of Dermatologists (BAD) guidelines were recorded in terms of frequency and percentage. The chi-square test was used for qualitative variables, while the independent samples t-test was used for quantitative variables for comparison between cases where recurrence developed or those where it did not, and a p-value of ≤ 0.05 was considered significant. Multivariate analysis was performed using binary logistic regression for variables which were found to be significant on univariate analysis.

Results

A general increase in the number of cases of melanoma was seen over the study period, with the highest number of cases seen in 2018, 2021, and 2022, accounting for 99 (17.3%), 95 (16.6%), and 98 (17.1%) cases, respectively. Details for the distribution of cases over the years is displayed in Figure 1.

The mean age of our study sample was 60.00 ± 18.03 years, with a slight female majority: 292 (51.0%). Of the 565 cases for whom data for site of primary lesion were available, 156 (26.7%) had trunk involvement, the upper and lower limbs were affected in 148 (26.4%) and 147 (26.2%) cases, respectively, while the head and neck were the least frequently affected: 114 cases (20.7%). We recorded the disease stage in the same number of patients (565 patients): 257 (44.7%) were stage T1a, and 45 (7.8%) were stage

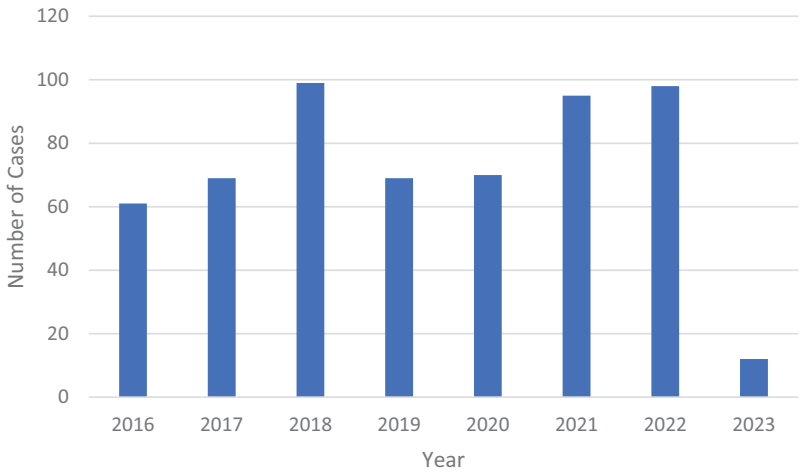


Figure 1. Distribution of cases by year.

T1b, while stages T2a, T2b, T3a, and T3b accounted for 88 (15.5%), 14 (2.7%), 42 (7.2%), and 36 (6.4%), respectively. Advanced disease in the form of stages T4a and T4b were found in 32 (6.0%) and 50 (9.5%) cases, respectively, while in situ disease was found in one (0.2%) case. The distribution of cases on the basis of patient and disease characteristics according to recurrence is displayed in Table 1.

The mean Breslow thickness of the sample was 2.28 ± 3.40 mm. The Clark Level was recorded for 565 patients; only one (0.2) patient had Stage 0 (melanoma in situ). Multiple Stage 1 cases (pT1a= 245, pT1b= 44) were identified, while the bulk of cases were almost evenly distributed across Stages 2, 3, and 4, with 179 (32.0%), 174 (30.9%), and 184(32.4%) cases, respectively. A total of 27 (4.5% of cases) were Stage 5 at presentation. The mean mitotic count per high-power field for the sample was 2.18 ± 3.96 per high-power field. A total of 111 (19.4%) cases had ulceration of the primary lesion at the time of presentation, while 28 (4.9%) had lymph vascular invasion. A sentinel lymph node biopsy was done in 134 (26.9%) cases, of which 47 (35.1%) were positive for malignant cells. Out of the total of 565 patients on whom surgery was performed, 504 (89.4%) had adequate margins according to BAD guidelines, while 61 (10.6%) did not. The distribution of cases on the basis of tumor and management characteristics according to recurrence is displayed in Table 2.

Univariate analysis showed that melanomas on the trunk, Clark Stage of II, Breslow thin lesions (≤1.00 mm), and a tumor stage 1B were all associated with a decreased chance of recurrence, all of which remained significant on multivariate analysis. Univariate analysis also showed that age ≥ 65 years, lesions on lower limb, stages 4A and 4B disease, Breslow thickness of >4.0 mm, Clark Stages 4 and 5, number of mitotic figures ≥1 per high-power field, presence of ulceration, lympho-vascular invasion, positive sentinel lymph node biopsy, and inadequate margins on excision were all associated with an increased chance of recurrence. However, lower limb lesions, tumor stage 4A, a mitotic rate ≥1 per high-power field, and adequate margins on excision lost statistical significance on multivariate analysis.

Discussion

We conducted this retrospective study on patients with melanoma with the aim of determining the association between clinicopathological focus and the development of recurrent disease. Recurrent disease in malignant melanoma is the reappearance of melanoma after it has been treated and appeared to be gone. This can happen at the original location (local recurrence), in nearby lymph nodes (regional recurrence), or in other parts of the body (distant or metastatic recurrence). The probability and location of recurrence are influenced by clinicopathological factors such as the initial stage of the melanoma, the success of the initial treatment, and specific patient characteristics [2]. Identifying patients who are at high risk of recurrence will help the treating clinician to maintain a higher degree of vigilance. Our data analysis showed that there was a steadily increasing trend in the number of cases of melanoma reporting to our institute every year, in keeping with existing data, making the conclusions of our study even more relevant [3,4].

We found that patients aged 65 years or more had a significantly higher frequency of recurrent disease, which was in keeping with other studies such as that by Fleming et al., where older patients were also found to be at an increased risk (Hazard Ration HR 3.34; 95% Confidence interval CI: 1.53–7.25; P<0.01) [11]. Univariate analysis showed that lower limb melanomas were associated with a higher risk of recurrence; however, this association became insignificant on multivariate review in this study, while head and neck lesions

Table 1. Distribution of Patient and Disease Characteristics according to Recurrence with Univariate Analysis.

Recurrence	Yes (N=44)	No (N=521)	p-value
Age (Years)	69.77 ± 15.56	59.21 ± 17.99	<0.001
Age ≥ 65 Years	31 (12.1%)	225 (87.1%)	<0.001
Sex			
Male (N [%])	24 (10.6)	203 (89.4)	0.542
Female (N [%])	20 (8.6)	213 (91.4)	
Site of Primary Lesion			
Trunk (N [%])	6 (5.0)	113 (95.0)	0.007
Upper Limbs (N [%])	8 (6.6)	114 (93.4)	0.258
Lower Limbs (n [%])	19 (15.6)	103 (84.4)	0.007
Head and Neck (N [%])	11 (11.8)	82 (88.2)	0.232
Stage at Presentation			
In Situ Disease	-	1 (100)	0.772
pT1a (N [%])	13 (5.0)	232 (95.0)	0.054
pT1b (N [%])	-	44 (100)	0.045
pT2a (N [%])	7 (8.1)	79 (91.9)	0.887
pT2b (N [%])	-	15 (100)	0.255
pT3a (N [%])	3 (7.3)	38 (92.7)	0.912
pT3b (N [%])	3 (8.3)	33 (91.7)	0.895
pT4a (N [%])	7 (20.6)	27 (79.4)	0.004
pT4b (N [%])	10 (19.2)	42 (80.8)	0.001

Table 2. Distribution of Tumor and Management Characteristics according to Recurrence with Univariate Analysis.

Recurrence	Yes (N=44)	No (N=521)	p-value
Breslow Thickness (mm)	4.13 ± 4.51	2.13 ± 3.27	<0.001
Thin (≤1.00 mm)	13 (4.4)	279 (95.6)	0.002
Intermediate (1.01 – 2.00 mm)	7 (7.1)	92 (92.9)	0.772
Intermediate (2.01 – 4.00 mm)	7 (8.8)	73 (91.2)	0.725
Thick (>4.00 mm)	16 (19.5)	66 (80.5)	<0.001
Clark Level			
Stage I (N [%])	-	1 (100%)	0.772
Stage II (N [%])	7 (4.0%)	168 (96.0%)	0.021
Stage III (N [%])	8 (4.8%)	160 (95.2%)	0.073
Stage IV (N [%])	21 (11.7%)	159 (88.3%)	0.021
Stage V (N [%])	7 (29.2%)	17 (70.8%)	<0.001
Mitotic Rate (Per High-Power Field)	4.55 ± 7.07	2.01 ± 3.56	<0.001
Mitotic Rate ≥ 1	32 (10.9%)	263 (89.1%)	0.004
Ulceration (N [%])	14 (12.8%)	95 (87.2%)	0.061
Lymphovascular Invasion (N [%])	7 (25.0%)	21 (75.0%)	0.002
Positive Sentinel Lymph Node Biopsy	8 (17.0%)	39 (83.0%)	0.007
Adequate Margins according to British Association of Dermatologist (BAD) Guidelines			
Yes	31 (5.8%)	469 (94.2%)	<0.001
No	17(22.8%)	48 (77.2%)	

Table 3. Multivariate Analysis of Significant Factors.

Variable	p-value
Variables with Decreased Risk of Recurrence	
Lesions of Trunk	0.008
Clark Stage II	0.022
Tumor Stage 1B	0.042
Breslow Thin Lesions (≤1.00 mm)	0.002
Variables with Increased Risk of Recurrence	
Age ≥ 65 Years	0.001
Lower Limb Lesions	0.609
Tumor Stage 4A	0.684
Tumor Stage 4B	<0.001
Breslow Thick Lesions (>4.00 mm)	<0.001
Clark Stage IV	0.029
Clark Stage V	0.035
Mitotic Rate ≥ 1	0.224
Ulceration	<0.001
Lymph vascular Invasion	<0.001
Positive Sentinel Lymph Node Biopsy	0.004

did not appear to have any association with an increased risk of recurrence. Previous studies on the subject such as that by von Schuckmann et al. have demonstrated that head and neck lesions are associated with an increased risk of recurrence (HR 1.67; 95% Cl 1.01–2.76; *P*<0.05) [12]. However, it is important to note here that not all studies agree with this result: Lyth et al. demonstrated that the site of lesion, whether head and neck, lower limbs, or any other, was not associated with an increased risk of recurrence [13]. We believe this subject requires further study prior to forming concrete conclusions.

Unsurprisingly, advanced stages of melanoma were associated with a higher rate of recurrence, while the converse was true for earlier stages, in our study. We found that Stage 4B was associated with a statistically significant increase in this risk. Additionally, Stage 1B was associated with good outcomes, while the stages between these two did not appear to have a statistically significant association with recurrence in our sample. Feigelson et al. reported similar results: the more advanced the stage, the higher the risk of recurrence [14]. Von Schumann et al. reported a significant increase in risk of recurrence in stage 4A (HR 1.48; 95% CI: 0.48–4.59; *P*<0.05) and 4B (HR 3.86; 95% Cl: 1.40–10.64; *P*<0.05) [12]. Moreover, Liang et al. noted that cases with a more advanced stage at the time of presentation not only had a higher risk of recurrence but were also at an increased risk of developing recurrence earlier than those patients with earlier stage disease at presentation [15].

A Breslow thickness, a key clinicopathological marker, of ≤1.0 mm was associated with a lower chance of recurrence, while for patients in our study sample with a thickness of >4.0 mm, the converse was true. Oh et al. reported that a Breslow thickness of >1.0 mm was associated with a higher risk of recurrence, (*P*=0.008), adding that there is a variation in male and female sex: a thickness of ≥2.5 mm in males was associated with higher rates of recurrence, while the value for females was>4.0 mm (*P*<0.05) [16]. Reschke et al. also reported a similar relation between thickness and recurrence, with the addition of an increased risk of metastases in patients who had increased thickness [17], as did von Lyth et al., who noted that a Breslow thickness of 2.01 mm to 4.0 mm was associated with a greatly increased risk of recurrence (HR 4.0; 95% CI: 2.1–7.6; *P*<0.05), while a thickness of >4.0 mm carried an even greater risk (HR 6.7; 95% CI: 3.4–13.0; *P*<0.05) [13].

As with tumor stage, early Clark stages were associated with a significantly lower frequency of recurrence versus advanced Clark stages (e.g., for stages 4 and 5), where recurrence was much more common; these conclusions were shared by Tas et al. [18]. Contrariwise, Kim et al. reported that Clark staging did not appear to have a statistically significant association with the development of recurrence; however, this study was conducted on thin melanomas, with the sample predominantly consisting of advanced Clark stage disease cases and a relatively small number of patients, which may have introduced confounding [19].

A mitotic rate of ≥1 per high-power field was not associated with an increased chance of recurrence in our study; using a higher cutoff may have been associated with significant results on multivariate analysis (Table 3). Tas et al. conducted a detailed study on the effect of a high mitotic index in patients with melanoma and found that melanomas with a mitotic count of 0-1/ mm^2 were associated with higher Clark stages at presentation (*P*=0.001), more aggressive tumor stages (*P*=0.003), ulcerated primary lesion (*P*=0.006), lymphovascular disease (*P*=0.0001), metastatic disease (*P*=0.005), and a higher chance of relapse (*P*=0.0001) [20]. Ulceration of the melanoma and lymphovascular invasion at the time of presentation were associated with a higher frequency of recurrence according to our analysis, which is in keeping with existing literature such as that by von Schuckmann et al. [12], Lyth et al. [13], and Kim et al. [19]–a clear indication that such cases need more aggressive management and surveillance.

A limitation of our study is that local, regional and distant recurrences were analyzed together. While these represent biologically distinct events, our retrospective database did not consistently differentiate between them. Future perspective studies should stratify recurrence by type to examine independent predictive factors for local versus metastatic disease.

This study's strength lies in its comparatively large sample size as well as in the confirmation of recurrence on tissue biopsy. Moreover, the data collected were diverse, broad-based, and covered a wide range of variables based on our institute's robust medical record keeping. Our study was limited by its retrospective nature and carries the restrictions inherent in this study design. In addition, as the patient data were collected from a single center which draws its patients from a specific part of the country, the results may not be generalizable to the whole population. Our findings help identify clinicopathological predictors of recurrence which can guide clinicians in tailoring follow-up intensity and surveillance. However, our study did not consider the variation in treatment modalities offered to each patient, which may have resulted in a degree of confounding within our results.

Conclusion

Advancing age, tumor stage, Breslow thickness, Clark stage, ulceration, and lympho-vascular invasion were all identified as significant clinicopathological factors associated with the increased frequency of melanoma recurrence. Future studies should aim to focus to incorporating these variables into a validated scoring system to predict recurrence and overall prognosis at the time of diagnosis. Such a tool should assist clinicians in tailoring surveillance and management strategies to the individual risk profile of each patient.

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Dermatology Practical & Conceptual

Re-evaluation of the Anatomical Distribution Patterns in Large Congenital Melanocytic Nevus

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Key words: Large congenital melanocytic nevus, Clinical classification, Half-bathing trunk, Anatomical distribution, Atypical nevus patterns

Citation: Aydoğdu Ş, Baykal C. Re-evaluation of the Anatomical Distribution Patterns in Large Congenital Melanocytic Nevus. *Dermatol Pract Concept*. 2025;15(4):5113. DOI: https://doi.org/10.5826/dpc.1504a5113

Accepted: July 12, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Large congenital melanocytic nevi (LCMNs) are mainly classified according to their distribution patterns, which are thought to reflect their embryological development.

Objectives: We aimed to test the validity of previously described clinical classification systems of LCMNs in a large, well-documented case series.

Methods: The retrospective cohort study including 111 LCMN patients focused on the anatomical distribution of the nevus's main mass.

Results: The trunk was most commonly affected (N=68), followed by the lower extremities (N=35). When the locations of the nevi were evaluated according to the previously described 6B (bolero, back, bathing trunk, breast/belly, body extremity, body patterns) and 7B (6B with the addition of bonce pattern) classification systems, 15 showed the typical bolero pattern, 13 back pattern, 23 bathing trunk pattern, five breast/belly pattern, 25 body extremity pattern, 14 bonce (head) pattern, and one body pattern. Among the 15 patients who could not be fully classified according to these patterns, five were grouped as "hood" (head and neck) pattern, eight as "half-bathing trunk," and two as "atypical bolero" sub-patterns. Isolated lesions on the extremities also exhibited two different sub-patterns: encircling the extremity or not.

Conclusion: Most of our cases demonstrated distribution patterns consistent with the 6B and 7B classification systems. However, the isolated head and neck involvement observed in our series may be described as hood pattern. Furthermore, certain variations, such as those seen in the bathing trunk and breast/belly patterns, may be considered subgroups of these patterns. Isolated extremity lesions of LCMNs exhibited two distinct patterns. These findings suggest that, although existing classification systems provide a valuable framework, further subclassifications may be necessary to account for regional variations observed in clinical practice.

Introduction

Large congenital melanocytic nevi (LCMNs) are rare neural-crest derived hamartomas that can affect almost every part of the body, with varying frequency [1]. In recent years, numerous studies have attempted to classify LCMNs based on their distribution patterns [2-7] and to correlate these patterns with embryological development [8]. However, most of these studies included a limited number of patients and were based solely on retrospective evaluations of electronic medical records from multiple centers or on clinical images published in the literature [2-5,7]. Therefore, the clinical understanding of this subject may still be incomplete.

Objectives

In this single center study, we evaluated a large cohort of LCMN cases to determine the predominant anatomical regions of nevi (main masses) and their characteristic distribution patterns. Our findings were then compared with the existing literature, including current classification systems for nevus distribution [2,3].

Methods

In this retrospective, cross-sectional study, we evaluated 111 consecutive patients diagnosed with LCMN between 2004 and 2020. Nevi located on the trunk or extremities with a projected adult size of ≥20 cm or on the head exceeding the size of a patient's own palm were included [2-10]. Although various size classification systems for LCMN exist, these criteria were used to ensure consistency across the study cohort [9-18]. Two types of LCMN were distinguished. The classical type presents as a main mass, usually associated with multiple satellite nevi distributed across the body, while the nevus spilus type consists of variable numbers of small-to-large congenital melanocytic nevi (CMN) superimposed on an extensive (>20 cm) café-au-lait-like macula [19]. Patients who had undergone partial or total excision of the LCMN prior to diagnosis were excluded.

Patient demographics were collected, and participants were stratified into pediatric (<18 years) and adult (≥18 years) groups [20]. The body was divided into five main anatomic regions for nevus localization: head, neck, trunk, upper extremities, and lower extremities. These main anatomical regions were further subdivided for detailed evaluation [Table 1]. Anatomical regions affected by the main mass of the nevus (classical LCMN) or café-au-lait-like macula on the base (nevus spilus type LCMN) were determined. The correlation between the regions in the series and well-known LCMN distribution patterns was examined.

IBM SPSS Statistics Version 26 was used to store and analyze the data. Descriptive statistics were calculated as median, minimum, and maximum values for continuous variables and as frequency and percentage for categorical variables. The study was approved by the ethics committee of the university faculty (approval number: 2020/06) and conducted in accordance with the Declaration of Helsinki.

Results

The study included 111 patients (44 males; 39.6%, 67 females; 60.4%), with a mean age at admission of 15.2 + 11.8 years (median: 12, range 0–61 years); 80 were pediatric patients and 31 were adults. Classical LCMN was observed in 106 patients (95.5%), while nevus spilus-type LCMN was seen in five (4.5%) [Figure 1A].

The main mass of the nevus was most commonly located on the trunk (N=68), followed by the lower extremities, upper extremities, head, and neck [Table 1]. While 66 patients (59%) had involvement of a single anatomical region, 45 patients (41%) had nevi affecting multiple regions. The frequency of involvement of each anatomical region by the nevus mass is summarized in Table 1.

The classification of the patients according to the previously defined anatomical distribution patterns of LCMN [2-3] revealed the following frequencies: bathing trunk (N=23) [Figure 1B], body extremity (N=25) [Figure 1C], bonce (N=14) [Figure 1D], back (N=13) [Figure 1E], bolero (N=15) [Figure 1F], breast/belly (N=5) [Figure 2A], and body (N=1) [Table 2]. The remaining 15 patients did not fully conform to previously defined clinical patterns. Ten of these cases were considered as special clinical variants (subgroups) of the bathing trunk and bolero patterns. Nevi involving only the upper part of gluteal region, upper part of the gluteal region and lower back together [Figure 2B], or unilateral iliac region with or without extension to the genital area, gluteal folds, or upper legs [Figure 2C and D] were observed in eight patients and were considered a clinical subgroup of the well-known bathing trunk pattern. The nevi of two patients with anterior trunk involvement extending partially to the back were categorized as atypical bolero pattern due to the absence of neck involvement [Figures 2E and F]. The other five patients had LCMNs limited to the scalp and neck, resembling a distinct pattern called "hood," which has not been previously described as a specific distribution pattern in existing classification systems [Figure 3A].

Among the 25 cases with isolated upper and lower extremity nevi, two previously undescribed distribution patterns were identified: in 11 cases, the nevus encircled the extremity [Figure 1C], whereas in 14 cases, it did not [Figures 3B and C].

Table 1. Frequency of involvement of the anatomical regions by the nevus's main mass in the patients. Abbreviation: LCMN: Large Congenital Melanocytic Nevus.

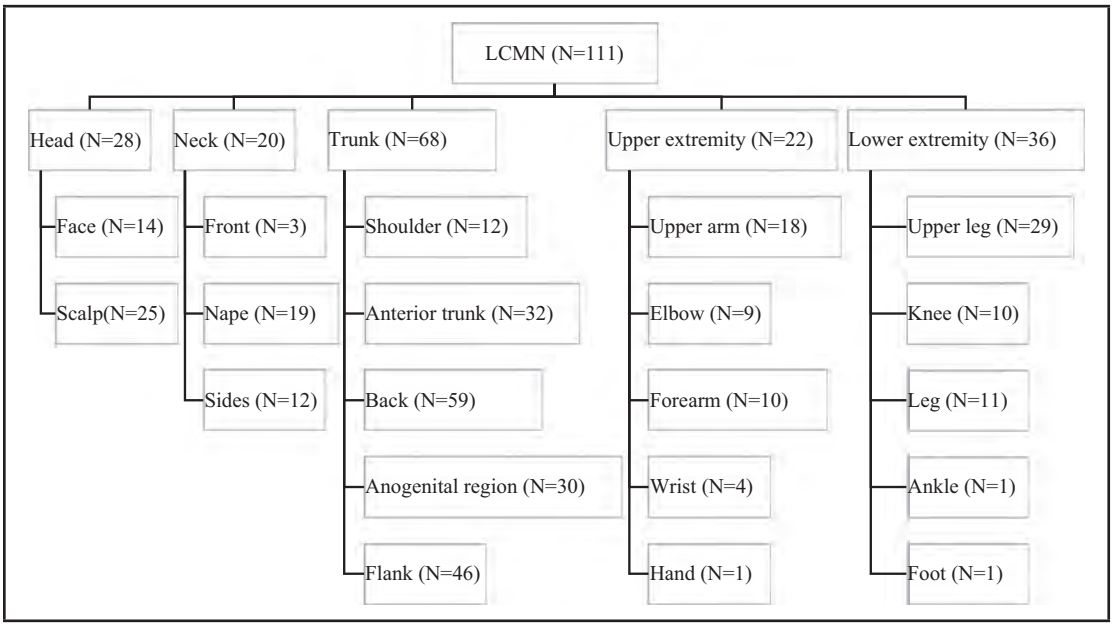




Figure 1. (A) Nevus spilus-like large congenital melanocytic nevus on the lower trunk. (B) Symmetrical large congenital melanocytic nevus on upper legs, genitalia and lower trunk representing classical bathing trunk pattern. (C) Large congenital melanocytic nevus encircling a large part of the arm, representing body extremity pattern. (D) Large congenital melanocytic nevus on the scalp and face. (E) Large congenital melanocytic nevus on the back, representing back pattern. (F) Large congenital melanocytic nevus on the upper back and neck, representing classical bolero pattern.

Among the 28 patients with head involvement, 14 had isolated lesions, and 14 exhibited extension of the main mass to additional body areas. Of the patients with head involvement (regardless of extension to other regions), two presented with isolated facial lesions [Figure 3D], 14 had isolated scalp lesions [Figure 3E], and 12 showed combined scalp and facial involvement [Figures 1D and 3F]. Among the 14 patients with involvement of other body areas along with the head [Figure 1F], four had both scalp and facial involvement, while 10 had only scalp lesions. Of the 14 patients with LCMN limited to the head region [Figures 3D–F], four had only scalp lesions, two had only facial lesions, and eight had both scalp and facial involvement. Among the 20 patients with neck involvement, five had extension to the

Table 2. Classification of the patients based on the specific location patterns of the nevus' main mass.

Location pattern of nevus' main mass	Case number	Proportion (%)
Breast/belly	5	4.5%
Back	13	11.7%
Bathing trunk	31	27.9%
Classical bathing trunk	23	
Half-bathing trunk*	8	
Bolero	17	15.3%
Classical bolero	15	
Atypical bolero*	2	
Body extremity	25	22.6%
Encircling the extremity*	11	
Not encircling the extremity*	14	
Body	1	0.9%
Head (bonce)*	14	12.6%
Hood*	5	4.5%

*Patterns or subgroups not described in 6B and 7B clinical classifications.

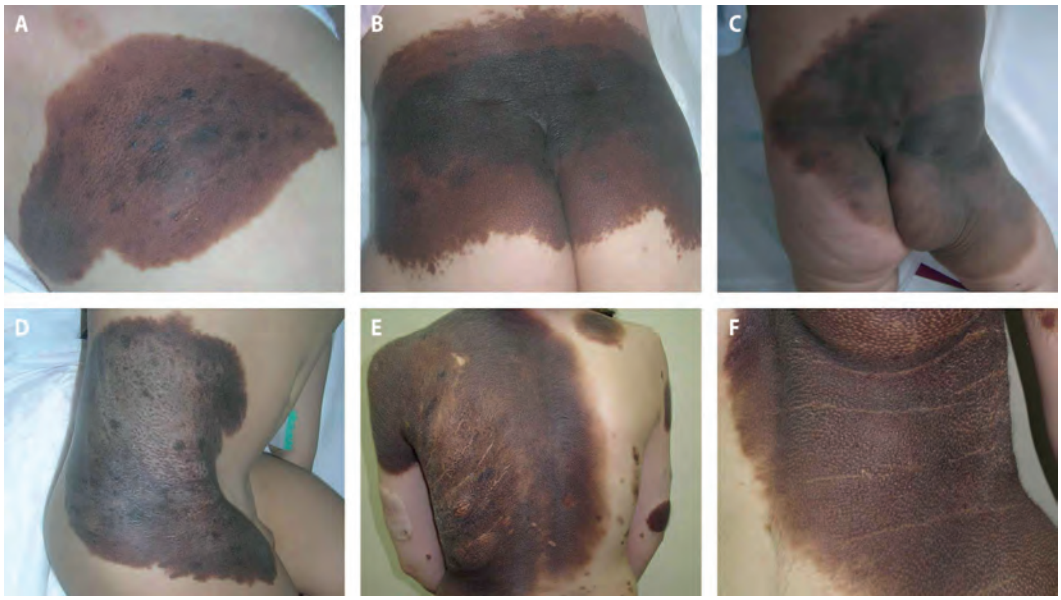


Figure 2. (A) Large congenital melanocytic nevus on the anterior trunk, representing breast/belly pattern. (B) Large congenital melanocytic nevus restricted to bilateral upper gluteal region, classified as half-bathing trunk pattern. (C) Large congenital melanocytic nevus on both sides of the lower back, gluteal area, and right upper thigh, classified as half-bathing trunk pattern. (D) Large congenital melanocytic nevus on located unilaterally iliac region and upper thigh classified as half-bathing trunk pattern. (E, F) Large congenital melanocytic nevus located on anterior trunk, shoulder, and upper back unilaterally but not extending to the neck, which represents atypical bolero pattern.

head, six to the trunk, and nine had involvement of both head and trunk [Figure 1F]. None of the patients had isolated neck lesions.

Of the 19 LCMN patients with lesions confined to the head (N=14) or both the head and neck without extension to neighboring body areas (N=5), the nevi were predominantly distributed unilaterally (N=11) [Figures 3D and F] or along the midline (N=8) [Figure 3E]. Patients with predominantly unilateral involvement were divided into subgroups. The first subgroup (N=3) had nevi confined to the forehead and scalp. The second subgroup (N=6) presented with lesions extending from the scalp to the nose and eyelids, with partial ear involvement but none extended to the chin. The third subgroup (N=2) also had unilateral head involvement but showed additional extension to the neck. Nevi with midline distribution were likewise classified into three subgroups: those limited to the scalp (N=6) [Figure 3E], those confined to the face (N=1), and those involving both the scalp and face (N=1).

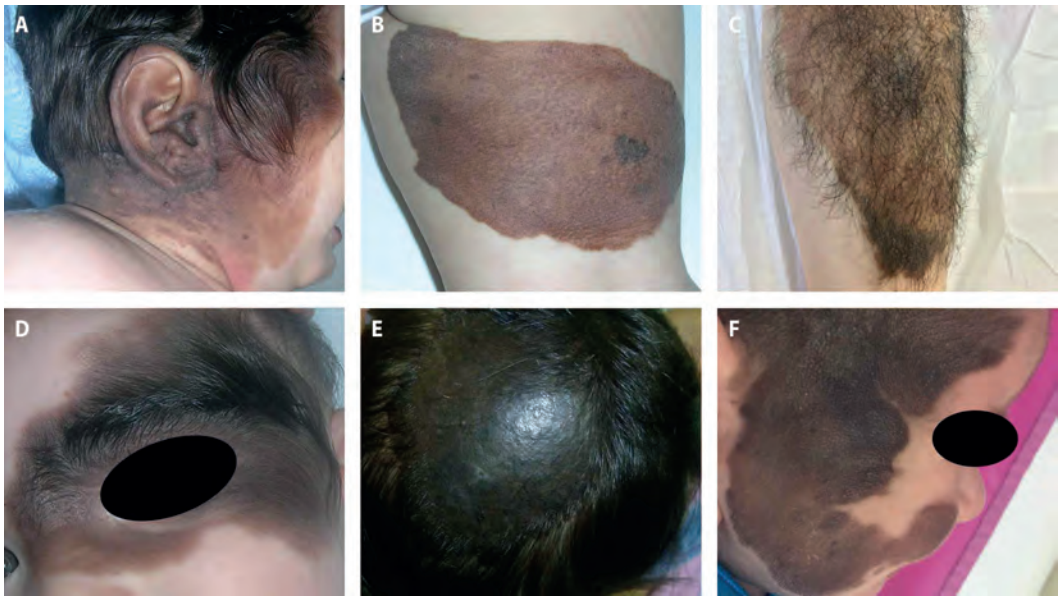


Figure 3. (A) Large congenital melanocytic nevus restricted to the scalp and neck, defined as hood pattern. (B) Large congenital melanocytic nevus located only on one side of the thigh. (C) Large congenital melanocytic nevus on the pretibial area which is not circumferential to the extremity, resembling a shin guard. (D) Large congenital melanocytic nevus on the nose, periorbital area, and forehead showing unilateral distribution. (E) Large congenital melanocytic nevus on the midline of the scalp. (F) Large congenital melanocytic nevus limited to scalp and face in unilateral distribution.

Discussion

Our study demonstrated that the main distribution patterns of the nevi were generally consistent with the classical 6B and 7B classification systems, which include terms such as breast/belly, back, bathing trunk, bolero, body extremity, body, and bonce [2.3]. In addition, we identified a novel distribution pattern and distinct variants of known patterns that may constitute their subgroups.

LCMNs can involve a single anatomical region (59% in our series) or multiple regions (41% in our series), with patterns often named anatomically for single-region involvement (e.g., back, breast/belly, body extremity, bonce) and after clothing items for multi-region involvement (e.g., bolero, bathing trunk) [2,3,7]. The "body" pattern denotes involvement of multiple anatomical regions. The 6B rule was originally defined for giant CMN (projected adult size >40 cm), while the 7B rule, which additionally includes "bonce" (head) was proposed for LCMN cases (>20 cm) [3]. Our series, consisting of 93 LCMNs with projected adult size over 20 cm (excluding the head) and 19 lesions located on the head and/or neck larger than one palm area of the patient's own hand was evaluated within the framework of these classification systems.

In a study by Kinsler and Larue, which examined the distribution of pigmented lesions in animal models to explore their embryological origins, CMNs were found to develop in a non-segmental pattern [8]. Thirteen distinct distribution areas were identified, including three body regions (two dorsal, one ventral), six extremity regions (four distal, two middle), and four head regions (one dorsal, three ventral), each corresponding to a specific melanocyte precursor [8]. The ventral body area described by Kinsler and Larue [8] clinically corresponds to the "breast/belly" pattern, while the upper dorsal region, extending from the cranial vertex on through the neck and arms and down to the lumbar area, matches the classical "bolero" pattern in existing classifications [2,3]. In addition to the 15 cases exhibiting the typical bolero pattern in our series, we identified two LCMNs that were primarily located within the same anatomical region but partially differed in distribution. These lesions mainly located within this specific area did not extend to the neck; instead, they involved the anterior trunk, spreading from flank to back [Figures 2E and F]; although they partially resembled the breast/belly pattern due to anterior trunk involvement, they were not confined to that region. Therefore, we called them "atypical bolero" pattern. The lower dorsal body area, starting from the upper thoracic vertebrae and covering the gluteal region and perineum, extending to the upper part of the legs [8], corresponds to the "bathing trunk" pattern described in clinical classifications [2,3]. In our series, 23 cases displayed this pattern. However, eight LCMNs did not encircle the lower body like a typical bathing trunk and did not extend to both legs; instead, they were usually retsricted to the upper gluteal region and lower back with limited extensions [Figures 2B and C] or were unilaterally located in the same region [Figure 2 D]. We propose describing these as "half-bathing trunk" pattern.

According to the description by Kinsler and Larue, a total of four specific areas are defined in lower extremities: two distal region (left and right), extending from the toes to just below the knee (stocking-type), and two middle regions (left and right), extending from the mid-thigh to the mid-calf [8]. In contrast, only two specific areas have been identified in the upper extremities–one on each side–extending from the fingertips to the shoulders [8]. The "body extremity" pattern used in clinical classifications aligns with the extremity regions defined in embryological studies [2.3]. In our cohort, analysis of involvement frequencies across these regions revealed a predominance of proximal localization over distal localization in both the upper and lower limb [Table 1]. This finding was interpreted as reflecting the involvement of the proximal extremities as a part of the dorsal body area. Notably, we observed LCMNs in the upper extremities that resembled the anatomical distribution patterns previously described as the middle extremity areas of the lower limbs. This observation raises the possibility that a middle segment may also exist in the upper extremities. Additionally, we identified two previously undescribed distribution patterns in patients with isolated nevi of the upper and lower extremities: one characterized by circumferential (encircling) extremity-like involvement resembling a knee pad and bracelet (N=11) [Figure 1C] and the other by lesions confined to one side of limb, resembling a shin guard (N=14) [Figure 3C]. Therefore, nevi with encircling involvement were aligned with the distal extremity areas, while those with partial involvement were more consistent with the middle extremity areas described by Kinsler and Larue. Further studies should evaluate whether these newly defined extremity subgroups possibly characterized by distinct embryological origins hold clinical prognostic significance. Their standardized classification could provide clinicians with a practical framework for describing complex nevus patterns that would otherwise require overly detailed topographic descriptions.

In our study, head involvement was observed in 28 patients, with isolated lesions occurring in half of the cases (N=14). Among the remaining patients, this presentation was associated with the bolero pattern in eight cases and with the body pattern in one case. The other five patients exhibited a distinct distribution extending from the vertex to the neck [Figure 3A], a pattern not previously defined in LCMN classifications, we propose the term "hood" to describe this scalp-neck continuum. For the 14 isolated head cases, lesions were further categorized as scalp only, face only, or combined scalp-facial involvement. Given this anatomical specificity, "head" (rather than the 7B rule "bonce") better reflects the observed patterns. Incorporating these observations including the addition of "hood" pattern and the replacement of the term "bonce" with "head" [Table 2], we suggest to update the terminology of anatomical distribution in LCMN classification as "6B+2H rule".

While the 7B classification acknowledges the head-region involvement, it does not define specific clinical patterns of these nevi [3]. Embryologically, the head is divided into dorsal and ventral cranial areas [8]. The dorsal area demonstrates bilateral symmetry along the midline, particularly near the vertex, whereas the ventral area comprises three midline-centric regions (upper, middle, and lower face). In our cohort, head nevi clustered into two groups: lesions perfectly matching these predefined embryological zones and nevi involving multiple contiguous zones simultaneously. This heterogeneity underscores the need for larger-scale studies to establish a standardized pattern classification for cranial lesions.

Clinical pattern classifications generally align with embryologically defined areas. They essentially map the territorial expansion of melanocyte precursor cells, which, depending on the timing of postzygotic mutations–a key etiological factor–across a broad spectrum. This spectrum ranges from extensive LCMNs encompassing entire anatomical regions to a small CMNs arising from a single melanocyte clone [20,21]. Notably, we encountered limited forms of classic patterns (bathing trunk, bolero, and body extremity variants), all of which can be mechanistically interpreted through this developmental framework.

Conclusion

For LCMNs exhibiting isolated head and neck involvement, we propose the term "hood" distribution pattern. Lesions predominantly localized on the bathing trunk or bolero regions but demonstrating limited anatomical extension may be classified as "half-bathing trunk" and "atypical bolero" variants, respectively. LCMNs limited to the extremities manifest two distinct patterns: encircling involvement, resembling a knee pad or bracelet configuration, and non-encircling lesions, mimicking a shin guard distribution. While the classical 6B and 7B classification systems cover most cases, our observations suggest that terminology revisions are necessary to account for these pattern variations.

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Dermatology Practical & Conceptual

Stabilizing Progressive Vitiligo with Systemic Treatment: Identifying Factors Associated With Patients Requiring Prolonged Treatment Duration

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Key words: Active vitiligo, Immunosuppression medications, Repigmentation

Citation: Yang TT, Lan CC. Stabilizing Progressive Vitiligo With Systemic Treatment: Identifying Factors Associated With Patients Requiring Prolonged Treatment Duration. *Dermatol Pract Concept*. 2025;15(4):5210. DOI: https://doi.org/10.5826/dpc.1504a5210

Accepted: March 6, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Patients with active vitiligo are treated with systemic immunosuppressants to halt disease progression. However, clinical features associated with patients whose condition is more difficult to control are unknown.

Objective: This study aimed to identify the clinical features of patients requiring extended periods of systemic immunosuppressants and the real-world clinical course of active vitiligo patients receiving systemic treatments.

Methods: This was a single-center retrospective study. Records of actively progressing vitiligo patients from September 2017 to August 2023 were reviewed.

Results: One hundred and fifty-nine patients with non-segmental actively progressing vitiligo were enrolled. In the six-month follow-up period, 101 (63.52%) patients required oral systemic immunosuppressants for ≤ 16 weeks without reactivation (Group 1), 51 (32.08%) patients required continuous systemic immunosuppressants for more than 16 weeks to achieve disease stabilization (Group 2), and seven (4.4%) patients achieved disease stabilization ≤16 weeks of oral immunosuppressants but recurred within nine months after stabilization (Group 3). Patients in Group 2 were significantly younger (39.69±11.51 vs. 46.47±14.91 years old; *P*=0.013) and had a lower proportion of facial involvement (56.86% vs. 76.24%; *P*=0.016) compared to Group 1. Similarly, both age (odds ratio

(OR): 0.968; *P*=0.016) and facial involvement (OR: 0.432; *P*=0.023) were identified as significant factors associated with decreased risk for Group 2. At one-year follow-up, 10.89% of Group 1 patients experienced disease reactivation.

Conclusions: Older patients and patients with facial involvement were more likely to achieve disease stabilization. Careful photo documentation is essential to optimal vitiligo management as disease reactivation is common after systemic treatment, even if initial disease stabilization is achieved.

Introduction

Vitiligo affects approximately 1% of the world's population and significantly impacts patients' quality of life [1,2]. Currently, treatment of vitiligo includes topical and/or oral immunosuppressants in combination with phototherapy [3,4]. For chronic stable vitiligo, topical corticosteroids or topical calcineurin inhibitors in combination with phototherapy are suggested [3,4]. For patients with rapidly progressing disease, however, systemic oral immunosuppressants for three to six months are recommended to suppress immune-mediated destruction of melanocytes in addition to phototherapy [3,4]. Various regimens of systemic immunosuppressants have been proposed. Oral mini-pulse corticosteroid therapy with doses equivalent to 2–10 mg dexamethasone/ betamethasone twice weekly on two consecutive days has been shown to halt disease progression while minimizing steroid-induced side effects [3-7]. Low-dose methotrexate, ranging from 7.5 to 25 mg weekly, is also effective [3,5,7-9]. However, the required length of treatment varies among patients, and some patients experience relapsing disease, making multiple courses of systemic treatments necessary [6,10]. Until now, there have been no known clinical features associated with actively progressive vitiligo patients whose condition is more difficult to control with systemic treatments. The proportion of patients experiencing disease reactivation after systemic immunosuppressants is also seldom documented.

Objective

In this study, we aimed to evaluate the clinical features associated with vitiligo patients who require prolonged or multiple courses of systemic immunosuppressants to control disease activity and to report the recurrence rate after systemic treatment.

Methods

This was a single-center retrospective study. Patient records from September 2017 to August 2023 at a specialized pigmentary disease clinic in a tertiary teaching hospital were retrospectively reviewed. All patients over age 18 years with non-segmental active vitiligo and who had received follow-up for more than six months starting from the day of treatment initiation were included. Our treatment protocol for active vitiligo is as follows: oral dexamethasone 2 mg on two consecutive days weekly or oral methotrexate 7.5 mg weekly for 12 to 16 weeks. If continuous disease progression is observed, oral immunosuppressants are prolonged until stabilization. Active vitiligo is defined as having any newly developed depigmented lesions or nontreated vitiligo lesions within the preceding three months. Disease stabilization is defined as no new depigmented lesion observed for three months. Systemic therapy was resumed if a recurrence of disease activity was observed. All patients received low-dose maintenance phototherapy for repigmentation [11]. Patients who refused systemic therapy, were under immunosuppressants for other diseases, or were receiving treatment for active cancer were excluded. This study was approved by the hospital institutional review board (KMUHIRB-E(I)-20240106).

To identify patients whose condition was more difficult to stabilize under the above treatment protocol, the enrolled patients were grouped into three groups. The first group included patients who only required oral systemic immunosuppressants for ≤16 weeks, without reactivation within six months from treatment initiation. The second group included patients who required continuous systemic immunosuppressants for more than 16 weeks. Patients whose disease activity could be controlled with ±16 weeks of oral immunosuppressants but which recurred within six months from treatment initiation were included in the third group.

Statistical analyses were performed by R software version 3.6.3. One-way ANOVA was used to compare the mean ages, and Fisher's exact test was used to compare the percentage frequencies among categorical variables. A p-value equal to or less than 0.05 was considered significant. Post hoc analyses were adjusted using Tukey's post hoc test or Bonferroni correction. In order to control for confounding factors, multivariate logistic regression was implemented to identify factors associated with active vitiligo more difficult to stabilize (Group 2). Bidirectional stepwise selection was used to select relevant variables for the logistic regression model.

Results

A total of 166 patients with active vitiligo received follow-up for more than six months in the study period. After excluding two patients under concomitant cancer treatment, two patients who refused systemic treatment, two patients under immunosuppressants for other diseases (Sjögren's syndrome and psoriasis), and one pregnant patient, a total of 159 patients were enrolled. The first group consisted of 101 (63.52%) patients, the second group included 51 (32.08%) patients, and the third group consisted of seven (4.4%) patients. The characteristics of patients are summarized in Table 1. Patients in Group 2 were significantly younger than patients in Group 1 (39.69±11.51 vs. 46.47±14.91 years; Tukey's post hoc test p=0.013). After post-hoc analysis with the Bonferroni correction (p< 0.05/3 = 0.017 was considered significant), the proportion of patients with facial involvement was significantly lower in Group 2 compared to Group 1 (56.86% vs. 76.24% vs.; P=0.016).

Age and facial involvement were independent variables selected in the multivariate logistic regression model to predict patients in Group 2 using bidirectional stepwise selection. Both age (β= -0.033; odds ratio (OR): 0.968; 95% confidence interval (CI): -0.059– -0.006; P=0.016) and facial involvement (β= - 0.84; OR: 0.432; 95% CI: -1.568– -0.115; P=0.023) were identified as significant factors associated with decreased risk for Group 2.

We further examined the number of patients requiring subsequent systemic treatment due to disease reactivation at 1-year follow-up despite initial disease stabilization. At 1-year follow-up, 70 patients remained in Group 1, and 11 (10.89%) patients experienced disease reactivation. To summarize, 108 (101+7; 67.92%) patients had their active vitiligo stabilized at month 3, and 101 (63.52%) patients remained inactive at month 6 from treatment initiation. At least 69 (51+7+11; 43.4%) patients required extended or additional systemic treatment at 1-year follow-up from treatment initiation. Patients experiencing disease reactivation despite initial stabilization were significantly younger (39.8±11.39 vs. 44.85≤14.32 years; P=0.03) and were more likely to have lesions involving the upper limbs (68.12% vs. 49.15%; P=0.046).

Conclusion

Patients with actively progressing vitiligo often require systemic treatments in addition to phototherapy to achieve good disease stabilization and induce repigmentation. There remains no standard systemic treatment for active vitiligo. However, mini-pulse therapy with oral dexamethasone and low-dose methotrexate have been demonstrated to provide good disease control with minimal adverse events in active vitiligo patients [5,6,12]. Currently, the recommended treatment duration for these systemic immunosuppressants is three to six months [3,4]. Nevertheless, the clinical profiles of difficult-to-control patients and the likelihood of recurrence once stabilization has been achieved have not been well-documented.

In the present study, both univariate and multivariate analyses showed that older patients and patients with facial

Table 1. Patient characteristics.

	Group 1 N = 101	Group 2 N = 51	Group 3 N = 7	P-value
Age, mean (SD)	46.47 (14.91)	39.69 (11.51)	40.71 (9.46)	**0.02**
Sex (female)	61 (60.40%)	28 (54.90%)	5 (71.43%)	0.71
Positive family history of vitiligo	4 (3.96%)	4 (7.84%)	0 (0%)	0.61
Positive family history of thyroid disease	11 (10.89%)	4 (7.84%)	2 (28.57%)	0.21
Abnormal thyroid tests	29 (28.71%)	14 (27.45%)	3 (42.86%)	0.71
Abnormal ANA	8 (7.92%)	3 (5.88%)	0 (0%)	1
Concomitant autoimmune disease	6 (5.94%)	2 (3.92%)	0 (0%)	1
Anatomic location				
Face	77 (76.24%)	29 (56.86%)	6 (85.71%)	**0.03**
Neck	36 (35.64%)	16 (31.37%)	1 (14.29%)	0.55
Trunk	40 (39.60%)	27 (52.94%)	5 (71.43%)	0.11
Upper limbs	52 (51.49%)	34 (66.66%)	5 (71.43%)	0.14
Hands	40 (39.60%)	26 (50.98%)	2 (28.57%)	0.34
Lower limbs	26 (25.74%)	21 (41.18%)	3 (42.86%)	0.11

Bold numbers indicate P<0.05. Abnormal ANA test was defined as ANA titer >1:80. Abbreviations: ANA: antinuclear antibody; SD: standard deviation.

involvement were less likely to require continuous systemic treatment for more than 16 weeks to achieve disease stabilization. However, within six months from treatment initiation, more than one-third of active vitiligo patients required prolonged systemic treatment or multiple courses of systemic treatments to stabilize their disease. In many clinical studies, the efficacy of systemic treatment is evaluated at the sixth month of treatment, and information regarding the clinical course of vitiligo beyond the follow-up period is lacking [5,6,12]. In this study, we further examined the number of patients requiring subsequent systemic treatment due to disease reactivation one year after stabilization had been achieved by systemic treatment. Although 12 to 16 weeks of systemic immunosuppressant is adequate to induce stabilization for approximately 60% of vitiligo patients with active disease, flare-up of disease activity may occur in more than 10% of patients who showed initial stabilization at 1-year follow-up from treatment initiation. In previous studies, the 1-year recurrence rate of non-segmental vitiligo treated with topical tacrolimus 0.1% and narrowband UVB were reported to be 40% and 44%, respectively [13,14]. Recently, Xu et al. reported recurrence rates of 23.7% and 26.3% at 6-month and 1-year follow-up in vitiligo patients with >80% repigmentation receiving treatment with traditional Chinese medicine [15]. The lower reactivation rate in the present study may be due to the difference in treatment modalities.

This study has several limitations. First, the retrospective nature of this study may have resulted in potential biases in data collection. Second, the number of patients included in Group 3 is relatively small compared with the other groups, which may potentially have reduced statistical power. Thirdly, the progression of vitiligo lesions was not evaluated using standardized severity assessment tools such as vitiligo area scoring index (VASI) or vitiligo extent score (VES) but based on clinical documentation and photos during each visit, which may have produced less objective results. Lastly, patients were not stratified by treatment (oral mini-pulse corticosteroid or methotrexate), which may have influenced treatment outcomes. However, both treatments are recommended by several guidelines and are equally effective in suppressing the activity of active vitiligo [5]. In the present study, treatment choice was determined through shared-decision making with the patient. Of the 42 patients who received methotrexate treatment, only one patient did not receive any oral mini-pulse corticosteroid therapy, and 38 patients received mini-pulse corticosteroid therapy prior to methotrexate, making it difficult to isolate the effect of each medication.

Currently, it is difficult to predict which specific patient will require extended treatment. Given that vitiligo patients often require a long treatment course to obtain satisfactory repigmentation [1], and unsynchronized repigmentation [16] is often observed among different vitiligo lesions, careful photo documentation is essential to optimal vitiligo management so that immunosuppressants may be given promptly when disease activity flare occurs after initial stabilization.

Ethical Approval: This study was approved by the hospital institutional review board (KMUHIRB-E(I)-20240106).

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Dermatology Practical & Conceptual

Dermoscopic Features of Acral Palmoplantar Nevi: Age and Site Correlation in a North African Cohort

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Key words: Dermoscopy, Acral Nevi, Palmoplantar Nevi, Age Correlation, Lesion Location

Citation: Soughi M, Bouraqqadi O, Douhi Z, Elloudi S, Baybay H, Mernissi FZ. Dermoscopic Features of Acral Palmoplantar Nevi: Age and Site Correlation in a North African Cohort. *Dermatol Pract Concept*. 2025;15(4):5065. DOI: https://doi.org/10.5826/dpc.1504a5065

Accepted: May 14, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Palmoplantar nevi (PPN) are common and sometimes difficult to diagnose because of their unusual clinical, dermoscopic, and histological features, often mistaken for acral lentiginous melanoma.

Objective: This study aimed to investigate the different dermoscopic patterns of palmoplantar nevi and their correlation with age and location.

Methods: This was a retrospective-prospective cohort study of a sample of the Moroccan population collected over 2 years. The diagnosis was based mainly on clinical and dermoscopic evaluation, and a biopsy performed in a single patient.

Results: A total of 140 patients with 144 PPNs were included in this study. PPNs were more frequently located on the palms (64%) than on the soles (36%). The parallel furrow pattern (PFP) was the most frequent in 44% of patients, followed by the lattice pattern (17,4%), then the homogeneous pattern (16.7%), the fibrillar pattern (10,4%), the compound pattern (7%), the globular pattern (2 %), the dotted pattern (2 %), and finally, the atypical pattern (0.7%). We found a correlation between fibrillar and globular patterns with younger patients (P <0.05) lattice pattern with pressure-free regions such as the arch and palmar region. In contrast, the fibrillar pattern was associated with heels and PFP with digital location.

Conclusion: Recognition of these patterns is crucial for accurate diagnosis and to avoid unnecessary excisions.

Introduction

Acral lentiginous melanoma (ALM) is the most common subtype of melanoma among individuals with darker skin tones [1]. It presents a significant diagnostic challenge in its early stages due to its clinical similarity to palmoplantar naevi [2]. In a Moroccan study analyzing 100 cases of cutaneous melanoma from 2013 to 2022, the ALM subtype was observed in 38% of cases. The lower limb was the most affected site, accounting for 66% of cases, with the sole being the predominant location [3].

The prevalence of melanocytic palmoplantar lesions varies significantly across populations, countries, and study groups, and generally mirrors the prevalence of benign melanocytic palmoplantar lesions, ranging from 36–42% in individuals with darker phototypes to 18–23% in Caucasians [4,5]. Therefore, early screening remains the only viable strategy with the potential to enhance prognosis.

Dermoscopy is a noninvasive clinical method crucial for diagnosing and managing pigmented lesions, particularly advancing the diagnosis of melanocytic lesions on acral volar skin [6]. Most dermoscopic patterns observed in acral volar skin have been studied primarily in European and Asian populations [1,7,11]. In a North African population, an Egyptian study highlighted the value of dermoscopy in acral pigmented lesions by analyzing their characteristic features and emphasizing its role in the early diagnosis of melanoma at this anatomical site [12]. These findings highlight the need for further studies in North African populations to assess potential differences in dermoscopic patterns compared to other regions.

The classic dermoscopic patterns described for plantar nevi include the parallel furrow pattern and its variants, the fibrillar pattern and the lattice pattern [2,6]. However, few studies have examined the correlation between these patterns, their location, and age.

This study aims to describe the dermoscopic patterns of palmoplantar nevi and correlate them with age and location in a sample of the Moroccan population.

Methods

Study Design and Patients

We conducted a retrospective-prospective cohort study involving 144 palmoplantar naevi (PPN) in 140 patients diagnosed in our department. This study included all nevi located below Wallace's line, specifically on the glabrous skin of palms, soles, and the volar skin of the fingers and toes. Lesions in dorsal and subungual areas were excluded from the analysis.

Data collection was carried out using a structured data processing form and recorded in an Excel file. The following parameters were evaluated:

Clinical data: age, sex, Fitzpatrick skin type, and localization (palms, soles, fingers, toes, thenar eminence, hypothenar eminence, central area of the palms, heels, forefeet, and non-pressure areas).

Dermoscopic patterns including:

- Parallel furrow pattern, characterized by brownish linear pigmentation along the sulci of the skin surface markings [7]. Variants include dotted-line and double-line forms, with single solid lines along the sulci representing the fundamental type [8]
- Lattice-like pattern, comprising parallel pigmented lines along the sulci, intersected by perpendicular lines [7].
- Fibrillar pattern, with ensely packed, fine, pigmented lines arranged perpendicular to the skin markings [7].
- Homogenous pattern, with uniform light brown pigmentation without distinct structural features [7].
- Compound pattern, a combination of parallel furrow pattern with globular pattern, or homogeneous and globular patterns, where the dominant pattern is indistinguishable [13] characterized by dots and/or globules arranged in a non-parallel distribution [7].
- Atypical pattern, applied when none of the defined dermoscopic patterns was identified [7].

The sample was divided into age groups: <15 years old, 16 to 30 years old, 31 to 45 years old, and >45 years old.

Diagnosis

The diagnosis was based on clinical and dermoscopic evaluation. Images were captured by a single examiner using Dermlite 4 device with a smartphone in both non-polarized and polarized light modes, with and without immersion. Images were analyzed by two examiners.

Histopathological confirmation was performed in a single patient, with biopsy samples fixed in formalin, embedded in paraffin, and stained with hematoxylin-eosin. An immunohistochemical study was subsequently performed.

Statistical Analysis

Statistical analysis was conducted using SPSS 20.0 software. Descriptive and analytical comparisons of dermoscopic findings were conducted, with fisher's exact test used to determine statistical significance ($P<0.05$).

Results

Patient Analysis

The study included 144 PPN in 140 patients. Half of the patients had phototype IV skin, followed by phototype III (39%), phototype V (10%), and phototype VI (1%).

The average age of the patients was 29.8 years, ranging from 1 to 74 years. The distribution by age group showed that 22% of patients were 0 to15 years old, 31% were 16 to 30 years old, 29% for were 31 to 45 years old, and 18% were older than 45 years.

Clinical and Dermoscopic Features of Nevi

PPN were more frequently located on the palms (64%) than on the soles (36%). The most common anatomical sites were the fingers, followed by non-pressure areas of the soles, the thenar region, the central part of the palms, the hypothenar region, the heels, the forefeet, and the toes (Figure 1). The parallel furrow pattern (PFP) (Figure 2) was the most frequent, observed in 44% of patients. The lattice-like pattern (Figure 3) was the second most common, accounting for 17.4% of cases, followed closely by the homogeneous pattern (16.7%) (Figure 4). The fibrillar pattern (Figure 5) was observed in 10.4% of cases, while the compound pattern (Figure 6) appeared in 7%. Less prequent patterns included the globular pattern (2%), the dotted pattern (2%) (Figure 7), and the atypical pattern (0.7%), which was observed in a single patient. This patient presented with a pigmented lesion exhibiting a parallel ridge and furrow pattern at the periphery and a blue-gray veil at the center;

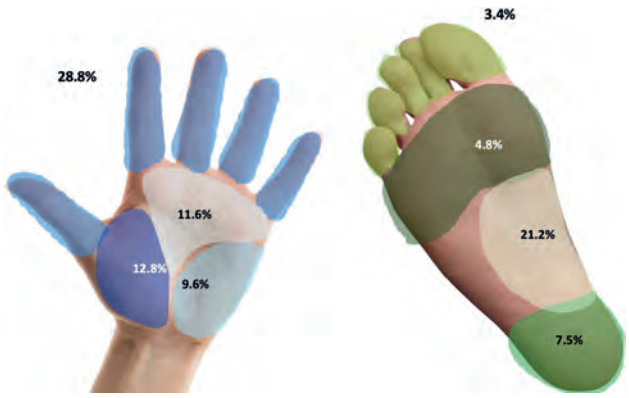


Figure 1. Distribution of palmar and plantar acral nevi.

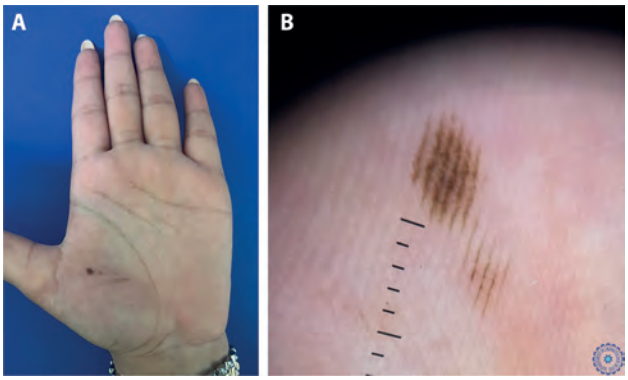


Figure 2. (A) Melanocytic nevus on the palm. (B) Dermoscopy: parallel furrow pattern.

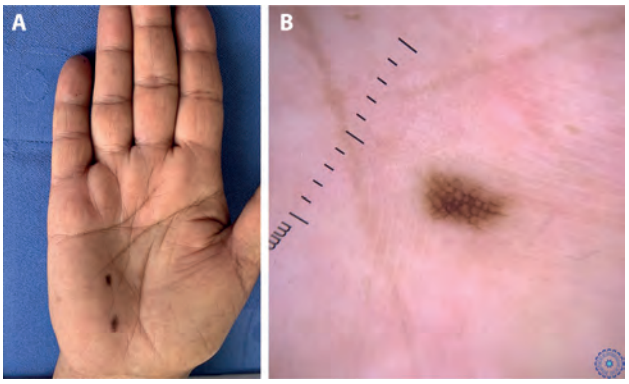


Figure 3. (A) Melanocytic nevus on the palm. (B) Dermoscopy: lattice pattern.

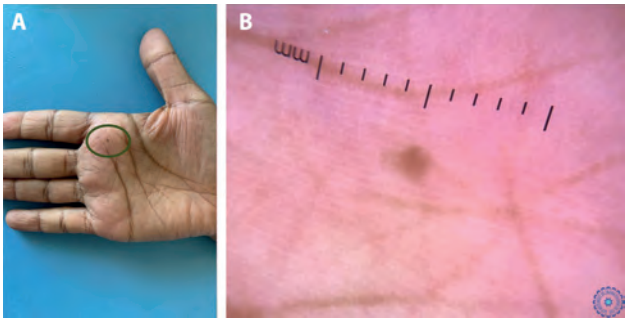


Figure 4. (A) Melanocytic nevus on the palm. (B) Dermoscopy: homogenous pattern.

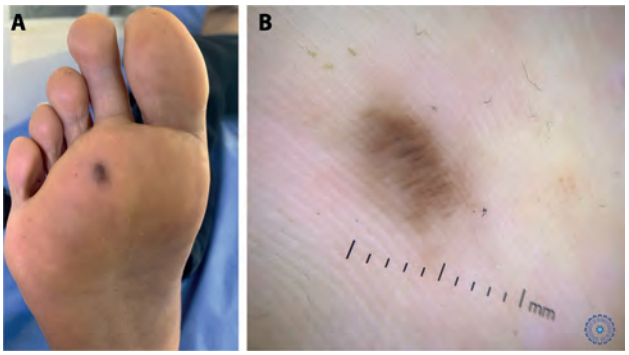


Figure 5. (A) Melanocytic nevus on the palm. (B) Dermoscopy: fibrillar pattern.

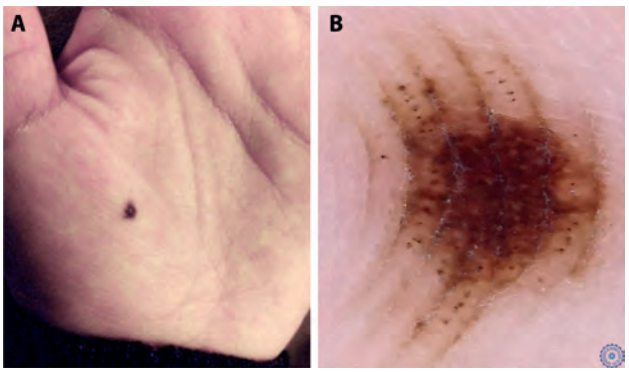


Figure 6. (A) Melanocytic nevus on the palm. (B) Dermoscopy: compound pattern, parallel furrow pattern.

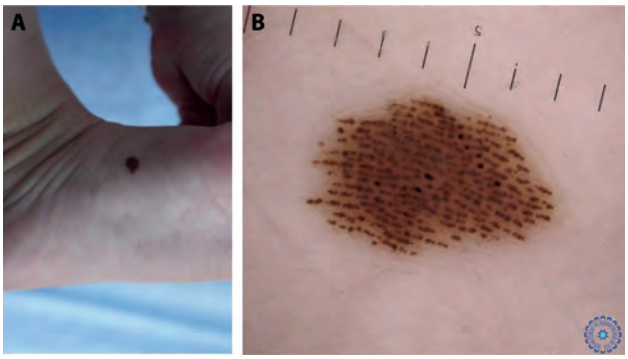


Figure 7. (A) Melanocytic nevus on the palm. (B) Dermoscopy: dotted pattern (peas-in-a-pod pattern).

histopathological examination confirmed the diagnosis of an acral nevus.

Analytical Study

A significant correlation was found between dermoscopic patterns and age. The fibrillar and compound patterns were more prevalent among younger individuals (Table 1). Additionally, specific dermoscopic patterns were associated with particular anatomical sites. The lattice-like pattern was most commonly observed in non-weight-bearing areas such as the foot arch and the palmar region, whereas the fibrillar pattern was more frequently found on the plantar surface, particularly on the heels. The PFP was predominantly associated with the digital location (Table 2).

Discussion

In Morocco, skin melanoma ranked as the 25th most common cancer, with 248 new cases in 2020, accounting for 0.42% of all new cancer cases, and 114 deaths (0.32%) [14]. Among melanoma subtypes, ALM was identified as one of the most frequent in a Moroccan study [3]. The prognosis for ALM is generally poor, primarily due to delayed diagnosis at advanced stages [9]. Therefore, early and accurate diagnosis, along with appropriate treatment, are crucial to improving patient outcomes.

Dermoscopy, a noninvasive imaging technique, has proved highly effective in differenciating early acral melanoma from acral nevi [9]. Most acquired acral nevi are junctional or compound nevi with a dominant junctional component, typically appearing as a brown-black macule, creating diagnostic challenges for clinicians [9]. Palmoplantar skin has distinct anatomical and histological characteristics, featuring a thick, compact cornified layer and dermatoglyphics composed of parallel ridges and furrows forming unique loops, whorls, and arches[1,12]. Consequently, the interpretation of dermoscopic patterns in this specific anatomical site is relatively easy to assess [12].

Saida et al. were the first to describe specific dermoscopic patterns of acral nevi in the Asian population and proposed a three-step algorithm for managing acquired acral melanocytic lesions [1,2,7,9]. The prevalence of acral nevi in the Japanese population is estimated to be 7–9% [7], but this prevalence remains unknown in Morocco. Given the frequency of acral melanomas, recognizing dermoscopic patterns of pigmented lesions in palmoplantar skin is essential to early detection.

The primary objective of this study was to examine the dermoscopic characteristics of melanocytic acral nevi in the Moroccan population. In our sample, the parallel furrow pattern was the most common, observed in 44% of cases, which aligns with the literature reports. The prevalence of this pattern in other reports ranges from between 42% and 59%, depending on the population studied [7,10,15,16]. The second most frequent pattern in our series was the lattice-like pattern, detected in 17.4% of lesions, a finding consistent with Egyptian and Italian studies [10,12,15]. The reported prevalence of this pattern varies from 7% to 22% [7], but it was found to be uncommon in two Turkish studies [6,16].

In our study, the homogeneous pattern (16.7%) was more frequently observed than the fibrillar pattern (10.4%), a result that aligns with Egyptian and Latin American studies [12,15], but contrasts with Italian and Turkish studies, where the fibrillar pattern was more presominant [10,16]. Interestingly, the homogeneous pattern appeared to be more frequent in our population compared to Japan [1]. The remaining dermoscopic patterns were observed less frequently, a finding consistent with studies from various countries [1,10,12,15,16]. (Table 3).

Saida et al. [7] raised an important question regarding the variation in dermoscopic patterns of acral nevi—whether these differences arise from **ethnic factors** or **variability in interpretation**, given that a single nevus can exhibit multiple patterns, with the dominant one typically being reported. However, based on these findings, it is believed that ethnic differences play a more significant role, as our results closely resemble those from Egyptian and Latin American studies.

The second objective of our study was to explore the correlation between the dermoscopic patterns of acral nevi observed in our sample with age and location. Our analysis revealed a statistically significant association between pattern types and age, with fibrillar and compound patterns being more frequent in younger individuals. The compound pattern refers to a combination of two superimposed patterns, where the dominant pattern is unclear, but globules are consistently present. This pattern was commonly observed in patients under age 15. Our findings align with those of Mingawa et al., who reported that fibrillar and peas-in-a-pod patterns were more prevalent in younger individuals [17]. However, their study also reported an association between age and atypical patterns, which were more frequently observed in older patients. In contrast, in our study, an atypical

Table 1. Correlation between age and dermoscopic patterns of nevi.

Age	PFP	Fibrillar	Lattice	Homogenous	Compound	Dotted	Globular	Atypical'
< 15 y	12	8	5	2	6	1	1	0
16–30 y	23	2	8	7	2	0	1	0
31–45 y	20	3	5	8	1	1	1	0
> 45 y	8	2	7	7	1	1	0	1
P value	.173	**.004**	.504	.056	**.026**	.679	.853	.406

Abbreviations: PFP: parallel furrow pattern; y: years.

Table 2. Correlation between nevus location and dermoscopic patterns.

	PFP	Fibrillar	Lattice	Homogenous	Compound	Dotted	Globular	Atypical
Palms								
Thenar eminence	10	1	4	1	2	0	1	0
Hypothenar eminence	5	1	5	1	1	0	0	0
Fingers	**22**	3	5	6	1	0	1	0
Central area	7	0	3	4	3	0	1	0
Soles								
Heels	0	**6**	0	2	2	1	0	0
Forefeet	1	**4**	0	1	1	0	0	0
Toes	3	0	0	2	0	0	0	0
Non-pression	15	0	**8**	7	0	2	0	1
p-value	**.031**	**<.001**	**.049**	.539	.233	.477	.409	.475

Abbreviations: PFP: parallel furrow pattern.

Table 3. Comparison of dermoscopic features of acral nevi across various countries.

	Our Study Morocco, N (%)	Emiroglu et al [3](Turkey), N (%)	Ozdemir et al [13] (Turkey), N (%)	Elwan et al [10] (Egypt), N (%)	Barquet et al [11] (Uruguay), N (%)	Altamura et al [12] (Italy), N (%)	Saida et al [1] (Japan), N (%)
Parallel furrow	63 (44)	87 (41)	110 (59)	148 (66)	81 (51)	304 (42)	40 (42)
Lattice	25 (17.4)	15 (7)	12 (6)	20 (9)	21 (13)	108 (15)	13 (13)
Fibrillar	15 (10.4)	22 (11)	23 (12)	14 (6)	11 (7)	78 (11)	20 (21)
Parallel ridge	NE	4 (2)	NE	5 (2)	NE	NE	NE
Globular	3 (2)	24 (11)	4 (2)	4 (2)	15 (10)	15 (2)	5 (5)
Reticular	NE	2 (1)	8 (4)	4 (2)	NE	39 (5)	3 (3)
Homogeneous	24 (16.7)	12 (6)	12 (6)	17 (8)	20 (13)	67 (9)	8 (2)
Globular streak-like	NE	16 (8)	10 (5)	NE	6 (4)	NE	NE
Nontypical	1 (0.7)	8 (4)	6 (3)	12 (5)	4 (3)	99 (14)	14 (14)
Compound	10 (7)	NE	NE	NE	NE	NE	NE

pattern was noted in only one patient, whose biopsy confirmed a benign acral nevus diagnosis.

A recent European study, conducted across 21 dermatology centers in 14 countries, analyzed 542 atypical melanocytic palmoplantar lesions, including 113 melanomas and 429 atypical nevi. The study revealed a trend toward using cameras for documenting benign atypical melanocytic palmoplantar lesions, whereas videodermatoscopes were primarily used for malignant cases.[18] The authors concluded that, in patients over age 50 years, an atypical melanocytic palmoplantar lesion exceeding 8 mm on the heel, plantar arch, or fingers carries a high risk of melanoma, regardless of sex. Furthermore, for patients over age 65.3 years with a palpable lesion larger than 17 mm, immediate wide-margin

excision is recommended. Conversely, in patients under age 49, a flat lesion measuring less than 7 mm on the palmar or plantar surfaces is likely benign [18].

Similarly, Emiroglu et al. [6] found a significant association between age and dermoscopic patterns, reporting that atypical patterns were seen in 28.6% of the elderly patients (>60 years old). In the pediatric population (0–15 years old), parallel furrow (dotted variants) and globulo-streak-like patterns were predominant. The higher presence of globules in children suggests ongoing nevus growth. Zalaudek et al. [13] Similarly demonstrated that the globular pattern was most frequent in younger individuals when studying acquired melanocytic nevi on the trunk and extremities, excluding the palms and soles. Our findings also align with a Turkish study on the dermoscopic features of acral nevi in children and adolescents [13]. In this study, dotted variants of the parallel furrow pattern were more common in children aged 0–12 years (58.2%) compared to adolescents aged 13–18 years (41.7%). Additionally, compound patterns, particularly the parallel furrow + crista dotted pattern, were significantly more prevalent in the younger group (22.1% and 16.3%, respectively) compared to the older group (11.4% and 6%, respectively). The fibrillar pattern was most frequently observed in congenital acral melanocytic nevi.

Regarding the anatomic location, we observed that the lattice-like pattern was predominantly found in non-weight-bearing areas such as the foot arch and the palmar region, whereas the fibrillar pattern was more frequent on the plantar surface, particularly on the heels ($P< 0.001$). These results are consistent with findings of Emiroglu et al. [6] and Miyazaki et al. [19] Miyazaki reported that the fibrillar pattern results from an oblique arrangement of melanin pigment within the inclined cornified layer, which is thought to be induced by mechanical pressure from body weight [19]. However, our findings differ from those of Elwan et al., who did not observe the fibrillar pattern on the soles, but reported its presence on the palms in eight cases. They attributed this to the **occupational habits** of their patients, primarily **housewives and farmers**, who **wore flat shoes** and engaged in **manual labor**. They proposed that the fibrillar pattern on the hands may arise from lateral shear forces on the stratum corneum overlying the nevi due to repetitive manual work.

According to a multicenter study analyzing the characteristics of benign and malignant atypical melanocytic palmoplantar lesions (aMPPL), early-stage melanomas (EMs) and palmoplantar atypical melanocytic lesions were most frequently located on the heel (40.3% of EM/aMPPL cases) and fingers (33% of EM/aMPPL cases), areas characterized by chronic trauma and friction [20].

We also observed that the PFP was significantly associated with digital locations, a result also reported by Savas Erdoğan et al. [13] and González-Ramírez et al. [21] However, González-Ramírez et al. found no statistically significant difference ($P>0.05$) in the classification of lesions on the soles. In contrast, Altamura et al. observed that lattice-like, atypical, fibrillar, and homogeneous patterns were most frequent on the soles, while transition patterns, comprising features characteristic of both volar and non-glabrous skin, were more commonly observed in lesions located on the fingers [10].

Despite its valuable findings, our study has some limitations. First, it was conducted at a single center with a limited sample size, and all the participants belonged to a single ethnic group. Additionally, we lacked long-term follow-up data, preventing us from assessing the evolution of dermoscopic patterns over time.

Conclusion

Dermoscopy is a highly useful tool for distinguishing acral nevi from ALM. The interpretation of dermoscopic patterns should take into consideration the anatomical location on the plantar surface as well as the patient's age.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki.

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Dermatology Practical & Conceptual

Brodalumab Efficacy in Psoriasis Patients with Inadequate Response to IL-23 or IL-12/23 Inhibitors: Multicenter Italian Retrospective Analysis - IL PSO (Italian Landscape Psoriasis)

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Key words: Brodalumab, Psoriasis, Comorbidity, IL-7 inhibitors, IL-23 inhibitors, Switch

Citation: Orsini D, Fargnoli MC, Burlando M, et al. Brodalumab effectiveness on psoriasis patients who failed anti-interleukin 23 or 12/23: a multicenter, retrospective study – IL PSO (Italian Landscape Psoriasis). *Dermatol Pract Concept*. 2025;15(4):6010. DOI: https://doi.org/10.5826/dpc.1504a6010

Accepted: March 6, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: D. Orsini has been a speaker and/or consultant for Abbvie, LeoPharma, UCB, Bristol-Meyer-Squibb, and Boehringer Ingelheim. R. Balestri has received support for attending meetings and/or travel from AbbVie, Amgen, Leo Pharma, Lilly, Novartis, and Sanofi. M. Burlando acted as a speaker or consultant for Abbvie, Eli Lilly, Janssen, Leo-Pharma, UCB, Novartis, Bristol-Meyer-Squibb, and Boehringer Ingelheim. G. Caldarola has received honoraria as speaker and consultant for Abbvie, Almirall, Biogen, Eli Lilly, LEO Pharma, Novartis, Janssen, Sanofi, Pfizer, and UCB Pharma outside the submitted work. A. Campanati has served as a speaker, consultant, or advisory board member for Abbvie, Almirall, Amgen, Eli-Lilly, Leo Pharma, Janssen-Cilag, Novartis, Pfizer, Sanofi-Aventis, Boehringer Ingelheim, and UCB Pharma. E. Campione has served as advisory board member, received fees for lectures, and/or research grants by Almirall, Amgen, Abbvie, Bristol Myers Squibb, Incyte, Leo Pharma, and UCB. A. Carugno has been a speaker and/or consultant for Almirall, Amgen, Abbvie, Boehringer Ingelheim, Eli Lilly, Leo Pharma, Janssen-Cilag, Novartis, and UCB Pharma. A. Costanzo has been a consultant and/or speaker for AbbVie, Almirall, Amgen, Janssen, Leo Pharma, Eli Lilly, Galderma, Boehringer, Novartis, Pfizer, Sandoz, and UCB. E. Cozzani acted as a speaker or consultant for Abbvie, Almirall, Eli Lilly, Leo-Pharma, and Novartis. G. Dal Bello has been a consultant for Abbvie, Eli Lilly, Janssen, Sanofi, UCB, and Novartis. A. Dattola has served as a speaker, consultant, or advisory board member for Abbvie, Almirall, Amgen, Eli Lilly, Leo Pharma, Janssen, Novartis, Boehringer Ingelheim, and UCB Pharma outside the submitted work. M. Esposito has served as speaker/consultant for Abbvie, Amgen, Almirall, Eli Lilly, Janssen, Leopharma, Novartis, Pfizer, Sanofi, and UCB. M.C. Fargnoli has served on advisory boards, received honoraria for lectures and/or research grants from AMGEN, Almirall, Abbvie, Boehringer-Ingelheim, BMS, Galderma, Kyowa Kyrin, Incyte, LEO Pharma, Pierre Fabre, UCB, Lilly, Pfizer, Janssen, MSD, Novartis, Sanofi, Regeneron, and Sun Pharma. C. Guarneri has received consultation fees and/or grants for research projects, advisory panels, and giving educational lectures from Wyeth-Pfizer, Abbott Immunology-Abbvie, Janssen-Cilag, Novartis, LEO-Pharma, LEO-Pharma Denmark, Ely-Lilly, Celgene, Merck-Serono, UCB Pharma, Sanofi-Aventis, Amgen, and Almirall. P. Malagoli has been a speaker for AbbVie, Lilly, Novartis, Janssen-Cilag, Celgene, Leopharma, and Almirall. A. Narcisi has served on advisory boards, received honoraria for lectures and research grants from Almirall, AbbVie, BMS, Leo Pharma, Celgene, Eli Lilly, Janssen, Novartis, Sanofi-Genzyme, Amgen, and Boehringer Ingelheim.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: The use of brodalumab in patients with psoriasis who have failed other biologic drugs is an underexplored topic.

Objectives: To evaluate the safety and the efficacy of brodalumab in a subgroup of psoriasis patients who already failed anti-IL23 or anti-IL12/23 treatment.

Methods: Using the Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI), we retrospectively evaluated a cohort of 23 patients with psoriasis who underwent a change in therapy with brodalumab exclusively following primary or secondary therapeutic failure of anti-IL-23 or anti-12/23 drugs.

Results: The mean PASI decreased significantly following the introduction of brodalumab after four weeks of treatment, continuing to decrease at 16 and 36 weeks, reaching the nadir at 52 weeks (baseline PASI baseline: 14.6 ± 9.2 vs. 52 weeks PASI: 1.1 ± 1.8; $P<0.001$). Sixty-three point six percent of patients reached PASI 100 just after 16 weeks. The same trend of improvement was also observed for the DLQI. The adverse effects observed in our study population were generally mild.

Conclusions: Our results are in line with the current literature and suggest that patients who have failed therapy with IL-23 or IL-12/23 inhibitors may benefit from switching to brodalumab, which could be considered a good choice for patients who need a rapid resolution of the inflammatory skin condition.

Introduction

The recent worldwide deployment of anti-interleukin (IL)-17 and anti-IL-23 drugs has revolutionized the treatment paradigm of psoriatic disease, allowing a dramatic improvement in the rate of achievement and maintenance of clinical remission [1, 2].

However, regardless of psoriasis forms and the disease domains involved, a variable percentage of patients still experience primary therapeutic failure, incomplete response, or progressive loss of treatment efficacy (secondary therapeutic failure). In this context, switching treatments among different mechanisms of action has been explored in previous studies conducted on psoriatic patients [3-5].

However, criteria providing a clear clinical rationale for such transitions are lacking, and no clear guidance is provided by international guidelines to date.

Considering that most patients treated with anti-IL drugs have previously experienced failure of at least one traditional DMARDs and in some cases even one or more biologics, the most obvious and widely used strategy to manage this difficult subgroup of patients is to attempt an interclass switch from an anti-IL-23 to an anti-IL-17 and vice versa. Brodalumab is the only monoclonal antibody directed toward the IL-17 receptor A. Because of this peculiar mechanism of action, brodalumab could block IL-17A, IL-17F, IL-17A/F, and IL-17E isotypes, providing deeper cytokine inhibition and faster anti-inflammatory activity than other drugs of the same class [6].

Results from the AMAGINE 1-2-3 randomized controlled trials (RCTs) showed that 51% of patients achieved complete skin clearance (PASI 100) after 52 weeks of treatment. Efficacy was sustained over a long period, with more than half of patients maintaining PASI 100 and more than 75% of patients maintaining almost clear skin (PASI 90) up to 120 weeks [7-9].

Objectives

We performed a real-life retrospective study to evaluate the safety and the efficacy of brodalumab in a subgroup of psoriasis patients who already failed anti-IL23 or anti-IL12/23 treatment.

Patients and Methods

We retrospectively evaluated over a follow-up period of 52 weeks a cohort of 23 psoriasis patients who underwent a medical switch to brodalumab exclusively following primary or secondary therapeutic failure of anti-IL-23 or anti-12/23 drugs. Patients who transitioned for adverse effects or because of any reason other than anti-IL23 or anti-12/23 failure were excluded from the study. Clinical and quality-of-life parameters collected at baseline (start of brodalumab treatment) and at four predefined timepoints (4, 16, 36, 52 weeks of continuous brodalumab treatment) were included for the purposes of this study. The following parameters were used for statistical comparisons: Psoriasi Area and Severity Index (PASI), Dermatology Life Quality Index (DLQI), presence/absence of active psoriatic arthritis, presence/absence of adverse events. Data were summarized by means of descriptive analysis. Means and standard deviations (SDs) were

calculated for continuous variables, while absolute values and frequency (%) were calculated for categorical variables. A *t*-test or analysis of variance was performed to compare mean values, while a paired t-test compared mean values at different timepoints. The chi-squared test was used to compare frequencies. The statistical significance was defined as $P<0.05$. All analyses were performed with IBM SPSS Statistics for Windows, Version 26.0.

Results

The mean age of the patients enrolled was 56.7 ± 13.9 years. Only 4/23 (17.4%) patients were normal weight, while the remaining were overweight or obese (mean BMI= 28.8 ± 5.9). The mean PASI at baseline was 14.4 ± 9.1, and 100% of participants had at least one difficult-to-treat area involved. Almost 13% (3/23) of patients had been diagnosed with oligoarticular psoriatic arthritis (PsA) yet were in complete and stable remission at the time of brodalumab prescription. Baseline demographic characteristics were summarized in Table 1.

Table 1. Clinical and Demographic Characteristics of our Population at Baseline Visit.

Demography	N=23
Male, N (%)	18 (78.3%)
Age (years), mean ± SD	56.7 (± 13.9)
Disease duration (years), mean ± SD	20.4 (± 9.7)
BMI, mean ± SD	28.8 (± 5.9)
Obese, N (%)	7 (30.4%)
Overweight, N (%)	19 (82.6%)
Normal weight, N (%)	4 (17.4%)
Diabetes, N (%)	2 (2.9%)
Hypertension, N (%)	10 (43.5%)
Hyperlipidemia, N (%)	8 (34.8%)
Thyroid disease, N (%)	1 (4.3%)
Cardiopathy, N (%)	3 (13.0%)
Other, N (%)	3 (13.0%)
PsA, N (%)	3 (13.0%)
≥ 1 Difficult-to-treat areas, N (%)	23 (100%)
PASI baseline, mean ± SD	14.4 (± 9.1)
Naïve for systemic therapies, N (%)	0

All patients involved in the study (N=23) had previously received unsuccessful treatment with traditional DMARDs and were receiving, at the time of enrollment, one of the following anti-IL-23 or 12/23 inhibitors–guselkumab, tildrakizumab, risankizumab, or ustekinumab–as their first biological treatment. Most participants (14, 60.8%) were on anti-IL23 treatment at the time of switching to brodalumab, while nine patients (39.1%) were on ustekinumab (anti-IL12/23). Previous biological treatments used by the study population are summarized in Table 2.

The mean PASI decreased significantly after the introduction of brodalumab as early as week 4 of treatment, from a mean value of 14.6 ± 9.2 to 6.0 ± 7.1 ($P<0.001$). The trend of PASI improvement persisted during follow-up assessments performed at 16 and 36 weeks, reaching the nadir at 52 weeks (PASI: 1.1 ± 1.8; $P<0.001$) (Table 3, Figure 1). The percentages of patients who progressively achieved the PASI 75, 90, and 100 clinical responses on assessments performed at the scheduled timepoints are shown in Table 4 and depicted graphically in Figure 2. Mirroring the results obtained on disease severity, the DLQI also improved significantly in our study population, dropping to 1/3 of the baseline level after just four weeks of treatment with brodalumab (baseline: 16.9 ± 7.6 vs. 4 weeks: 5.1 ± 7.0; $P<0.001$) and reaching the lowest value after 52 weeks of treatment (1.8 ± 3.8; $P<0.001$). The trend of the DLQI across all assessments is summarized in Table 5 and graphically represented in Figure 3. Of note, two patients (8.7%)

Table 2. Last Previous Biological Therapies.

Last previous biological therapy	N=23	Reason for discontinuation
Guselkumab	6 (26.1%)	primary inefficacy (1, 16.7%) loss of efficacy (5, 83.3%)
Risankizumab	3 (13.0%)	primary inefficacy (1, 33.3%) loss of efficacy (1, 33.3%) other (1, 33.3%)
Tildrakizumab	5 (21.7%)	primary inefficacy (1, 20.0%) loss of efficacy (4, 80.0%)
Ustekinumab	9 (39.1%)	primary inefficacy (1, 11.1%) loss of efficacy (7, 77.8%) other (1, 11.1%)

12/23 (52.2%) patients have taken more than one previous biologic drug.

Table 3. Mean PASI by Visit.

Visit	Mean PASI (SD)	mPASI decrease	Paired t-test
Baseline (N=22)	14.6 (± 9.2)		
4 weeks (N=22)	6.0 (± 7.1)	-8.6 (± 6.0)	<0.001
16 weeks (N=22)	2.6 (± 5.7)	-11.9 (±6.8)	<0.001
36 weeks (N=22)	1.7 (± 3.4)	-12.9 (±6.9)	<0.001
1 year (N=21)	1.1 (± 1.8)	-12.0 (± 6.0)	<0.001

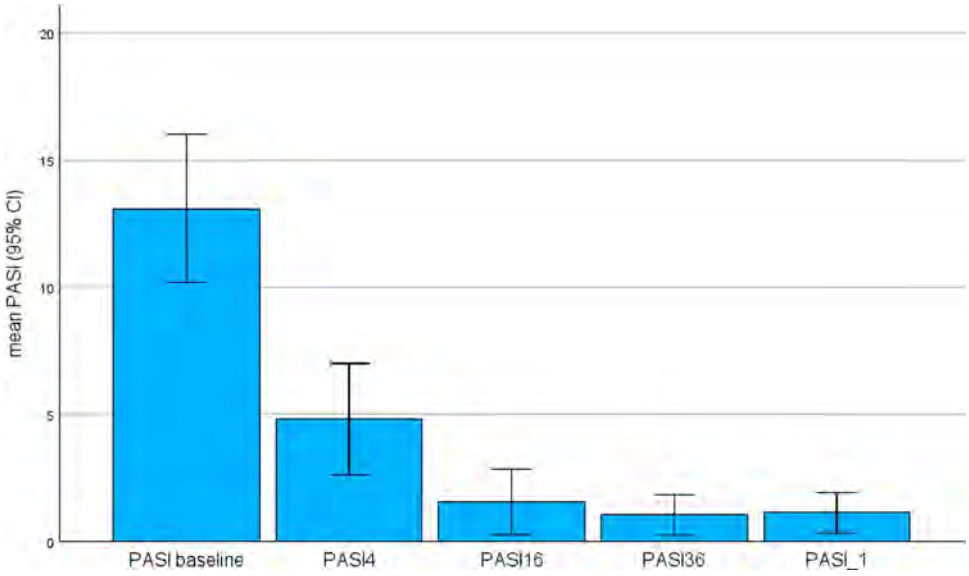


Figure 1. mPASI by Visit.

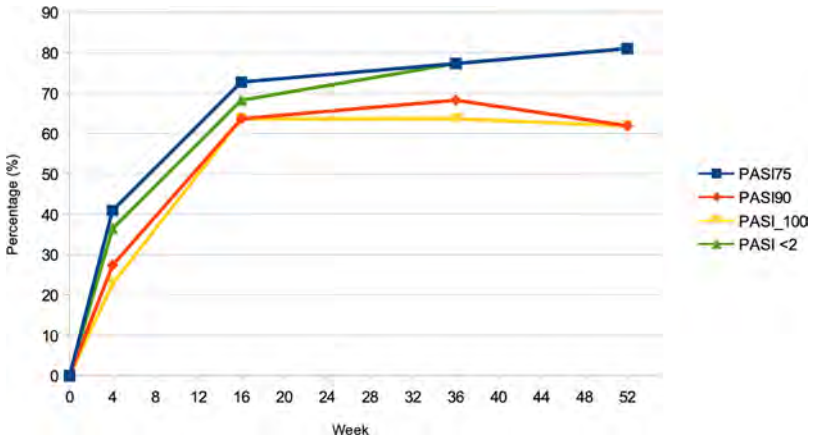


Figure 2. Relative PASI over One Year.

experienced a primary non-response to brodalumab treatment (median PASI at baseline: 9.3 vs median PASI at 16 weeks: 7.8; *P*= 0.3). Both subjects discontinued therapy after the assessment performed at 16 weeks of treatment and were further switched to a biologic of a different class. All three PsA patients maintained clinical remission; however, none of them underwent ultrasound assessment for subclinical disease detection. We found no significant difference in clinical response to brodalumab among the previous failed anti-IL23 or anti-IL12/23. None of patients included in the study experienced any major adverse effect, while 9/23 patients (39.1%) reported mild adverse events mainly related to an increased susceptibility to transient rhinopharyngeal infections and oral candidiasis. Furthermore, no significant depressive symptom was reported by patients enrolled during the scheduled follow-up period.

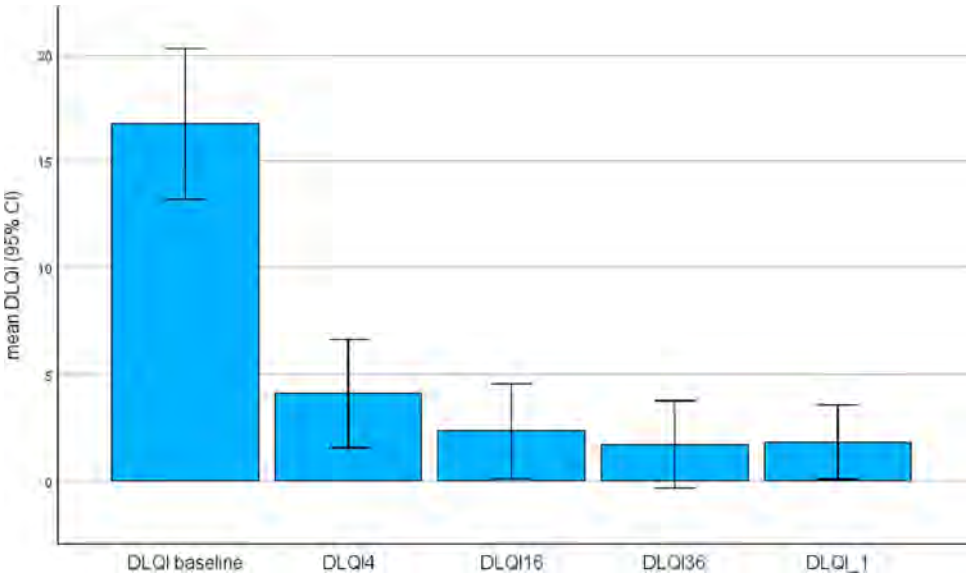


Figure 3. Mean DLQI by Visit.

Discussion

A critical question in the clinical management of psoriasis, and particularly in the case of therapeutic failure of a biologic drug, is whether it is more appropriate to use a drug of the same class or to switch to another class. Some real-world evidence has shown that failure of a specific cytokine-directed treatment does not preclude the use of biologics from other classes or from the same class, making this an interesting research topic regarding the long-term management of psoriasis [10-12].

Unfortunately, to date there is a lack of biomarkers to guide treatment changes. Therefore, intra- or interclass switching in the treatment of psoriasis is currently based on the dermatologist's experience, the severity of the disease, the skin areas involved, and the patient's comorbidities. In this context, real-world data supporting the availability and the rate of efficacy and safety of these treatment changes are highly needed. A recent study showed brodalumab to be one of the biologic drugs with lowest anti-drug-antibody (ADAs) formation rates. This finding supports this biologic agent as a suitable drug for patients who have experienced therapeutic failures potentially due to the presence of ADAs [13]. A recent trial on psoriatic patients experiencing a failure of ustekinumab showed a favorable and earlier effect of brodalumab as compared to guselkumab, thus providing important information to help physicians in the choice of therapy for this subgroup of patients [14].

Recently, Papp et al. conducted an open-label study on a large cohort of patients with psoriasis that demonstrated how brodalumab can be useful in patients who do not respond to TNF-α, IL-12/23, or IL-17 inhibitors. These authors found a PASI 100 response in 40.3% of patients after 16 weeks of treatment with brodalumab and in 45.5% of patients after 26 weeks [15].

Table 4. Percentage of Patients with PASI Score Reduction of 75, 90, and 100, by Visit.

PASI 75		
Visit	**N**	**%**
4 weeks	9/22	40.9
16 weeks	16/22	72.7
36 weeks	17/22	77.3
1 year	17/21	81.0
PASI 90		
Visit	**N**	**%**
4 weeks	6/22	27.3
16 weeks	14/22	63.6
36 weeks	15/22	68.2
1 year	13/21	61.9
PASI 100		
Visit	**N**	**%**
4 weeks	5/22	22.7
16 weeks	14/22	63.6
36 weeks	14/22	63.6
1 year	13/21	61.9
PASI <2		
Visit	**N**	**%**
4 weeks	8/22	36.4
16 weeks	15/22	68.2
36 weeks	17/22	77.3
1 year	17/21	81.0

As shown in Table 4, the percentage of our patients who achieved PASI 100 just after 16 weeks of treatment was 63.6%, a significantly higher proportion compared to the results obtained by Papp et al.

Table 5. Mean DLQI by Visit.

Visit	MeanDLQI (SD)	mDLQI decrease	Paired t-test
Baseline (N=22)	16.9 (± 7.6)		
4 weeks (N=22)	5.1 (± 7.0)	-11.9 (± 9.2)	<0.001
16 weeks (N=22)	2.9 (± 5.5)	-14.0 (± 8.4)	<0.001
36 weeks (N=22)	2.6 (± 5.9)	-14.4 (± 8.6)	<0.001
1 year (N=21)	1.8 (± 3.8)	-15.0 (± 8.2)	<0.001

Additional data on brodalumab efficacy after anti-IL 23 failure are lacking. In this context, our real-life 52-week retrospective study demonstrates good efficacy, speed of action, and safety of brodalumab in psoriasis patients with previous exposure to IL-23 and 12/23 inhibitors with performances similar or superior to those shown in RCTs. The excellent results obtained in our group of patients unresponsive to IL-23 inhibitors could be explained by a more extensive suppressive effect exerted by this drug on the Th-17 pathway. Interestingly, this feature was not associated in our study population with a higher incidence of infectious events or the occurrence of inflammatory bowel disease.

Limitations of the study

The main limitations of our study include its retrospective design and the relatively small number of patients involved. However, it should be noted that IL-23 inhibitors have very high response rates and a consequently limited number of treatment failures. Another limitation of our study was the inability to demonstrate whether main clinical and anamnestic variables could influence the therapeutic performance of brodalumab. Despite the implementation of a Cox regression model, the small sample size, and high remission rate achieved in patients (only two primary failures) probably precluded us from identifying any variable that could affect the key endpoint of the study.

Conclusions

In conclusion, our results suggest that patients who had previously failed therapy with IL-23 or IL12/23 blockers may respond to medical switch to another class of biologics. In particular, brodalumab could be considered a good choice for this group of difficult-to-treat patients because, burdened by several therapeutic failures, they could be considered high-need of an effective and fast-acting drug which also shows a very low immunogenicity risk. However, more data are needed to further explore the possibility of switching therapy among different classes of biologics for the treatment of psoriasis.

Ethics Approval: Institutional review board approval was exempted for this study as its procedure did not deviate from good routine clinical practice. The study was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments.

Consent to Participate: All patients gave written informed consent for the retrospective retrieval of anonymized data.

Consent for Publication: All patients gave written informed consent for the publication of anonymized data.

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Dermatology Practical & Conceptual

Treatment Failure in Scabies: Assessment of Risk Factors in a Multicenter Cross-Sectional Study

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Key words: Scabies, Treatment failure, Permethrin, Information sheet

Citation: Erdem Y, Polat Ekıncı A, Ergun M, Bulat C, Kırker A, Turgut HD, Cesur A, Altunay IK, Topkarcı Z. Treatment Failure in Scabies: Assessment of Risk Factors in a Multicenter Cross-Sectional Study. *Dermatol Pract Concept*. 2025;15(4):5360.
DOI: https://doi.org/10.5826/dpc.1504a5360

Accepted: July 7, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Recent reports of increased prevalence and treatment failure in scabies have raised concerns worldwide. Drug efficacy as well as adherence to treatment are important in treatment failure, and data on the latter are limited.

Objective: We aimed to determine the factors associated with treatment failure in scabies.

Methods: This prospective, multicenter observational study was conducted in three centers, enrolling 230 patients diagnosed with scabies. Treatment outcomes were assessed one month after treatment initiation. Patients completed a questionnaire evaluating factors potentially affecting treatment outcomes. Demographic and clinical characteristics and adherence to treatment recommendations were compared in two groups: successful treatment and treatment failure.

Results: The study included 125 males and 105 females, with a mean age of 24.6 ±17.6 years. Treatment failure was found in 58 patients (25.2%). No demographic parameter or medication was associated with treatment failure. Three independent risk factors for treatment failure (multivariate regression analysis) were lack of application of topical medication to the whole body, (odds ration (OR): 14.33; 95% confidence interval (CI): 2.9–71.4), lack of reapplication after washing hands (OR: 3.5; 95% CI: 1.5–8.0), and not reading of the information form (OR: 13.7; 95% CI: 1.3–80.6).

Conclusion: Treatment failure in scabies is quite common. Incorrect or incomplete application of topical treatment and lack of hygiene measures are the main factors leading to treatment failure. Providing a written information sheet with step-by-step treatment recommendations may contribute to treatment success.

Introduction

Scabies is a highly contagious ectoparasitic disease caused by *Sarcoptes scabiei* var. *hominis* [1]. It primarily spreads through close skin-to-skin contact with an infected individual and less commonly through contaminated objects and clothing [2]. The World Health Organization (WHO) has designated scabies a Neglected Tropical Disease and one of the most common dermatological diseases in developing countries, affecting approximately 400 million people worldwide each year [1].

Scabies are more prevalent in certain geographical areas, including hot, tropical countries, regions with limited water resources, low-income countries, and in special groups such as large families, children, immigrants, and immunosuppressed patients. However, growing data suggest that the scabies outbreaks happen in populations without these risk factors and in some high-income countries [3,4]. In recent years, several studies have also reported a rise in the incidence of scabies in Turkey [5,6].

Clinical diagnosis of scabies has become significantly easier and more practical with the use of dermoscopy in daily practice. Various oral and topical treatment options for scabies are now available in most countries. Despite these diagnostic and treatment advantages, epidemics continue to occur, as in our country [3,4]. It seems necessary to address all potential gaps in patient management, such as drug resistance, inappropriate treatment practices, lack of hygiene practices, and re-infestation. A recent meta-analysis reported drug-related treatment failure as 15.2%, although some studies have reported that this rate increased to 53.3% [7]. The several studies investigating the factors associated with treatment failure have indicated that treatment failure may be related not only to the ineffectiveness of the drugs used but also to additional factors [8-11].

Objective

We aimed to investigate the factors associated with treatment failure in scabies, including demographic, clinical, and treatment-related factors, including topical medications, application, and hygiene measures.

Methods

This multicenter prospective observational study was conducted between January 2022 and June 2023 at three different dermatology clinics. A total of 230 patients diagnosed with scabies were involved in the study. In all patients, diagnosis of scabies was confirmed by a microscopic (applying potassium hydroxide to epidermal scraps to identify scabies mites, eggs, and/or feces under a light microscope) or dermoscopic examination (visualizing scabies mites and/or eggs using dermoscopy) [12].

Baseline visit

At baseline, patient records included demographic and clinical findings, living and environmental conditions, and previous treatments after diagnosis of scabies. Based on the patients, clinical and social features and on the physician's decision, one of the following therapies were administered; permethrin 5%, precipitated sulfur ointment 10%, or a combination treatment (tar cade oil 12.5%-sulfur 12.5%, permethrin 5%-precipitated sulfur ointment 10% or permethrin 5%-tar cade oil 12.5%-sulfur 12.5%). Due to local regulations, only one patient used oral ivermectin during the study period. All patients were verbally informed about how to use the related medication and personal and environmental hygiene processes. Furthermore, all patients were advised to read and follow the information sheets provided, which outlined drug application procedures, including application times, body parts to be applied, and personal and environmental hygiene measures, including cleaning of clothes and house (Supplementary file). These sheets were prepared in line with guideline recommendations [2,13-15].

Second Visit (Control visit)

The control visits were performed one month after the baseline visit. Patients were evaluated and examined for scabies symptoms by the dermatologist who had previously examined that patient. Successful treatment was defined as the complete resolution of previous symptoms and the absence of any evidence of scabies on microscopic or dermoscopic examination. Treatment failure was defined as the presence of symptoms and signs of scabies and confirmation of disease using microscopic and/or dermoscopic examination. Nodular lesions were evaluated by dermoscopic examination, and successful treatment was considered if there was no evidence of active infestation. Pruritus related to xerosis-irritation caused by topical medications that persisted after treatment was distinguished from active infestation by detailed examination and history. Additionally, patients were assessed on their adherence to medication instructions, whether they had read the provided information sheets, and their compliance with hygiene recommendations. In this assessment, the physician used standardized questionnaires; however, individual variations in the responses could not be completely eliminated.

Patients were divided into two groups: those with "successful treatment" and those with "treatment failure". These two groups were compared in terms of demographic, clinical, lifestyle, and environmental characteristics (Table 1).

Table 1. Demographic and Clinical Features of Successful Treatment and Treatment Failure Groups.

	Total Number of Patients (N=230)	Successful Treatment (N=172)	Treatment Failure (N=58)	P
Demographic features				
Sex, N (%) Male Female	 125 (54.3) 105 (45.7)	 96 (55.8) 76 (44.2)	 29 (50.0) 29 (50.0)	0.442
Age, mean (SD)	24.6 ±17.6 20 (0-74)	25.2±17.2 21 (0-74)	22.5±18.8 18 (1-71)	0.311
Age group, ≥18 age	136 (59.1)	106 (61.6)	30 (51.7)	0.217
Comorbidities, n (%)				
Systemic disease*	46 (20.0)	33 (19.2)	13 (22.4)	0.595
Immunsuppression	7 (3.0)	7 (4.1)	0 (0)	0.196
Dermatological disease**	13 (5.7)	9 (5.2)	4 (6.9)	0.742
Atopic dermatitis	8 (3.5)	7 (4.1)	1 (1.7)	0.683
Scabies history				
Disease duration, day, mean (SD)	50.9±116.9 0 (0-900)	45.9±105.6 0 (0-900)	65.7±145.5 0 (0-730)	0.267
Time from onset of symptoms to diagnosis, day, mean (SD)	42.8±69.2 30 (0-700)	38.4±61.5 30 (0-700)	55.8±87.3 30 (3-540)	0.097
Lifestyle and environmental characteristics, n (%)				
Having a baby	33 (14.3)	20 (11.6)	13 (22.4)	**0.043**
Having an elderly or bedridden person	27 (11.7)	18 (10.5)	9 (15.5)	0.301
Having someone with pruritus	185 (80.4)	137 (79.7)	48 (82.8)	0.704
Having a household member with scabies	98 (42.8)	73 (42.7)	25 (43.1)	0.956
Having an immunosuppressed patient	8 (3.5)	7 (4.1)	1 (1.7)	0.683
Treatment, n (%)				
Permethrin 5%	129 (56.1)	90 (52.3)	39 (67.2)	0.066
Precipitated sulfur 10%	115 (50.0)	88 (51.2)	27 (46.6)	0.544
Oral ivermectin	1 (0.4)	1 (0.6)	0 (0)	1.00
Topical corticosteroid	2 (0.9)	2 (1.2)	0 (0)	0.162
Combination treatment***	60 (26.3)	47 (27.6)	13 (22.5)	0.097
Details on topical treatment, n (%)				
Whole body, including between the toes, genital area	213 (92.6)	170 (98.8)	43 (74.1)	**<0.001**
Reapplication to the hands after washing	181 (78.7)	147 (85.5)	34 (58.6)	**<0.001**
Other treatment-related parameters, n (%)				
Information sheets unread	11 (4.8)	2 (1.2)	9 (15.5)	**<0.001**
Nonadherence to cleaning recommendations	36 (15.7)	18 (10.5)	18 (31.0)	**0.001**
Successful treatment of close contacts	210 (91.7)	163 (94.8)	48 (82.8)	**0.004**

* Diabetes mellitus, hypertension, bronchial asthma , hypothyroidism and others.

** Psoriasis vulgaris, seborrheic dermatitis, lichen planus, acne vulga,ris, hand eczema, acne rosacea.

*** Tar cade oil 12.5%+ precipitated sulfur 12.5% or permethrin 5%+precipitated sulfur ointment 10% or permethrin 5%+tar cade oil 12.5%+ precipitated sulfur 12.5%.

Table 2. Multivariate Analysis to Identify Independent Risk Factors Associated With Treatment Failure.

Variables	P	OR	95%CI
Having a baby (<2 years) at home	0.13	0.32	0.130-0.790
Application of the medication to the whole body, including between the toes, genital area	**0.001**	14.33	2.875-71.426
Re-application of the medication to the hands after washing them for any reason	**0.003**	3.47	1.516-7.978
Having a household member with scabies	0.253	2.03	0.602-6.878
Reading the information sheet	**0.004**	13.67	1.321-80.555
Correct implementation of cleaning recommendations	0.224	1.78	0.701-4.548

Logistic regression analysis was used to define independent risk factors. Abbreviations: CI: confidence interval; OR: odds ratio.

The study was approved by the local ethics committee at the İstanbul University, İstanbul Faculty of Medicine, İstanbul, Türkiye (approval number:1065/2022) and was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using SPSS software version 15 (SPSS Inc., Chicago, Illinois, USA). The descriptive statistics comprise the mean, standard deviation, minimum and maximum scores for the numerical variables, and numbers and percentages for the categorical variables. Comparison of independent variables between the two groups was made using Student's t-test for normal distribution and Mann-Whitney U test for those not showing normal distribution. For comparisons of more than two groups, the Kruskal-Wallis test was used. A logistic regression analysis was used to estimate ORs and 95% CIs for the association between the presence of treatment failure and risk factors found to be statistically significant (P<0.05) in univariate analysis.

Results

A total of 230 patients, 125 males (54.3%) and 105 females (45.7%), with a median age of 20 years (range 0–74) were included in the study. The mean time from the onset of symptoms to scabies diagnosis was 42.8±69.2 days, and the mean time from the initial diagnosis was 50.9±116.9 days. Detailed demographic characteristics of the patients are summarized in Table 1.

The most commonly applied topical treatments were permethrin (56.1%), precipitated sulfur ointment (50%), and combination therapy (26.3%). Topical medication applications and hygiene practices were evaluated. The majority of the patients (92.6%) had applied the medication properly to the whole body, including between the fingers, genital area, and body folds. However, 78.7% of the patients had reapplied the medicine to their hands after washing their hands for any reason. On average, 4.8% of the patients did not read the information sheets, and 15.7% did not adhere to cleaning/hygiene recommendations (Table 1).

Treatment failure was identified in 58/230 patients (25.2%). No demographic parameter or topical medication was associated with treatment failure. Socioeconomic status was similar in both groups. On the other hand, the following parameters related to the treatment procedures were found to be significantly lower in the treatment failure group; "the whole-body application including between the fingers," "re-applying the medication after washing hands," and "successful treatment of close contacts " (P<0.001, P<0.001, and P=0.004, respectively). Moreover, the treatment failure group included a higher percentage of patients who did not read the information sheet and did not perform appropriate personal and environmental hygiene procedures. The other factor associated with treatment failure was 'having a baby at home' (P=0.043) (Table 1).

Multivariate regression analysis showed a lack of application to the whole body, including between the fingers (OR: 14.33; 95% CI: 2.9–71.4), lack of reapplication after washing hands (OR: 3.5; 95% CI: 1.5–8.0), and not reading the information sheet (OR: 13.7; 95% CI: 1.3–80.6) (Table 2) to be independent risk factors for treatment failure.

Discussion

In the present study, treatment failure was observed in approximately one-quarter of the patients. Incorrect application of the medication and not reading the information sheet were identified as independent risk factors associated with treatment failure. Treatment failure in scabies has been increasingly reported in recent years, ranging from 15.2% to 53.3% [7-9]. This variability may be attributed to differences in relevant patient populations, medications, treatment methods, countries, communities, and study methodologies. Three possible causes for treatment failure

in scabies have been suggested: misuse of the prescribed medications, reinfestation through untreated close contacts and inadequately cleaned clothing, bedding, and furniture, and lastly, resistance of mites to drugs [13]. Identifying which of these factors has led to treatment failure is critical to the management of this annoying disease.

In our study, the most common factor associated with treatment failure was incorrect or incomplete application of topical medications, such as not applying treatment to the entire body, including between the fingers, and not reapplying medication after washing hands. As the guidelines emphasize in detail, the appropriate application of topical treatments is critical to the successful treatment of scabies [2,14-16]. A limited number of studies in the available literature evaluated errors/deficiencies associated with the application of medications in scabies. Ulff et al. used a fluorescent test cream to assess neglected areas during topical medication application. The striking result was that even individuals without physical limitations neglected a third of the target body area [17]. Another study evaluated 21 scabies patients by applying fluorescent cream after being instructed on how to apply the medication [18]. Of these patients, 62% neglected the ankles, 33% neglected the areas between the toes, 24% neglected the sacral area, and none of the patients applied the treatment correctly [18]. Since the use of topical treatments requires a high degree of patient compliance, patients should be instructed on negligible areas and the duration and intervals of application of the drug [2,14]. In some resistant patients, hospitalization and application by a nurse may be considered [18].

Another factor associated with treatment failure in the present study was not reapplying the medication after washing hands (41.4% in the treatment failure group). In an observational study investigating treatment failure in scabies, 58% of patients reported not reapplying medication after washing their hands [11]. Since effective topical treatment in scabies requires that the medication remain on the skin for a certain period, all patients should be instructed to reapply the medication immediately after washing it off or removing it before the recommended time. The latest guidelines also specifically emphasize reapplying scabies medication after washing and drying the hands [14,16]. Another finding of the present study that shows the importance of step-by-step instruction for effective treatment is the correlation between not reading the information sheets and treatment failure. The details of topical medications and additional hygiene measures used in the treatment of scabies can be difficult to remember. Therefore, providing a written form with step-by-step instructions, as recommended by the guidelines, may increase patient compliance and therefore treatment success [2,14].

The development of resistance to drugs used for scabies is a controversial issue, and it is debated whether treatment failure is due to real drug resistance or to incorrect application of drugs. In recent years, studies have reported resistance to permethrin, suggesting that this resistance may be more related to the drug itself than to its improper application [19,20]. Currie et al. identified genetic mutations in voltage-gated sodium channels of the mite that causes permethrin resistance [21]. A recent systematic review and meta-analysis examining treatment failure in scabies revealed that ivermectin and permethrin had lower rates of failure, while a single dose of ivermectin increased the risk of treatment failure compared to two doses [7]. There is also evidence that there is no resistance to permethrin. Yürekli exposed live mites to concentrations of 5%, 7%, and 10% permethrin and found that all tested concentrations were lethal to the parasites [22]. The author emphasized that, rather than resistance to permethrin, treatment failure was most likely due to incorrect application of the medication or lack of effective treatment of family members [22]. In our study, we found no statistically significant difference between the two groups in terms of topical medication options, suggesting that proper application and hygiene measures were more critical to successful treatment than was the type of medication. To assess real drug resistance, studies conducted in homogeneous groups and examining drugs specifically are needed.

Improper or incomplete application of cleaning measures, lack of successful treatment in close contact, and having a baby at home were found to be associated with treatment failure in univariate analysis. These were also factors that had the potential to cause treatment failure through reinfestation.

Several studies have evaluated the causes of treatment failure in scabies. Some of the factors reported are inadequate treatment of close contacts, lack of second treatment within 7–14 days, inadequate effectiveness of current treatments [11], limited mobility and use of topical corticosteroids before diagnosis [9], a delay of more than one month between the onset of pruritus and scabies treatment, the use of single-dose ivermectin, and failure to disinfect objects with acaricides [8]. Magikami et al. reported that impaired immunity and problematic behavior increased the recurrence of scabies [10]. Both our study and the existing literature show that success in treating scabies depends not only on the presenting patient but also on those living with the patient, their behavior, and general cleaning measures.

Limitations

The main limitations of our study include a relatively small number of patients, considering the high prevalence of the disease. Other limitations are the lack of standardization across patient groups and an assessment of baseline disease severity. Variations in demographic characteristics, disease severity, socioeconomic status, sociocultural levels,

and environmental conditions may have impacted the study's outcomes and limited the generalizability of the results. On the other hand, the existence of these variations is valuable in that they represent a cross-section of real-life society.

Finally, the other important point was that the use of systemic ivermectin due to local factors was very limited. The use of ivermectin reduces the likelihood of treatment resistance, so limited use may have increased treatment failure.

Conclusion

Treatment failure for scabies has become a growing global concern affecting individuals across all socioeconomic groups. Our prospective study examining factors associated with treatment failure showed that inappropriate use of topical medication was the major risk factor for treatment failure, regardless of the medication used. In addition, inadequate cleaning of living space, untreated close contact(s), and having a baby at home were also found to be associated with treatment failure. To improve treatment outcomes, we recommend providing patients with written information sheets that outline the treatment process step by step, encouraging them to read; this can increase patient compliance and improve overall success rates.

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Dermatology Practical & Conceptual

Non-Invasive Skin Imaging of Pseudoxanthoma Elasticum Using Dynamic Optical Coherence Tomography: Insights from a Case-Control Study

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Key words: Pseudoxanthoma elasticum, Optical coherence tomography, Elastic tissue alterations, Cutaneous imaging, Noninvasive skin assessment

Citation: Chello C, Laghi A, Melchiorri L, et al. Non-Invasive Skin Imaging of Pseudoxanthoma Elasticum Using Dynamic Optical Coherence Tomography: Insights from a Case-Control Study. *Dermatol Pract Concept*. 2025;15(4):5260. DOI: https://doi.org/10.5826/dpc.1504a5260

Accepted: May 19, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Pseudoxanthoma elasticum (PXE) is a rare genetic disorder characterized by progressive mineralization and fragmentation of elastic fibers, leading to multisystem involvement. Diagnosis relies on clinical features, histopathology, and, in selected cases, genetic testing, with cutaneous manifestations often representing the earliest signs.

Objective: To validate dynamic optical coherence tomography (D-OCT) as a noninvasive diagnostic method for detecting PXE-related dermal abnormalities.

Methods: In this case-control study, PXE patients evaluated at Umberto I Policlinic (Rome, Italy) between May 2023 and September 2024 underwent clinical and instrumental assessment. The left lateral cervical, retrocervical, left axillary, and periumbilical folds were analyzed using a standardized 0–3 clinical severity scale and D-OCT imaging. Control subjects were individuals undergoing routine mole checks. D-OCT quantified fiber density, attenuation, and vessel density at 300 µm and 500 µm depths. Statistical analysis included Spearman's correlation and the Mann-Whitney U test, with $p < 0.05$ considered significant.

Results: Twenty-three PXE patients and eleven controls were included. Cutaneous involvement was observed in 91.30% of patients, predominantly in retrocervical (86.95%) and lateral cervical (82.60%) areas. Clinical severity significantly correlated with D-OCT fiber density in the retrocervical region ($\rho = 0.507$). Compared with controls, PXE patients showed reduced fiber density and increased attenuation across most regions, except the axillae. At 500 µm depth, vessel density was markedly decreased in the axillary area, with approximately 2.5-fold fewer vessels in PXE skin.

Conclusion: D-OCT effectively detects dermal alterations in PXE, including subclinical changes, providing a promising noninvasive alternative to skin biopsy.

Introduction

Pseudoxanthoma elasticum (PXE) is an autosomal recessive disorder characterized by mineralization and fragmentation of elastic fibers, leading to symptoms in the skin (papular lesions in flexural areas), eyes (angioid streaks, peau d'orange, subretinal neovascularization, and hemorrhage), and cardiovascular system (peripheral artery disease, gastrointestinal bleeding, ischemic stroke) [1]. It is caused by biallelic pathogenic variants in the ATP (adenosine triphosphate)-binding cassette subfamily C member 6 (*ABCC6*) gene, with over 500 identified pathological variants [2]. Although the precise role of *ABCC6* in PXE pathogenesis remains unclear, it encodes a transmembrane transporter protein that mediates ATP efflux, which is hydrolyzed to inorganic pyrophosphate (PPi) and adenosine monophosphate (AMP). Extracellular PPi provides a potent anti-mineralization effect (which is deficient in PXE), while AMP hydrolysis to inorganic phosphate and adenosine affects cellular properties by modulating the purinergic pathway [3,4].

Currently, PXE diagnosis can be definitive, probable, or possible based on standardized clinical signs, histological features, and *ABCC6* mutational status, although genetic confirmation is not mandatory [5].

The worldwide prevalence of PXE is estimated to be between 1 per 25000 and 1 per 100000, with a female predominance and onset typically in childhood or adolescence [4]. The skin is generally the first affected organ, with flexural surfaces, probably because of the repetitive friction, developing isolated papules or plaques that may coalesce into reticulated plaques, giving a cobblestone appearance [6]. Later, skin laxity and wrinkles may appear [4]. The yellow tone of affected skin, resembling true xanthomas, has led to the name "pseudoxanthoma elasticum" [4].

Specific stains such as Verhoeff-van Gieson for elastin and Von Kossa for calcium deposits can demonstrate short, fragmented, clumped, and calcified mid-dermal elastic fibers in affected skin biopsies [5]. Collagen fibers may also exhibit splitting, thickening, coiling, calcification, and even flower-like deformation [7].

Thus far, studies on PXE cutaneous features have relied on clinical examination, dermoscopy, and histology. However, given that cutaneous manifestations are typically the earliest signs of PXE, noninvasive imaging techniques targeting the dermis such as cutaneous optical coherence tomography (OCT) could be valuable for early detection of abnormalities in collagen and elastic fibers and ectopic calcifications in suspected PXE individuals and for patient follow-up [8,9].

OCT is based on the principles of Michelson interferometry. It uses an optical probe to direct a light beam from a broad-bandwidth light source, typically around 1300 nm, through a beam splitter into both a sample arm and a reference arm. The reflected light is then sent back to the interferometer for detection, where interference fringes are observed when the optical path length from the sample arm matches the short coherence length of the reference arm's laser [10]. OCT provides in vivo, two-dimensional, cross-sectional en-face images of skin areas covering several square millimeters, with a penetration depth of up to 1.5 mm and a spatial resolution between 3 and 15 µm [11]. High-definition OCT enables visualization even of individual cells [12]. Another technique, named dynamic OCT (D-OCT), also detects motion in the OCT images and can reveal both tissue structure and blood vessel morphology by capturing changes between consecutive frames [11].

Objective

The study aimed to validate D-OCT as a noninvasive diagnostic tool for detecting PXE-related abnormalities in dermal tissue.

Methods

Design and Settings

This case-control study was conducted at the Neurocutaneous Rare Diseases Center of Umberto I Policlinic (Rome, Italy). We enrolled all patients with a definitive diagnosis of PXE, established according to the criteria proposed by Plomp et al. [5] who attended our outpatient clinic from

May 2023 to September 2024 and agreed to participate in the study. Controls comprised individuals who voluntarily underwent general dermatology examinations for oncological prevention (mole check-up) during the same period, with no preexisting severe dermatological condition.

Written informed consent was obtained from all participants, and the study adhered to the principles outlined in the Declaration of Helsinki, good clinical practice guidelines, and all applicable laws and regulations.

Patient Evaluation

Dermatological Evaluation

All patients underwent dermatological evaluation of the lateral cervical, retrocervical, axillary, and periumbilical regions. To minimize variability due to potential asymmetries and to ensure a consistent and standardized assessment, only the left sides of the lateral cervical and axillary folds were examined.

Clinically, each fold was scored using a 4-point scale ranging from 0 to 3:

0: no cutaneous sign

1: presence of papules

2: presence of confluent papules or plaques

3: skin laxity and wrinkles

No intermediate grades were assigned.

Instrumental Evaluation

A VivoSight Dx multi-beam OCT dermatological scanner (manufactured by Michelson Diagnostics Ltd., Kent, UK) equipped with proprietary D-OCT imaging software was used to evaluate all the aforementioned anatomical sites. The optical resolution of the scanner is 7.5 µm laterally and 5 µm axially, providing clear visualization of skin morphology and fine blood vessels. The probe offers a field of view of 6 mm x 6 mm and an imaging depth ranging from 1.0 to 2.0 mm. Additionally, the handheld probe features a color camera to facilitate accurate lesion placement and provide contextual images. No skin preparation, such as gel application, was necessary [13].

Data Analysis

D-OCT images were examined focusing on collagen and elastic fibers and vessels. For fiber analysis, an automatic software, namely OCT attenuation coefficient, provided two parameters: density coefficient and attenuation coefficient. For vascular analysis, images acquired at depths of 300 µm and 500 µm were processed using graphic reprocessing software (ImageJ), which provided vessel density measurements at these specific depths.

Descriptive statistics (mean, median, standard deviation) were employed to synthesize the data, and correlations were determined using Spearman's ρ. To identify differences between patients and controls, the non-parametric Mann-Whitney U test was utilized, with a significance level set at $P<0.05$.

Results

A total of 23 patients with PXE and 11 healthy controls were included in the study. The mean age of the PXE patients was 46.39 years (standard deviation: 15.91), with five males (21.74%) and 18 females (78.26%) (Table S1). The control group had a mean age of 46.72 years (standard deviation: 16.78), with four males (27.27%) and seven females (72.73%).

Cutaneous involvement was observed in 21 of the 23 PXE patients (91.30%). The most frequently affected site was the retrocervical fold, involved in 20 patients (86.95%), followed by the lateral cervical fold in 19 patients (82.60%), the axillary region in 12 (52.17%), the inguinal fold in nine (39.13%), and the cubital fold in five patients (21.74%). Notably, no clinical alterations were detected in the periumbilical region (Table 1).

Analysis of fiber characteristics revealed a statistically significant positive correlation between clinical severity (graded on a 0–3 scale) and the fiber density coefficient, measured via D-OCT, specifically in the retrocervical fold, the most frequently affected area in this cohort (Spearman's $\rho=0.507$; $P=0.014$). However, this correlation was less pronounced in patients with milder clinical manifestations (severity index <2), as shown in Figure 1.

When comparing PXE patients with healthy controls, significant differences in fiber density and attenuation were observed across all examined anatomical sites (Figure 2), except for axillary region (Table 2). It should be noted that the p-value for attenuation in the periumbilical region appeared as 0.05 due to rounding; however, the actual value was slightly below 0.05, thus fulfilling the criterion for statistical significance. Overall, PXE patients demonstrated lower fiber density values (ranging from 82.89% to 88.04%) and higher attenuation values (ranging from 114.53% to 138.21%) compared to controls.

Table 1. Number of PXE patients showing cutaneous involvement in the anatomical regions examined.

Region	Patients (N)	Percentage (%)
Retrocervical fold	20	86.95%
Left lateral cervical fold	19	82.60%
Left axillary fold	12	52.17%
Inguinal fold	9	39.13%
Cubital fold	5	21.74%
Periumbilical fold	0	0.00%

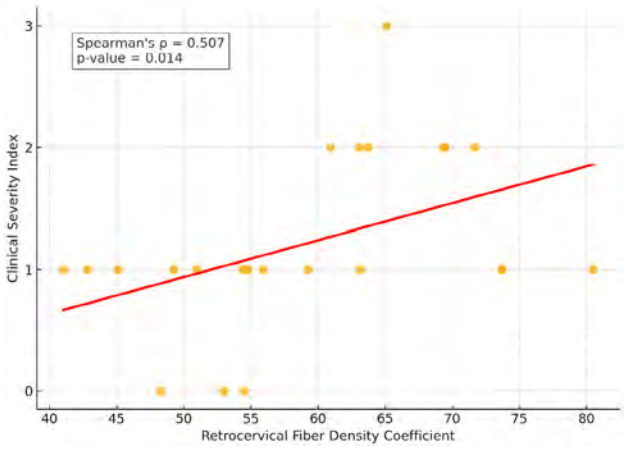


Figure 1. A positive statistically significant correlation was observed between the retrocervical fiber density coefficient and the clinical severity index (Spearman's ρ=0.507; *P*=0.014), as illustrated by the red regression line. This association appeared more consistent in patients with moderate-to-severe clinical involvement (severity index ≥2), whereas values were more scattered among those with milder manifestations (severity index <2).

Regarding vascular parameters, D-OCT assessments at depths of 300 µm and 500 µm revealed no significant correlation with clinical severity, nor significant differences between patients and controls, except at 500 µm depth in the axillary region (Figure 3). At this level, vessel representation was nearly 2.5 times lower in PXE patients compared to controls (3479.83 vs. 8599.73), as detailed in Table 3.

Discussion

Pseudoxanthoma elasticum is a rare genetic metabolic disorder in which dermal changes often manifest earliest and most prominently in friction-prone flexural areas. In line with previous studies, the retrocervical, lateral cervical, and axillary regions were among the most affected in our cohort, while the periumbilical area, less subject to mechanical stress, was typically spared (Table 1) [4,6].

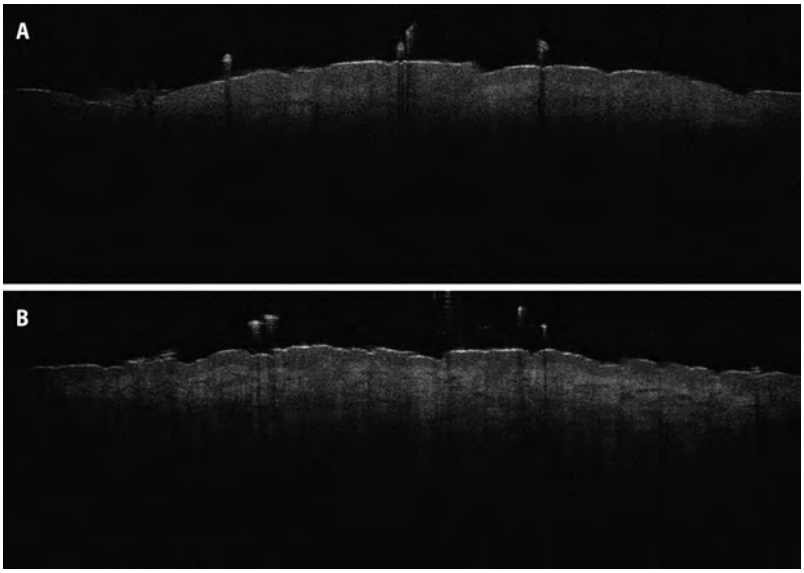


Figure 2. D-OCT images of (A) the left lateral cervical region in a PXE patient and (B) a control. In the PXE patient, the upper dermis exhibits decreased reflectivity and a more heterogeneous structure compared to the control. Quantitative analysis highlights a significant reduction in collagen density, along with noticeable disorganization of elastic fibers (refer to Table 2 for details).

Table 2. Mean Fiber Density and Attenuation Coefficients in PXE Patients and Controls, as Calculated using the OCT Attenuation Coefficient Software. All differences were statistically significant, except in the left axillary region.

	Retrocervical fold		Left lateral cervical fold		Left axillary fold		Periumbilical fold	
	Mean density	Mean attenuation	Mean density	Mean attenuation	Mean density	Mean attenuation	Mean density	Mean attenuation
Cases	59.29	0.0026	62.82	0.0025	63.15	0.0026	62.21	0.0024
Controls	71.53	0.0019	71.35	0.0019	70.33	0.0024	72.90	0.0021
Cases/Controls Ratio	82.89	138.21	88.04	132.40	89.79	107.55	85.34	114.53
P-value	0.00	0.00	0.01	0.00	0.19	0.12	0.00	0.05

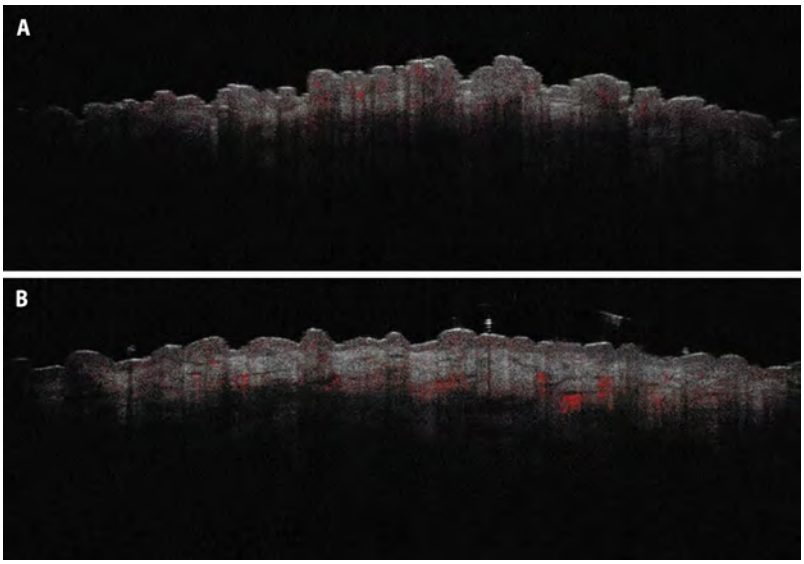


Figure 3. D-OCT images of (A) the left axillary fold in a PXE patient and (B) a control. In the PXE patient, vessel density is markedly reduced in this area, as confirmed by quantitative analysis (refer to Table 3 for details).

Table 3. Mean Vessel Density at 300 µm and 500 µm Depths in PXE Patients and Controls, analyzed using ImageJ Software. A statistically significant difference was observed only in the left axillary region at 500 µm depth.

	Retrocervical fold		Left lateral cervical fold		Left axillary fold		Periumbilical fold	
Average Vessel Density:	300 µm Depth	500 µm Depth	300 µm Depth	500 µm Depth	300 µm Depth	500 µm Depth	300 µm Depth	500 µm Depth
Cases	9923.39	21659.41	8330.91	16654.48	1487.52	3479.83	677.83	2488.91
Controls	7200.36	18064.00	11705.18	26030.55	1891.91	8599.73	611.55	3043.27
Cases/ Controls Ratio	137.82	119.90	71.17	63.98	78.63	40.46	110.84	81.78
P-value	0.61	0.11	0.42	0.80	0.21	0.00	0.91	0.66

Noninvasive techniques like D-OCT, which provides precise numerical data regarding fiber density, attenuation, and tissue vascularization, can effectively complement clinical assessments. In our study, D-OCT showed concordance with clinical findings, particularly in evaluating fiber density in the retrocervical region, the area most frequently involved (Figure 1). Conversely, in less frequently affected areas, or in cases of milder retrocervical involvement, this concordance tended to decrease. This is likely because D-OCT, being more sensitive, can detect minimal abnormalities that are not clinically visible. In fact, D-OCT revealed lower fiber density and higher attenuation even in the periumbilical region, despite the absence of clinical signs (Table 2).

A larger cohort may help to identify statistically significant differences in fiber parameters in additional areas, including the axillary folds, where p-values in the present study exceeded 0.05 (Table 2).

Given these findings, D-OCT may emerge as a valuable tool for the early, noninvasive diagnosis of PXE, potentially reducing the need for invasive procedures such as skin biopsy, which remains a useful diagnostic criterion [5]. For example, D-OCT could be used for rapid, painless screening of family members of PXE patients and could improve monitoring of disease progression by enhancing both sensitivity and specificity.

However, D-OCT encounters challenges in vascular assessment. No significant difference in vascular parameters was observed between PXE patients and controls, particularly at the 300 µm depth (Table 3). This may be explained by age-related vascular changes, such as increased stiffness, decreased density, and disorganized architecture [14], that affect both PXE patients and healthy individuals. Interestingly, at 500 µm depth, only in the axillary region, notable differences emerged. This could be because the deep histological alterations typical of PXE in the axilla may outweigh the effects of photoaging, which more heavily impacts other sun-exposed areas evaluated in this study [14].

Limitations

While this study included a relatively small sample size, it should be noted that it represents a pilot investigation into a rare disease, whose incidence is estimated to be between 1 in 25,000 and 1 in 100,000 individuals. Moreover, this is the first study to apply D-OCT in this specific context. Another limitation is that D-OCT does not clearly distinguish between elastic and collagen fibers, which may both be morphologically altered and calcified in PXE patients, particularly when their thickness falls below the optical resolution of the technique [5,7]. However, these histological changes indirectly influence D-OCT parameters, allowing for their measurement. Future studies with larger patient cohorts and more advanced technology will corroborate or contradict our findings.

Conclusion

D-OCT can identify dermal alterations in PXE patients, even in clinically unaffected areas. This technique offers a promising, sensitive, noninvasive diagnostic alternative to skin biopsies, with great potential for early detection and ongoing monitoring of the genetic disorder.

Ethical Issues: The authors warrant that any national or international law on human and environmental rights was not violated.

Ethics Statement: The patients in this manuscript have given written informed consent to publication of their case details.

Consent to Publish: The authors give the *Dermatology Practical & Conceptual Journal* the exclusive rights to publish their article, in whole or in part, in the aforementioned journal. The data that support the findings of this article are available from the corresponding author upon reasonable request.

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Supplementary file

Table S1. Demographic Characteristics (Age and Sex) of Cases and Controls Included in the Study.

Cases		Controls	
Age (years)	Sex	Age (years)	Sex
39	Female	59	Female
25	Female	51	Female
46	Male	39	Male
42	Female	25	Male
21	Female	68	Male
23	Female	38	Female
30	Female	40	Female
61	Female	38	Female
72	Female	22	Male
50	Female	63	Female
43	Female	71	Female
56	Female		
76	Female		
53	Male		
29	Male		
56	Female		
41	Female		
68	Male		
45	Male		
37	Female		
33	Female		
53	Female		
68	Female		

Dermatology Practical & Conceptual

Post-COVID Hair Loss in the Indian Subcontinent: Clinical Patterns and Association with Disease Severity

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Key words: Alopecia, COVID-19, Post-COVID hair loss, Stress, Telogen Effluvium

Citation: Vurimindi Kadudas A, Katta TP, Gala N, et al. Post-COVID Hair Loss in the Indian Subcontinent: Clinical Patterns and Association with Disease Severity. *Dermatol Pract Concept*. 2025;15(4):5417. DOI: https://doi.org/10.5826/dpc.1504a5417

Accepted: March 6, 2025; **Published:** October 2025

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Funding: The authors gratefully acknowledge the financial support provided for this study by the ICMR-STS Research project grant.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

ABSTRACT

Introduction: As the pandemic plateaus, post-COVID alopecia is resurfacing in India. COVID-19 remains a pivotal cause of alopecia, and the diagnosis of post-COVID alopecia aids in better treatment outcomes.

Objectives: To estimate the prevalence of post-COVID alopecia and to evaluate the association between alopecia and COVID severity among other factors.

Methods: A retrospective cross-sectional study was conducted among patients admitted to the COVID ward. Patients willing to participate were asked to fill in a pretested semi-structured questionnaire, and the PSS-10 (Perceived Stress Scale) was used to evaluate stress. Data were analyzed using the SPSS version 24.

Results: Prevalence of COVID-19-induced hair loss was 37.8%. Age, sex, COVID severity, and higher stress were the significant factors, with p-value <0.05. Female sex, COVID severity, and high stress

levels came to be significant independent predictors of hair loss. A majority of participants (46.9%) noticed hair loss within three months of contracting the disease.

Conclusion: This study stands to be a pioneer project to investigate the prevalence of COVID-19-induced alopecia in India. The prevalence rate of 37.8% with a significant association with severity of COVID-19 highlights the importance of reviewing patient history to provide proper treatment and reassurance.

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Introduction

The COVID-19 pandemic caused by SARS-CoV-2 has wreaked havoc across the globe, with over 774 million cases reported [1]. Post-acute COVID-19 syndrome, with long-term complications emerging after four weeks, is a growing area of research [2]. Diffuse non-scarring alopecia resembling telogen effluvium has been documented, predominantly within the first month after COVID diagnosis [3-6]. Pandemic-induced stress could potentially aggravate alopecia [5, 7, 8]. Pathological alopecia is indicated by a daily hair loss count of 100 or more, necessitating clinical examination [9]. This underscores the importance of early diagnosis, regular dermatological evaluation, and psychological support. Limited research in India necessitates further studies to determine the prevalence and associated factors, facilitating targeted management and counseling strategies.

Review Of Literature

SARS-CoV-2 has caused a global pandemic, with diverse clinical manifestations including dermatological issues such as alopecia [1, 10]. Post-acute COVID-19 syndrome, characterized by long-term complications emerging beyond four weeks from onset, including telogen effluvium (TE), has been documented in numerous patients [11-19]. Telogen effluvium, an alopecia generally seen three months after a systemic insult such as febrile states, stress, or nutritional insult, is usually self-limited [7, 11, 12, 20-22]. Multicenter studies have documented a rise in diffuse, non-scarring alopecia suggestive of TE after recovery from COVID-19 [2-5, 8, 11, 13-16, 23-26].

Evidence suggests a stronger association between TE and COVID-19 compared to other alopecia forms [27]. Potential mechanisms for post-COVID alopecia include direct endothelial damage by the virus, immune-mediated microthrombi, cytokine-induced follicular inflammation, and drugs used for treatment [5, 6, 28]. ACE2 receptors, which have a 10–20-fold higher affinity for SARS-CoV-2 than for SARS-CoV-1, are present in the basal hair follicle layer [29]. COVID-19 may also exacerbate alopecia through the TMPRSS2 gene affecting androgen pathway [23, 30].

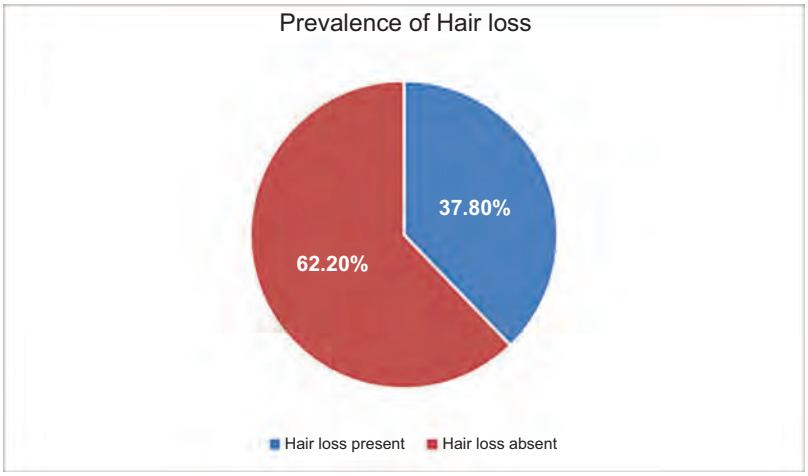


Figure 1. Prevalence of alopecia among post COVID patients. This pie chart illustrates the prevalence of hair loss among study participants, showing the percentages with and without hair loss.



Figure 2. Dietary habits of study participants. This figure illustrates the distribution of dietary habits among participants, comparing mixed and vegetarian diets, presented as percentages.

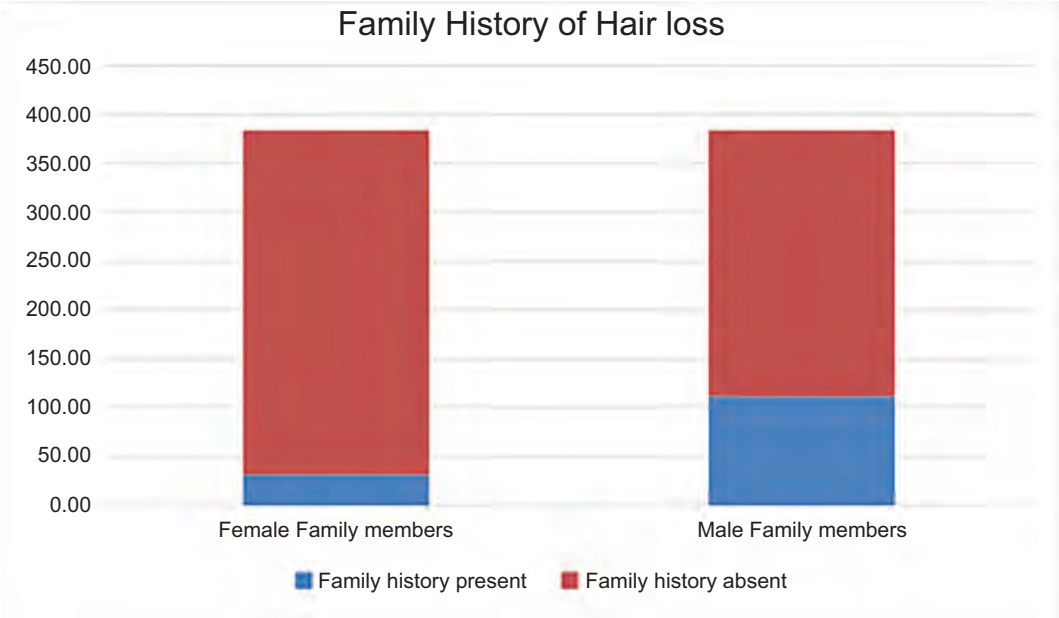


Figure 3. Family history of hair loss. The figure shows the prevalence of hair loss in male and female family members, with data presented as the percentage of participants reporting a family history of hair loss in each group.

Table 1. Distribution of COVID Severity among Study Participants

COVID severity	Frequency (N)	Percentage
Mild	168	43.8 %
Moderate	175	45.6 %
Severe	41	10.7%
Total	384	100%

N: number of participants

Abdulwahab R A et al. found the prevalence of post-COVID hair loss to be 48.5%, predominantly affecting females within 2–3 months post-infection [4]. Other studies focusing on the variables associated with post-COVID alopecia have found female sex, longer hospital stays, or disease severity to be significant [14, 19, 25, 26, 31]. However, Monari P et al. reported no association between TE and COVID-19 features [25].

Table 2. Hair Loss Noticed for the First Time by Study Participants.

When was hair loss first noticed?	Frequency (N)	Percentage
Within 3 months	68	46.9%
4–6 months	19	13.1%
Not sure	45	31%
Longer	13	9%
Total	145	100%

N: number of participants

Table 3. Duration of Hair Loss among Study Participants.

Duration of hair loss noticed	Frequency (N)	Percentage
Within 3 months	20	13.8%
3–6 months	20	13.8%
Not sure	44	30.3%
Longer	61	42.1%
Total	145	100%

N: number of participants

Table 4. Type of Hair Loss expressed as by Study Participants.

Type of hair loss	Frequency (N)	Percentage
Patterned hair loss	7	4.8%
Generalised hair loss	138	95.2%
Total	145	100%

N: number of participants

Table 5. Perceived Stress Scale among Study Participants.

PSS	Frequency (N)	Percentage
Low stress	89	23.2%
Moderate stress	268	69.8%
High stress	27	7%
Total	384	100%

N: number of participants

Stress from the pandemic and hair loss itself likely exacerbate alopecia via the brain-hair follicle axis and by a shift to the telogen phase [7, 17, 20, 28, 31-33]. Studies have revealed that post-COVID patients generally suffer from moderate-to-high stress, which may be related to alopecia [2, 34-38]. Post-COVID TE generally resolves spontaneously but can impact mental well-being due to the importance given to cosmesis. The limited research in India underscores the need for studies to elucidate the associated factors, allowing for effective management and patient counseling.

Objectives

The primary objective was to estimate the prevalence of alopecia among post-COVID patients who were admitted to a tertiary care center in Telangana. The secondary objectives were to investigate the association between alopecia and disease severity of COVID-19 and to investigate factors associated with alopecia among post-COVID-19 patients.

Materials and Methods

A cross-sectional study was conducted among patients admitted to the COVID ward in a tertiary care center in Telangana from January 2021 to December 2021. There were 1120 patients admitted in this period. On obtaining approval from the institute's ethics committee, the medical records department was approached to access the patient records. Medical records were retrieved, and information on patients' COVID severity and investigations were collected. COVID-19 severity was graded according to ICMR guidelines [39].

The patients were contacted, and those willing to participate after being informed regarding the purpose of research were included. A meeting was arranged for data collection at the hospital at the patient's convenience.

The inclusion criteria were as follows: i) patients who had tested positive for COVID-19 by RTPCR and who were admitted to the tertiary care center in Telangana between January 2021 and December 2021; ii) patients with no previous history of alopecia or scalp disorders; iii) patients who gave their consent for the study.

The exclusion criteria were: i) pregnant patients and patients below 18 years of age; ii) patients suffering from comorbidities such as hypertension, diabetes mellitus, thyroid disorders, anemia, and any endocrine and metabolic disorders.

Sample size calculation: The prevalence of alopecia among COVID-19 patients was reported to be 48% [4]. At a 95% confidence interval(CI), considering absolute precision of 5%, the calculated sample size was 384.

Study tool: A pre-tested semi-structured questionnaire was used to collect information on alopecia, its duration,

and information of co-existing comorbidities at the time of admission. Perceived Stress Scale (PSS)-10 was used to assess the stress level of post-COVID patients to find any association with alopecia. A score of 0–13 was considered low stress, 14–26 was moderate stress, and 27–40 was considered high stress [40].

Statistical Analysis

Data were entered in an excel spreadsheet and analyzed using SPSS version 24. The prevalence of alopecia is expressed as frequency and percentages. All the quantitative variables, like age and duration of illness, are expressed as mean +/- standard deviations. Qualitative variables like severity of illness are expressed as proportions. Factors associated with alopecia in COVID patients were found using the Chi-squared test. Multivariate analysis was done using multiple logistic regressions and is expressed as adjusted odds ratio (OR) with 95% CI. A p-value of <0.05 was considered as statistically significant.

Results

The sociodemographic details of the study participants were as follows: the mean age of the participants was 41.2 years (SD=15.1 years), ranging from 18 to 83 years; 50% of the participants were ≥40 years. Most of the participants (N=205, 53.4%) were female.

Regarding the severity of COVID-19 among our study participants, the ICMR Guidelines were used for severity categorization; it was noted that the majority had moderate illness, i.e., 175 (45.6%) (Table 1).

Regarding the prevalence and characteristics of alopecia expressed by the study participants, the prevalence of alopecia among the patients of this study was 37.8% as depicted in Figure 1, with the majority (N=68, 46.9%) of the study participants reporting alopecia starting within three months of suffering from COVID-19 as shown in Table 2. The duration and type of hair loss are detailed in Tables 3 and 4, respectively.

Most (N=98, 68.1%) of the participants did not take any action after suffering from alopecia, while 16.7% reported having approached a dermatologist; 5.7% reported having had hair styling / chemical procedures done during pandemic.

When asked regarding the frequency of hair washing, 49.7% reported washing on alternate days, 39.8% washed once weekly, and 10.4% washed daily. Figure 2 presents an overview of the participants' dietary habits.

As for information regarding menstrual cycle among female study participants, 47 (23.3%) of the 205 females included in this study had attained menopause, and 74 (36.3%) reported irregular cycles. Unwanted or excessive hair growth on face and body was reported by 40 (19.5%) females. Figure 3 presents the family history of hair loss

Regarding stress among COVID patients per the Perceived Stress Scale (PSS), 268 (69.8%) of the study participants had a moderate level of stress, and 7% had high stress. (Table 5).

Concerning associated factors of alopecia among COVID patients, a bivariate analysis was done using chi-squared test to find the associated factors of alopecia among post-COVID patients, the results of which are depicted in Table 6.

Age, sex, COVID severity, stress, hair styling or chemical treatments, menstrual irregularities, and attaining menopause were significant, with p-value <0.05.

Among the sociodemographic factors, age and sex were found to be statistically significant. The age group <40 years was found to have a higher prevalence of alopecia (N=84, 43.8%) compared to the age group >40 years (N=61, 31.8%), with a p-value of 0.015. Females were found to have a higher prevalence of alopecia (N=107, 52.2%) compared to males (N=38, 21.2%), p-value <0.001.

Participants with moderate-to-severe COVID were found to have a higher prevalence of alopecia (92,42.6%) when compared to those with mild disease (N=53, 31.5%), p-value 0.027. Study participants who experienced moderate-to-high stress per the Perceived Stress Scale reported a higher prevalence of alopecia (N=122, 41.4%) compared to those who experienced low stress (N=23, 25.8%), p-value 0.008.

Hair styling was found to be significant, with a p-value of <0.001. Hair washing patterns were not found to be associated with alopecia (p-value 0.813).

Among the females, regular menstrual cycles (P=0.038) and not attaining menopause (P=0.039) were found to be significantly associated with alopecia. Dietary habits and special diets did not have a significant association with alopecia, with p-value 0.403 and 0.111, respectively.

Multivariate logistic regression was used to find predictors of post-COVID alopecia, considering confounding factors. All the variables which had a p-value of <0.25, i.e., age, sex, COVID severity, stress, hairstyling, and special diets followed, were included in the model. Forward stepwise method was used to run the logistic regression command.

Four out of the six variables included, i.e., female sex, COVID severity, high stress, and hairstyling, came to be significant independent predictors of alopecia (P<0.05) as shown in Table 7. Females were found to have 4.084 times higher odds of having post-COVID alopecia. Patients affected with moderate-to-severe COVID had higher odds of experiencing alopecia compared to those with mild illness, with an OR of 1.763. Patients with moderate-to-high stress were found to have 2.519

Table 6. Associated Factors of Alopecia among Post-COVID Patients.

Variables		Alopecia		Chi-square	Degree of freedom	p-value	OR (95% CI)
		Absent	Present				
Age	<40years	108(56.3%)	84 (43.8%)	5.86	1	**0.015**	**1.669 (1.101-2.531)**
	≥40 years	131 (68.2%)	61 (31.8%)				
Sex	Male	141 (78.8%)	38 (21.2%)	39.0	1	**<0.001**	**4.048 (2.577-6.802)**
	Female	98 (47.8%)	107 (52.2%)				
COVID severity	Mild	115 (68.5%)	53 (31.5%)	4.91	1	**0.027**	**1.61 (1.05-2.46)**
	Moderate-to-severe	124 (57.4%)	92 (42.6%)				
Stress	Low	66 (74.2%)	23(25.8%)	7.00	1	**0.008**	**2.02 (1.19-3.43)**
	Moderate-to-high	173(58.6%)	122(41.4%)				
Hair styling/ chemical procedures	Not done	233(64.4%)	129(35.6%)	12.1	1	**<0.001**	**4.82 (1.84-12.6)**
	Done	6(27.3%)	16(72.7%)				
Menstrual cycle	Irregular	43(57.3%)	32(42.7%)	4.30	1	**0.038**	**1.83 (1.03-3.26)**
	Regular	55(42.3%)	75(57.7%)				
Menopause	Not Attained	69(44.5%)	86(55.5%)	4.26	1	**0.039**	**2.008 (1.029-3.921)**
	Attained	29(61.7%)	18(38.3%)				
Family History of Hair loss	Absent	166(63.8%)	94(36.2%)	0.884	1	**0.347**	**1.23 (0.796-1.91)**
	Present	73(58.9%)	51(41.1%)				

Table 7. Independent Predictors of Post-COVID Alopecia.

Variables	Reference Category	Adjusted OR (CI)	P-value
Age	>40 years	1.446 (0.907-2.305)	0.121
Sex	Male	4.084 (2.531-6.590)	<0.001
COVID severity	Mild	1.763 (1.102-2.819)	0.018
Stress	Low	2.519 (1.409-4.505)	0.002
Hair styling/chemical procedures	No	4.103 (1.484-11.343)	0.006
Special diet	No	1.524(0.528-4.397)	0.436

times higher odds of getting alopecia. Patients who had hairstyling/chemical treatments done were found to have 4.103 times higher odds of developing alopecia.

Discussion

The present study investigated post-COVID-19 alopecia prevalence and its related variables in India. Wadhwa D et al. have previously focused on associated factors such as female sex, age, duration of illness, and stress in patients with post-COVID hair loss [10].

This study revealed a 37.8% prevalence of alopecia in the study population, with females being significantly more affected (N=107, 52.2%) than males (N=38, 21.2%). Similar studies worldwide have reported prevalences ranging from 20% [41] to 52.70%, [31] with females often being the majority affected. A Saudi Arabian study of 343 participants showed a 48.5% prevalence, of which 60.2% were females [4]. A Chinese study reported a 28.6% prevalence of alopecia, of which 48.5% were females [16].

Societal pressures on appearance and longer hair in many females may influence the higher rate of hair loss reported compared to males.

Age was found to be a significant factor, with those younger than 40 years reporting more alopecia, consistent with Alkeraye et al.'s observations of greater hair loss in

individuals under 46 years of age [31]. Younger individuals may notice hair changes sooner due to greater appearance concerns, explaining this age-related trend. Average ages in multiple papers ranged from 30 to 61 years, with many in their 40s, similar to our study [4, 5, 11, 14, 19, 25, 34, 42].

Analysis revealed that moderate-to-severe COVID-19 significantly increased alopecia risk, and the majority had moderate disease; 42.6% (N=92) of moderate-to-severe disease cases experienced alopecia. In another study, 60% of those with alopecia required ward level care [4]. Similar patterns were observed in other studies, with most alopecia occurring in moderate-to-severe cases [11, 19]. Starace et al. found that 66.7% of their 128 patients with alopecia had grade 1 COVID, contrary to this study's findings, which may be attributed to the discrepancy in sample size [5].

In this study, 46.9% of patients noticed alopecia within three months, consistent with other research, where 52.2% noticed it within three months of COVID-19 [5]. In two other studies, the mean time to notice hair loss was 57 days [34] and 45 days [18]. A Saudi Arabian study reported that 28% had onset within one week of COVID [31].

Our study found that 42.1% experienced alopecia for over six months, mirroring a similar study, where about 33% experienced it for over six months [31]. Pandemic-related stress, inadequate nutrition, disease severity, and comorbidities may have contributed to these findings.

Ninety-five point two percent experienced generalized hair loss, consistent with stress-induced TE [7, 20, 28]; 68.1% of participants took no action, reflecting a lack of perceived seriousness or influence of financial and familial factors. Similarly, 86% of patients did not seek consultation in another study [31].

Hair washing and dietary habits were insignificant on analysis. Regular menstrual cycles correlated with higher risk of alopecia. Hair styling increased the risk fourfold, although this warrants further study. Family history of hair loss was not significant.

Participants with moderate-to-high stress on the PSS reported a higher prevalence of alopecia (41.4%). Several studies report that stress can induce hair loss, which could be linked to the brain-hair follicle axis [7, 17, 28, 31, 32]. The study's limitations include potential recall bias due to delayed data collection, single-center scope, and lack of representation of home-treated patients.

Conclusions

The COVID-19 pandemic disrupted global operations, necessitating extensive efforts to develop treatment protocols and vaccines. Initially presenting with respiratory symptoms, the pandemic later revealed other manifestations amidst heightened stress and financial insecurities. There is increasing concern about the prevalence of COVID-19-related alopecia in the Indian population given the recent increase in reports documenting this phenomenon across the world. While this often resolves without intervention, it necessitates reassurance.

Our study found a 37.8% prevalence of post-COVID alopecia, influenced by factors such as COVID severity, age, sex, stress levels, hairstyling practices, and menstrual status. Younger individuals (<40 years), females, and those engaging in hairstyling routines faced elevated risks. Moderate-to-severe COVID significantly increased the risk of alopecia, and a similar risk was seen in those with moderate-to-high stress. Alopecia typically occurred within three months for 46.9% of participants and persisted beyond six months for 42.1%. Addressing the underlying causes of alopecia is crucial, given the anxiety it provokes. Future research could validate the prevalence across broader populations and explore interconnected factors such as comorbidities for comprehensive understanding and management of this condition.

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Dermatology Practical & Conceptual

GRINCH Index: Measuring Patient Satisfaction During Christmas Holiday Gift Programs

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Key words: patients' satisfaction, grinch index, holiday gifts, hospital reputation, patient experience

Citation: Gualdi G, Bigi L, De Simone C, et al. GRINCH Index: Measuring Patient Satisfaction During Christmas Holiday Gift Programs. *Dermatol Pract Concept*. 2025;15(4):5527. DOI: https://doi.org/10.5826/dpc.1504a5527

Accepted: June 11, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT **Introduction:** Receiving gifts, especially during the Christmas festivities, is a common experience for healthcare providers. Gift-giving, being a spontaneous expression of gratitude, could enable the assessment of true patient satisfaction.

Objective: In this study we used the Gifts Received durINg Christmas Holidays (GRINCH) as a potential index of patient satisfaction.

Methods: GRINCH is an Italian national survey that started on 13 December 2022 and lasted until 6 January 2023. Fifty dermatologists, equally divided between males and females working in university hospitals, general hospitals, or private or public offices and covering almost all the Italian regions participated in data collection. The participants were asked to fill out a structured data sheet collecting the type and the estimated gift value, the demographic characteristics of the patient, and the type of condition that led the patient to seek medical attention.

Results: A total of 659 gifts were recorded during the study period. The mean ratio of gifts/dermatologist, GRINCH index, was 13.7. Notably, the Grinch index increased as the dermatologists' ages increased in both sexes, and the same trend was confirmed by the data concerning the doctors' number of years of professional activity. We observed a greater mean GRINCH value in male dermatologists compared to their female colleagues. Patients with chronic diseases were more prone to gifting; those affected by psoriasis, atopic dermatitis, or acne showed above-average GRINCH values. However, this finding seems unrelated to the dermatologist's field of expertise.

Conclusion: Overall, these data strongly underline the importance of the doctor-patient relationship. A structured and prolonged mutual knowledge determines a trustful relationship that appears to be one of the fundamental bases of patient satisfaction.

Introduction

Italy has a universal public healthcare system covered by public funding, but citizens can choose to receive care from private practitioners. In 2023, 74% of total healthcare expenditure was covered by public funding, and only 23% was paid out of pocket [1].

Healthcare providers often receive gifts from their patients, which is a common practice. Italians have a strong gift-giving tradition deeply rooted in their culture, dating back to Roman times, when people exchanged luck-bringingbranches on January 1st as a wish for prosperity and abundance [2].

According to Italian law, public employees (including doctors) can receive gifts with a value up to €150. There is no specific rule concerning private practitioners, although all doctors have the ethical duty to refuse gifts or donations that could influence their professional decisions.

Doctors usually perceive this practice as an excessive display of gratitude on the part of patients for successful treatment or for the effort healthcare providers put into resolving a specific therapeutic or diagnostic difficulty. Could patient gifting be viewed as an indirect measure of patient satisfaction?

To the best of our knowledge, while there are some published papers concerning the ethical aspects of gift giving by patients to doctorsfacility. The participants had an average of 17.7 years professional experience (range 1-37)).

During the study period, 659 gifts were recorded, with 305 falling in the food category, 194 as beverages, 112 as personal items, and 48 as household gifts. It is worth noting that none of the gifts was job-related.

Patients' Characteristics

From a study of 659 patients, it was found that 316 were females (52%) and 343 were males (48%). The average age of the patients was 57.5 years, with no notable differences between the sexes.

Of the patients, 68% regularly visited the doctor who received the gift, usually once every 3–4 months, 26% visited occasionally (once every 6 months or more), and 7% had just one consultation with the doctor.

As for the medical conditions that led to the consultations, 24.3% of patients had psoriasis, 14.3% had non-melanoma skin cancers, 13.2% had moles, 7.6% had melanoma, 5.3% visited for cosmetic reasons, 4.7% had atopic dermatitis, 4.6% had acne, 1.2% were scheduled for skin surgery, 0.6% had allergies, and 12.7% had other miscellaneous diseases.

Relationship Between Gifts and Dermatologists: the GRINCH Index

The data provided pertains to the GRINCH index, which represents the mean ratio of gifts received to dermatologists. The overall GRINCH value is 13.7, with a difference observed between males (14.3) and females (13.1). When analyzed according to different places of work, university dermatologists had a higher GRINCH index result (16.3) compared to that of general hospital dermatologists (13.1). Dermatologists working in public and private facilities had

considerably lower values, at 12 and 11.4, respectively (Figure 1). No significant difference was found based on the geographical location of the dermatologists' practice.

GRINCH value increased rapidly with the dermatologist's experience. Dermatologists with less than five years of experience had an average value of 4.3, while those with 5–10 years of experience showed a result of 12.5. The value increased to 14.6 for those with 11–20 years of experience and reached a peak of 24 for dermatologists with 21–30 years of work experience. For the group with over 30 years of work experience, the value decreased to 14.6, but this finding concerns only one dermatologist (Figure 2). Additionally, the GRINCH index appears to be linked to the dermatologist's age. Dermatologists under age 35 had lower values, with an average of 4.6, with males having 6.4 and females 2.8. The value progressively increased with age, reaching the highest mean value of 21.5 for doctors aged 51–55. The average value then decreased, reaching 10 in the group age >60. Up to the age of 50, the male and the female trends overlapped, showing two different peaks: one for males in the 51–55 years age group (GRINCH 37) and the second for females in the 56–60 years group (GRINCH 43) (Figure 2).

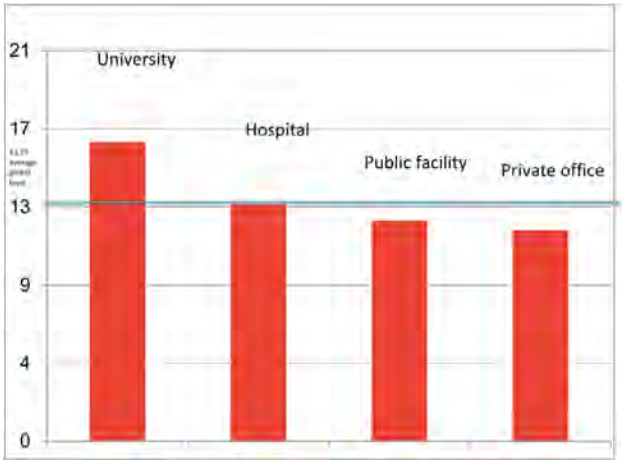


Figure 1. Gifts/doctor, based on work type.

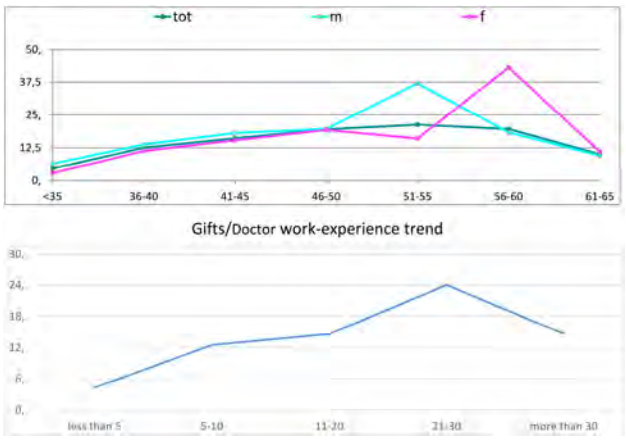


Figure 2. Gifts/doctor's age trend.

According to the dermatologist's field of expertise, the GRINCH index showed three categories with high values: psoriasis (18.7), atopic dermatitis (17.5), and acne (16). The second group, including melanoma, NMSC, nevi, and surgery experts, presented average values slightly below the mean (12.2, 12, 12, and 11.8, respectively). Finally, the pediatric, aesthetic, and heterogeneous " Other " group showed even lower values (respectively 9, 10, and 8.5) (Figure 3).

The estimated value of gifts received by dermatologists suggests a relationship with the dermatologist's age. Dermatologists under age forty mainly received gifts included in the first class of estimated price. In the age interval from 40 to 54 years, the different classes of estimated prices were homogeneous, while dermatologists over age 54 mainly received gifts included in the third and fourth price classes (Figure 4).

We also evaluated the gift flows between the patients' disease and the dermatologists' primary expertise. The analysis shows a high correlation between psoriasis and aesthetics, with more than half (51.5% and 53.3%) of the gifts received by specialists in psoriasis or aesthetics coming from patients examined for psoriasis or aesthetic problems, respectively. This correlation decreased for experts in NMSC (34.2%), acne (17.9%), and melanoma (15.4%). Lower relations were found for experts in AD and surgery, with the latter receiving about half of the gifts (49.8%) from patients with melanoma or NMSC (Figure 5).

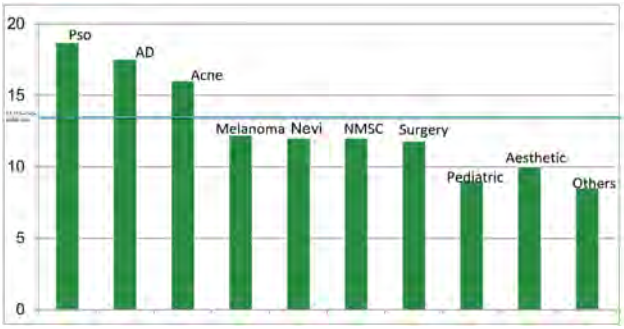


Figure 3. Gifts/doctor's related expertise.

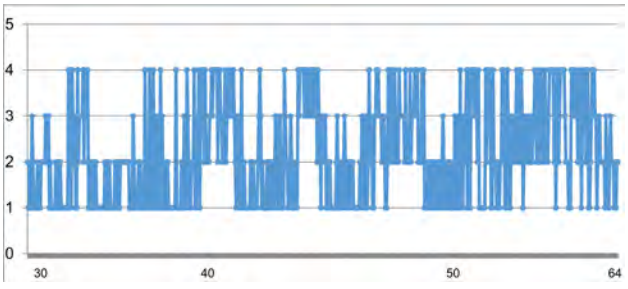


Figure 4. Distribution of gifts according to dermatologist's age and price range.

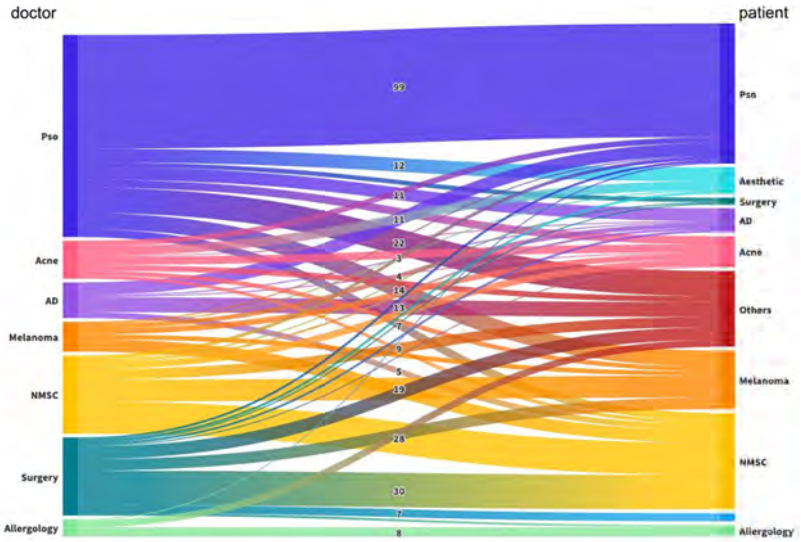


Figure 5. Gift flows according to patients' disease and dermatologist's field of expertise.

Discussion

Healthcare managers must evaluate patient satisfaction and determine the factors that influence it as patient satisfaction can impact healthcare institutions' financial success. However, assessing patient satisfaction can be complex and challenging. There is an ongoing debate about how to define patient satisfaction and to create a comprehensive conceptual model. One of the main challenges is the spontaneity of patients' responses. When patients complete questionnaires after a visit, their answers may be influenced by expectations and beliefs rather than by their experience [9,10].

To measure patient satisfaction with a doctor's care, we decided to use gifts as a potential indicator of satisfaction, as gifts are a concrete and spontaneous manifestation of satisfaction. The heterogeneity of dermatology specialists' work and the Christmas period provided an opportunity to evaluate the use of gifts to measure patient satisfaction. However, accepting gifts from patients raises ethical concerns [11,12]. While gifts are usually well-intentioned, they can create ethical uncertainty in healthcare. The national, regional, and hospital Code of Conduct guidance and guidelines regulate gift giving to healthcare professionals to ensure their integrity is not compromised and that they are not placed in a conflict-of-interest situation. In our study, the gifts received were of small monetary value, well below the threshold of €150, in compliance with Italian law. Moreover, all the involved dermatologists adhered to a strict behavioral guideline according to which gifts had to be spontaneous and must not interfere with medical decisions.

Our study was conducted in accordance with ethical models. The GRINCH index was derived from the sum of gifts received by all physicians, divided by the number of specialists. The average value was €13.7 and considered the cutoff. The GRINCH index increased with dermatologists' age in both sexes, reflecting the idea that more experienced physicians are recognized and rewarded. There was also a gender difference, with male physicians having a higher GRINCH index than did females. Patients with chronic diseases were also more likely to give gifts, particularly those with psoriasis, atopic dermatitis, or acne. The relationship between gift giving and chronic diseases did not appear to be related to the dermatologist's field of expertise. Dermatologic surgeons received fewer gifts than did colleagues dealing with inflammatory chronic diseases, mostly from "historic" patients who had several dermatological consultations yearly. This could be due to the fact that chronic patients tend to establish a closer personal connection with their doctors, which makes gift giving a more common occurrence. Moreover, thanks to novel treatments such as biological therapies, patients with chronic inflammatory diseases can experience life-changing improvement in their condition, which generally results in feelings of gratitude towards the prescribing doctor, thus making gift giving more likely.

Private dermatologists received fewer gifts, possibly due to the commercial nature of their relationship with patients. Italy has a universal public healthcare system covered by public funding, and patients who choose to receive treatment in a private practice mostly pay out of pocket. As a consequence, they may not be as prone to showing appreciation through gift giving.

Conclusions

These data strongly emphasize the importance of the doctor-patient relationship built on mutual understanding and prolonged interactions. Such a relationship fosters trust, a fundamental basis for patient satisfaction. In Italy, this satisfaction is often expressed through a "pensiero," a small gift or gesture of gratitude.

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Dermatology Practical & Conceptual

PRAME Immunohistochemical Expression in Recurrent/Traumatized Melanocytic Nevi and the Pitfall of Expression by Reactive Fibroblasts

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Key words: PRAME, Recurrent nevus, Recurrent/traumatized melanocytic nevi

Citation: Carraturo E, D'Abbronzo G, Argenziano G et al. PRAME immunohistochemical expression in recurrent/traumatized melanocytic nevi and the pitfall of expression by reactive fibroblasts. *Dermatol Pract Concept*. 2025;15(4):5564. DOI: https://doi.org/10.5826/dpc.1504a5564

Accepted: July 9, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: The recurrent/traumatized melanocytic nevus (RTMN) refers to melanocytic lesions that reappear following incomplete removal or trauma to a previous nevus, often presenting clinically and dermoscopically similar to melanoma, which complicates differential diagnosis. Histologically, RTMN exhibit melanocytic proliferation and scar tissue from prior trauma or excision. PRAME (preferentially expressed antigen in melanoma) immunohistochemistry (IHC) is emerging as a diagnostic tool for distinguishing between nevi, melanoma, and nevus-associated melanomas. However, its role in RTMN has not yet been established.

Objectives: This study aimed to evaluate the expression of PRAME in RTMN, specifically in the melanocytic and fibroblastic components, to explore its potential diagnostic utility.

Methods: A series of 22 RTMN cases from the Pathology Unit of the University of Campania Luigi Vanvitelli Hospital were reviewed. PRAME IHC was performed on formalin-fixed, paraffin-embedded tissue, and staining was evaluated in three compartments: junctional melanocytic, intradermal melanocytic, and fibroblastic scar tissue.

Results: PRAME IHC showed no positivity in the junctional or intradermal melanocytic components of any case. However, five out of 22 cases (22.7%) demonstrated PRAME positivity in the fibroblastic component, which was statistically significant (P=0.0169).

Conclusions: This study suggests that PRAME IHC is negative in the melanocytic components of RTMN, distinguishing it from melanoma. However, PRAME positivity in the fibroblastic scar component warrants careful interpretation to avoid diagnostic pitfalls. These findings emphasize the importance of considering the histological context when using PRAME as a diagnostic marker in RTMN.

Introduction

The recurrent nevus phenomenon describes the reappearance of a melanocytic proliferation at the site of a previously biopsied melanocytic nevus [1]. A closely related entity, the traumatized nevus, refers to a melanocytic lesion that has undergone physical trauma and typically exhibits reparative junctional melanocytic proliferation [2]. Owing to their overlapping histopathological features, these entities are collectively referred to as recurrent/traumatized melanocytic nevi (RTMN).

RTMN represent a significant diagnostic challenge in both clinical and dermoscopic practice due to their potential to mimic melanoma, including melanoma arising in association with a preexisting nevus [3]. Clinically, these lesions often manifest as hyperpigmented or hypopigmented areas with scar-like characteristics and asymmetrical borders [4].

The underlying biological mechanisms driving RTMN development remain poorly elucidated. However, it is postulated that recurrence may result from incomplete excision of the initial nevus, followed by subsequent skin trauma. In particular, shave excisions, frequently performed for aesthetic purposes, have been strongly associated with the emergence of recurrent nevi [5].

Histologically, RTMN may present as a junctional or compound melanocytic proliferation with mild to moderate cytologic atypia. This proliferation is frequently accompanied by dermal fibroblastic proliferation, indicative of scar formation from the prior biopsy, along with a perivascular chronic inflammatory infiltrate composed predominantly of lymphocytes and melanophages, often with melanin pigment deposition [1,6]. These histopathological features can raise concern about malignancy, particularly in the absence of clinical documentation of a previous excision [7]. Notably, intermediate- and late-stage melanomas commonly exhibit features of regression such as fibrosis and neovascularization within the papillary dermis, which may further obscure the distinction between benign reactive changes and malignant transformation.

RTMN are most commonly observed in females between the ages of 20 and 30, with the back being the most frequently affected anatomical site. Recurrence typically occurs within approximately six months following excision of the original nevus. However, there is currently no consensus regarding which specific histological subtype of nevus is most susceptible to recurrence [1,8].

Immunohistochemistry (IHC) for PRAME (preferentially expressed antigen in melanoma) is increasingly recognized as a useful adjunct in the differential diagnosis of melanocytic lesions, particularly in distinguishing between benign nevi, melanoma, and nevus-associated cutaneous melanoma [9-12]. PRAME plays a role in multiple cellular processes, including apoptosis, differentiation, growth regulation, transcriptional control, and ubiquitination. It is expressed in a range of both epithelial and non-epithelial neoplasms and has emerged as a promising target for immunotherapeutic approaches, with ongoing clinical trials investigating its potential applications.

In the context of melanocytic pathology, PRAME immunohistochemistry serves as a valuable diagnostic aid. The identification of a PRAME-positive melanocytic population within a nevus may support a diagnosis of melanoma arising in association with that nevus. However, a negative PRAME result does not definitively exclude melanoma, and interpretation should be integrated with clinical, histological, and additional immunohistochemical findings [13].

Although PRAME IHC holds potential in differentiating RTMN from melanoma, recent evidence indicates that PRAME expression may also be observed in reactive and cicatricial fibroblastic proliferations. This finding underscores a potential limitation in the specificity of PRAME IHC within the context of melanocytic lesions, particularly when evaluating recurrent or traumatized nevi [14,15].

The aim of this study was to evaluate a series of RTMN cases to assess PRAME expression in both melanocytic and fibroblastic cell populations, with the goal of elucidating PRAME's potential diagnostic utility in this specific histopathological context.

Methods and Materials

Case Selection

All cases included in this study were retrospectively selected from the archives of the Pathology Unit at the University Hospital of Campania Luigi Vanvitelli in Naples, Italy, covering the period from January 2019 to November 2024.

The inclusion criteria were: i) diagnosis of recurrent melanocytic nevus or traumatized melanocytic nevus; ii) formalin-fixed and paraffin-embedded (FFPE) tissue blocks and histological slides available; iii) histological evidence of fibroblastic proliferation.

Twenty-two cases satisfied the criteria. All the cases were reviewed by two experienced dermatopathologists and evaluated in their appropriate clinical setting. The diagnosis was confirmed in all cases.

PRAME Immunohistochemistry

Immunohistochemical staining was performed on 5 µm-thick sections obtained from formalin-fixed, paraffin-embedded (FFPE) tissue blocks using the automated Ventana BenchMark ULTRA system (Ventana-Roche Diagnostics, Meylan, France), according to the manufacturer's protocol. The antibody employed was anti-PRAME (rabbit monoclonal antibody, clone EPR20330, Ventana-Roche), provided in a prediluted, ready-to-use format with a standardized concentration. Sebaceous glands served as internal positive controls.

PRAME immunoreactivity was independently evaluated by two experienced pathologists. Assessment focused on three distinct compartments: the junctional (recurrent/proliferative) melanocytic component, the intradermal (mature) melanocytic component, and the scar-associated fibroblastic component. Nuclear staining was considered positive when more than 50% of the cells in a given compartment exhibited immunoreactivity, irrespective of staining intensity, in accordance with previously established criteria [16].

Statistical Analysis

To calculate the statistical significance of fibroblast positivity for the marker, a two-tailed binomial test was applied, assuming that the proportion of positive fibroblasts deviates significantly from a random distribution with a probability of 50% (P=0.5). The test considered both the exact probability of observing five positive cases out of 22 samples and the cumulative probability. Specifically, the probability of observing exactly five successes was calculated using the binomial distribution formula:

$$P = (X = k) = (n\ k) \cdot p^k \cdot (1 - p)^{n-k}$$

where $(n\ k)$ is the binomial coefficient.

Then, cumulative probability for values P(X≤5) and P(X≥5) was included to account for all outcomes as extreme as five observed successes. We applied the following formulas:

$$P(X \leq k) = \sum_{i=k}^{k} P(x = i)$$

$$P(X \geq k) = \sum_{i=0}^{k} P(x = i)$$

The p-value for the two-tailed test was calculated as:

$$p = 2 \cdot (P(X \leq k), P\ (x \geq k))$$

The significance threshold was set at α=0.05.

Furthermore, we analyzed potential correlations between age, sex, and anatomical site. Age was analyzed as a continuous variable using Spearman's rank correlation. The association between sex and fibroblast positivity was evaluated using Fisher's exact test, and the association with anatomical site was tested using the Chi-squared test.

Ethical Statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of University "Luigi Vanvitelli" (Naples, Italy) (protocol code 282/202, approval date 6 October 2020). Informed consent was obtained from all subjects involved in the study.

Results

The study cohort comprised 22 patients, including eight females (36%) and 14 males (64%), with ages ranging from 14 to 71 years (median age: 36 years). Of the 22 cases, 16 (72.7%) were diagnosed with traumatized melanocytic nevi, while six (27.3%) were classified as recurrent melanocytic nevi. Among the recurrent cases, five had a documented history of prior shave excision, whereas one had undergone a punch biopsy. Anatomical distribution of the lesions was as follows: the dorsal region in eight cases (36.4%), the lower limbs in five cases (22.7%), the lumbar region in three cases (13.6%), the shoulder in two cases (9.1%), the gluteal region in two cases (9.1%), the chest in one case (4.5%), and the abdominal region in one case (4.).

The clinical findings of the series are detailed in Table 1.

The histological findings of an exemplary case of RTMN are shown in Figure 1.

PRAME immunohistochemistry was negative in both the junctional and intradermal melanocytic components across all 22 cases (0%). However, PRAME positivity was observed in the fibroblastic component in five cases (22.7%). The results are summarized in Table 2.

Fibroblast positivity was observed in five out of 22 cases. The probability of observing exactly five successes under the null hypothesis P(X=5) was 0.00628. The cumulative probability for P(X≤5) was 0.008450, while P(X≥5) was 0.997. Applying the two-tailed binomial test, the overall p-value was computed as:

$$p = 2 \cdot (P(X \leq 5), P\ (x \geq 5)) = 0.0169$$

Table 1. Clinical Findings.

N.	Age	Location	Recurrent or traumatized melanocytic nevus	Phototype
1	27	Dorsal	Traumatized	II
2	36	Right leg	Traumatized	IV
3	17	Abdominal	Traumatized	III
4	28	Lumbar	Traumatized	II
5	34	Dorsal	Traumatized	III
6	22	Dorsal	Traumatized	III
7	49	Gluteal	Traumatized	III
8	34	Dorsal	Traumatized	III
9	40	Dorsal	Traumatized	III
10	14	Dorsal	Recurrent (previous shaving biopsy)	IV
11	41	Dorsal	Traumatized	III
12	22	Dorsal	Traumatized	II
13	28	Chest	Recurrent (previous shaving biopsy)	II
14	42	Gluteal	Recurrent (previous shaving biopsy)	III
15	41	Left shoulder	Traumatized	II
16	43	Lumbar	Traumatized	II
17	32	Right shoulder	Traumatized	III
18	35	Right leg	Recurrent (previous punch biopsy)	III
19	58	Right thigh	Traumatized	III
20	71	Right leg	Traumatized	II
21	46	Left thigh	Recurrent (previous shaving biopsy)	III
22	48	Lumbar	Recurrent (previous shaving biopsy)	II

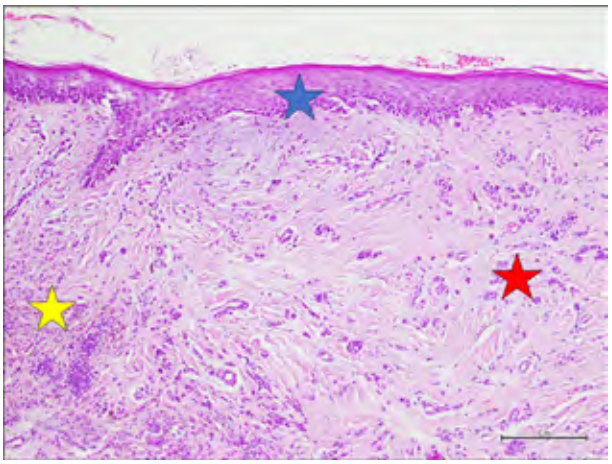


Figure 1. A traumatized nevus localized on the back of a 41-year-old female. Histological analysis revealed a compound melanocytic proliferation. The junctional component was characterized by large melanocytes arranged in small nests, exhibiting a lentiginous pattern (blue star). The dermal component consisted of mature, small melanocytes organized in extensive sheets (yellow star). A fibrous scar was present between the two components (red star) (hematoxylin and eosin stain, original magnification 100x).

Since the p-value (0.0169) is below the pre-defined significance threshold (α=0.05), we conclude that the probability of obtaining exactly five successes is very low under the null hypothesis, and it is not random but is instead statistically significant.

Table 2. PRAME Immunohistochemical Results in the Three Different Components.

Component	PRAME IHC positivity
Junctional	0/22 (0%)
Intradermal	0/22 (0%)
Fibroblastic	5/22 (22.7%)

Finally, we conducted exploratory correlative analyses to assess potential associations between PRAME fibroblast positivity and patient-related variables, including age (Spearman's rank correlation = 0.385, *P*=0.077), sex (Fisher's exact test, yielding an odds ratio of 1.05 with *P*=1.000), and anatomical site (Chi-squared test $\chi^2 = 6.39$, *P*=0.381). No statistically significant correlations was found in our dataset, although the observed trend with age may merit further exploration in larger cohorts.

Focal PRAME positivity, defined as staining in fewer than 50% of cells and thus considered negative, was observed in the junctional melanocytic component in six/ 22 cases (27.3%), in the intradermal melanocytic component in two/ 22 cases (9.1%), and in the fibroblastic population in 1/ 22 cases (4.5%).

Some examples are shown in Figures 2 and 3. Clinical and dermoscopical features of fibroblast-positive cases are shown in Figure 4.



Figure 2. Epigastric region, 48-year-old male. A) Junctional melanocytic proliferation was observed, organized into small nests and exhibiting a lentiginous pattern (blue star). The dermis displayed features of fibrosis, the presence of small vessels, fibroblastic proliferation, and an accumulation of melanophages (red star) (hematoxylin and eosin stain, original magnification 200x). B) PRAME immunohistochemistry resulted negative in the junctional melanocytes (blue star) and positive in the dermal fibroblasts (red star) (PRAME immunohistochemical stain, original magnification 200x). C) PRAME-positive dermal fibroblasts (red star) (PRAME immunohistochemical stain, original magnification 200x).

Discussion

Recurrent/traumatized melanocytic nevi (RTMN) are lesions characterized by the regrowth of residual melanocytes following incomplete excision or trauma to a preexisting nevus. RTMN are relatively common, with reported recurrence rates ranging from 5% to 10% in dermatology settings where nevi are frequently removed [13,17]. These lesions predominantly affect females in their second and third decades of life, with the back being the most commonly involved anatomical site. Recurrences typically manifest approximately six months post-excision, although consensus is lacking regarding which specific nevus subtype is most susceptible to recurrence [1,18].

RTMN often exhibit morphological characteristics that closely resemble melanoma, creating significant challenges in differential diagnosis at clinical, dermoscopic, and histopathological levels. While a history of prior trauma or incomplete removal can aid diagnostic suspicion, this information is not always available, as patients may be unaware of or unable to recall such events.

Clinically and dermoscopically, RTMN frequently display symmetry alongside irregular pigmentation, making them among the benign lesions that often exhibit dermoscopic features suggestive of malignancy [19]. Histologically, RTMN can be conceptualized as comprising three distinct components: i) a superficial/junctional melanocytic component representing the proliferative portion of the lesion; ii) a dermal melanocytic component corresponding to the residual pre-existing nevus; and iii) an intermediate component characterized by cicatricial fibroblastic proliferation and, occasionally, a chronic inflammatory infiltrate, reflecting the scar tissue resulting from trauma or excision.

From a diagnostic perspective, the superficial/junctional melanocytic component is of paramount importance, as it may display atypical morphological features that mimic melanoma in situ. These features include thickened and irregular rete ridges, mildly disorganized basal melanocytes, and subtle nuclear enlargement or hyperchromasia. Although pagetoid spread, and peri-adnexal dermal extension are uncommon, they can occasionally be observed [5]. The primary differential diagnosis is superficial spreading melanoma arising within a pre-existing nevus (nevus-associated melanoma). Accurate differentiation can be challenging and necessitates comprehensive integration of clinical, dermoscopic, and histopathological data.

PRAME (preferentially expressed antigen in melanoma) is a cancer-testis antigen expressed by melanoma and various other malignant neoplasms; it has recently emerged as a valuable marker in the differential diagnosis of melanocytic lesions. Immunohistochemical detection of PRAME has demonstrated significant differential expression patterns between melanoma and benign nevi [10,12,20]. Notably, prior studies have indicated that PRAME IHC is particularly useful in diagnosing nevus-associated melanoma, showing positivity in melanoma cells while remaining negative in benign nevus cells [13,21]. Consequently, PRAME may serve as a helpful diagnostic tool in evaluating RTMN, given that the primary differential diagnosis often involves nevus-associated melanoma. However, the presence of fibroblastic proliferation within RTMN can pose a diagnostic challenge, as emerging evidence has documented PRAME expression in reactive fibroblasts and scar tissue [14,15].

In this study, we evaluated PRAME immunohistochemical expression in a series of 22 RTMN cases, examining three distinct lesion components: superficial/junctional melanocytic proliferation, the intradermal nevus component, and fibroblastic proliferation associated with scar tissue. Notably, none of the cases demonstrated PRAME positivity in the junctional component. While the limited sample size represents a study limitation and constrains the generalizability of these findings, this observation remains clinically significant, given that the principal differential diagnosis for RTMN is melanoma arising from a pre-existing nevus.

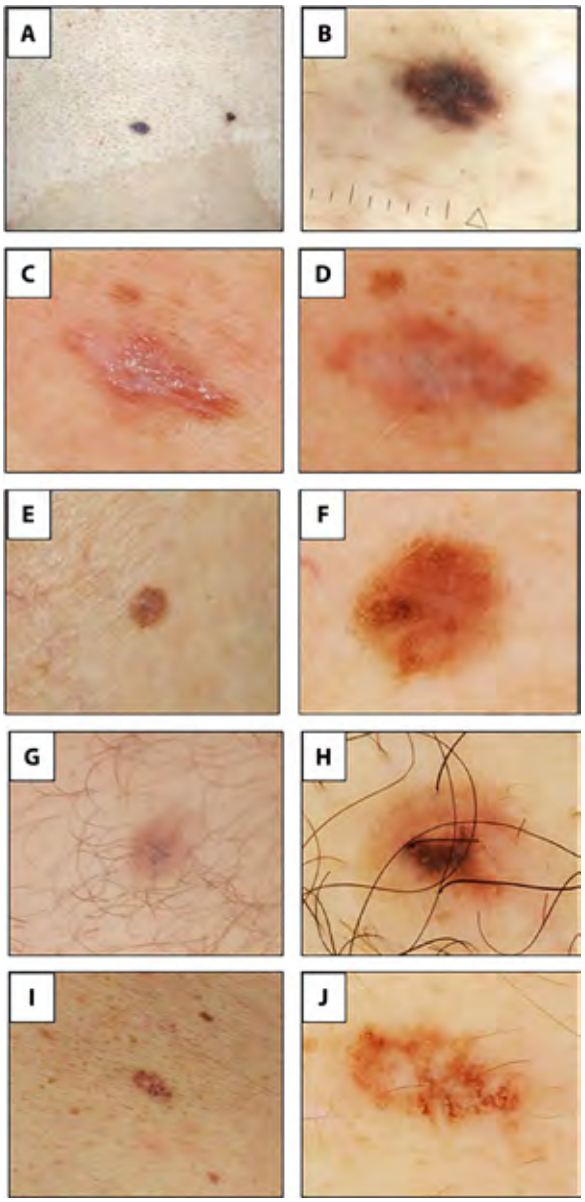


Figure 4: Clinical and dermoscopical features of fibroblast-positive cases. Case 1: 22-year-old male with a traumatized melanocytic nevus on the back. A) Clinical image: pigmented, asymmetric nevus with a slightly raised central area. B) Dermoscopy: asymmetric lesion with irregularly distributed hyperpigmented blotches and structureless brown areas. Case 2: 43-year-old female with a traumatized melanocytic nevus on the back. C) Clinical image: pinkish-brown lesion with dome shaped distributed areas and irregular borders. D) Dermoscopy: asymmetric structureless brown pigmentation with whitish-grey central area and crystalline structures. Case 3: 71-year-old female with a traumatized melanocytic nevus on the right leg. E) clinical image: brown macule with focally hyperpigmented central area. F) Dermoscopy: patchy reticular network with focal area of irregular hyperpigmented network. Case 4: 46-year-old male with a recurrent melanocytic nevus on the left thigh. G) Clinical image: pigmented lesion arising within a hypopigmented scar, with blurred and asymmetric borders. H) Dermoscopy: reticular and structureless pigmentation with radial streaming and central scar-like depigmentation. Case 5: 48-year-old male with a recurrent melanocytic nevus on the back. I) Clinical image: brown macule with irregular pigmentation located within a surgical scar, with blurred borders. J) Dermoscopy: brown structureless areas, atypical pigment network and crystalline structures.

PRAME IHC has proven valuable in this diagnostic setting, as prior studies have established its positivity in melanomas developing from nevi [13,21]. Our results, however, indicate that PRAME is consistently negative in the junctional component of RTMN.

The presence of cicatricial fibroblastic proliferation within RTMN introduces a potential diagnostic pitfall when interpreting PRAME staining. Indeed, several reports have documented PRAME expression in benign fibroblasts and scar tissue [14]. Specifically, Plotzke et al. found that 24% of scars exhibited diffuse and strong PRAME expression comparable to that seen in desmoplastic melanoma [15]. In their cohort, PRAME positivity exceeding 50% of fibroblasts was observed in 11 of 21 (52.4%) scar cases. In contrast, our study identified PRAME positivity above this threshold in the fibroblastic population in five of the 22 cases (22.7%). It is important to highlight that our analysis focused on fibroblastic proliferations within RTMN lesions rather than on simple scar tissue.

We found that PRAME expression in the fibroblastic proliferation of RTMN was statistically significant (P=0.0169). Histologically, these cases exhibited a population of PRAME-positive spindle-shaped cells within the dermis, embedded in a fibrotic stromal background. Careful morphological assessment using hematoxylin and eosin-stained sections is essential to accurately distinguish these PRAME-positive fibroblasts from melanocytes, thereby preventing potential diagnostic confusion. Distinguishing fibroblasts from spindle-shaped melanocytes in desmoplastic melanoma can be challenging due to their similar morphology, especially under routine histological examination. However, several key histological and immunohistochemical features help guide the differential diagnosis. Histologically, fibroblasts typically display small, uniform, elongated or oval nuclei with fine chromatin and inconspicuous nucleoli. Their cytoplasm is scant and often not easily visible. They tend to align in an orderly fashion along collagen bundles, showing a non-infiltrative, reactive pattern. Mitotic figures are usually absent or very rare. In contrast, spindle-shaped melanocytes in melanoma often have larger, more pleomorphic and hyperchromatic nuclei, frequently with prominent nucleoli [22-23]. These cells may show a more abundant eosinophilic cytoplasm and are arranged in a disorganized, infiltrative pattern. Atypical mitoses may be observed, and there is often evidence of invasion into surrounding structures, such as adnexal elements, nerves, or blood vessels. Immunohistochemistry is crucial to making a definitive distinction. Melanocytic cells in desmoplastic melanoma are typically positive for S100 protein and SOX10, both of which are highly sensitive markers. HMB45 and Melan-A are often negative in desmoplastic variants but may be expressed in other melanoma subtypes. In contrast, fibroblasts

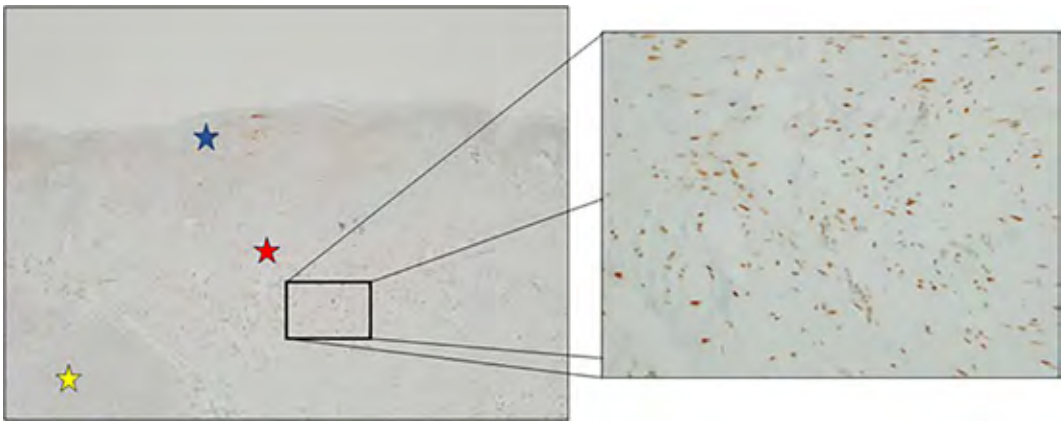


Figure 3. Left leg, 45-year-old male. PRAME immunohistochemistry was negative in both junctional (blue star) and dermal (yellow star) melanocytes, while it was positive in the dermal scar (indicated by the red star and the enlargement on the right).

are usually negative for melanocytic markers such as S100 and SOX10, but they may express CD34, which is helpful in identifying dermal fibroblastic populations. Vimentin is positive in both cell types and is therefore not diagnostically useful on its own. Clinical context also plays a significant role: the presence of a previous pigmented lesion or ulceration may point towards melanoma, especially if spindle cells are S100- and SOX10-positive in a desmoplastic stroma. On the other hand, spindle cells that are negative for melanocytic markers and positive for CD34 are more likely to represent reactive fibroblasts in a scar.

The main limitation of this study is its sample size. However, this is the first study to evaluate the role of PRAME in the diagnosis of RTMN.

Conclusions

In conclusion, our evaluation of PRAME expression in a series of RTMN highlights its potential diagnostic utility. PRAME was consistently negative in both the junctional and intradermal melanocytic components across all cases, contrasting with its established positivity in melanoma arising from a nevus and thereby reinforcing its role in differential diagnosis. Conversely, PRAME expression was significantly detected in the reactive fibroblasts within the scar component. This finding is critical for pathologists to recognize, as it may help prevent misinterpretation of PRAME positivity as melanocytic in origin.

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Dermatology Practical & Conceptual

Elective First-Line Use of Dimethyl Fumarate in Psoriasis: Insights from an Italian Cohort

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Key words: Dimethyl fumarate, Psoriasis, Systemic therapy, First-line treatment, Long-term treatment

Citation: Giunta A, Esposito M, Campione E, et al. Elective First-Line Use of Dimethyl Fumarate in Psoriasis: Insights from an Italian Cohort. *Dermatol Pract Concept*. 2025;15(4):5458. DOI: https://doi.org/10.5826/dpc.1504a5458

Accepted: June 25, 2025; **Published:** October 2025

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Funding: The work was unconditionally funded by Almirall S.A.

Competing Interests: M. Esposito has served as a speaker/board member for Abbvie, Almirall, Eli Lilly, Janssen, Leo Pharma, Novartis, Sanofi, and UCB. A. Giunta received grants or is an investigator for Biogen and Lilly and is a consultant/advisory board/speaker for AbbVie, Almirall, Celgene, Janssen, Leo Pharma, Eli Lilly, Merck Sharpe Dohme, Novartis, Pfizer, Sandoz, and UCB. M. Burlando served as a speaker or advisory board member for Almirall, AbbVie, Amgen, Eli Lilly, Janssen, Leopharma, Novartis, and UCB Pharma. G. Caldarola reports consulting fees or honorariums and payment for lectures from Lilly and Novartis. MC Fargnoli has served on advisory boards and received honoraria for lectures and/or research grants from AMGEN, Almirall, Abbvie, Boehringer-Ingelheim, BMS, Galderma, Kyowa Kyrin, Leo Pharma, Pierre Fabre, UCB, Lilly, Pfizer, Janssen, MSD, Novartis, Sanofi-Regeneron, and Sunpharma.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Dimethyl fumarate (DMF) is an approved conventional systemic treatment for psoriasis that does not exhibit any drug–drug interactions or cumulative organ toxicities.

Aim: This retrospective real-world study aimed to analyze the long-term efficacy, safety, and tolerability of DMF in patients with moderate psoriasis.

Methods: Data on safety and efficacy were collected from medical charts. The effect on disease severity was assessed using the Psoriasis Area Severity Index.

Results: Our study included 148 patients over a 48-week treatment period, confirming DMF as an effective option in the treatment of moderate psoriasis. Adverse events were only mild or moderate, principally flushing, epigastralgia, and diarrhea. However, DMF exhibited a delayed onset of action, and the dropout rate was high. These aspects highlight the importance of educating patients about the activity profile of DMF, the potential occurrence of side effects, and their management. However, side effects are self-limiting with discontinuation of treatment and generally occur early, allowing patients to be promptly switched to other therapies if DMF is not tolerated.

Conclusions: Our results confirm that DMF may be offered as a first-line treatment for moderate psoriasis as it demonstrated efficacy even in the long-term, when treatment is tolerated, especially in patients with a disease duration of less than five years. DMF may also be proposed when the patient presents comorbidities, when immunosuppression is undesired, and/or before the initiation of biological therapies.

Introduction

Psoriasis is a chronic inflammatory disease characterized by high prevalence and a relevant physical and psychological burden [1] often requiring systemic treatments, either with conventional or biological agents [2]. The introduction of biologicals targeting tumor necrosis factor-α (TNF-α), interleukin(IL)-12/23, IL-17A, IL-17RA, and IL-23 as well as the small-molecule apremilast has provided new and effective treatment options, partially reducing the use of conventional therapies [3]. However, in many countries, local guidelines recommend a stepwise approach, starting with traditional systemic therapies before initiating biological treatments [4]. The Italian SIDeMAST (Società Italiana di Dermatologia Medica, Chirurgica, Estetica e delle Malattie Sessualmente Trasmesse) guidelines recommend the use of biological therapies for patients with moderate-to-severe plaque psoriasis, defined as Psoriasis Area Severity Index (PASI) >10 or body surface area (BSA) >10, or PASI <10 and BSA <10 with involvement of sensitive areas such as the face, palms, soles, nails, or genital region or in those who have shown inadequate response or intolerance to conventional treatments [2,5]. Although the therapeutic target of new biological therapies is PASI 90 [6], PASI 75 remains an excellent tool for evaluating the efficacy of traditional therapies for psoriasis [7,8]. Traditional systemic treatments, including methotrexate (MTX), cyclosporin, acitretin, and, in Europe, fumaric acid esters (FAEs), have demonstrated moderate efficacy, with a proportion of patients achieving PASI 75 ranging from 15% to 60% [4]. Remarkably, except for FAEs, these drugs exhibit drug–drug interactions and cumulative organ toxicities [9]. Of note, the prescription of systemic drugs for psoriasis in Italy is regulated by the Agenzia Italiana del Farmaco (AIFA) and is influenced not only by the safety profile but also by approved indications and reimbursement policies. MTX is one of the most widely recommended first-line systemic therapies for moderate-to-severe chronic plaque psoriasis and is particularly indicated in patients with psoriatic arthritis or systemic inflammation. With over 50 years of clinical use, it is suitable for long-term management and is supported by solid efficacy evidence [10,11]. MTX's clinical utility is reinforced by established international dosing guidelines and consensus-based laboratory monitoring protocols [12]. However, its use is burdened by several drug interactions and potentially severe adverse events such as hepatotoxicity and myelosuppression [2]. Cyclosporin, on the other hand, is particularly useful for severe and rapidly progressive forms of plaque psoriasis or for cases requiring rapid disease control. It has also been used in non-plaque variants such as pustular or erythrodermic psoriasis. Its fast onset of action makes it valuable as a short-term induction therapy, particularly in adults without renal or cardiovascular contraindications [13]. While effective, its long-term use is limited by nephrotoxicity and other metabolic side effects [12]. Acitretin is mainly indicated for palmoplantar and erythrodermic psoriasis, where its systemic retinoid action provides significant therapeutic benefit. Its oral formulation and efficacy in chronic or treatment-resistant cases further support its role across various psoriasis subtypes [14]. It is contraindicated in women of childbearing potential due to its prolonged teratogenicity [15,16]. Acitretin's longstanding use in Europe underscores its utility in managing difficult-to-treat cases and

keratinization disorders. However, patient selection must account for lipid metabolism and liver function status [12].

Dimethyl fumarate (DMF) is an FAE with anti-inflammatory and immunomodulating effects, approved by the European Medicines Agency (EMA) for the treatment of patients with moderate-to-severe plaque psoriasis since 2017 [17,18]. Regarding DMF efficacy, the DIMESKIN-2 trial reported PASI 75 in 81.1% of patients at week 52 [19], and the BRIDGE Study achieved PASI 75 in 37.5% of patients at week 16 [20]. In a real-world multicenter study, PASI 75 was achieved in 23.3% of patients at week 12, with a further 17.4% reaching it by week 26. Side effects occurred in 61.1% of patients, with the most common being diarrhea, epigastric discomfort, nausea, and flushing. However, DMF does not display major contraindications [21]. Despite these considerations, DMF is still infrequently prescribed for psoriasis treatment, and real-life evidence on its use is scarce. We report the results from an Italian multicenter retrospective study on the use of DMF.

Objectives

The objective of this study was to evaluate the long-term efficacy, safety, and tolerability of DMF in a real-world clinical setting focused on moderate forms of the disease. The study aimed to assess the achievement of disease severity reduction of 50% or 75% (PASI 50 and PASI 75), treatment retention rates, and the occurrence of adverse events over 48 weeks. This work may thus help clarify the role of DMF as first-line systemic therapy, especially for patients with early-stage disease and significant comorbidities.

Patients and Methods

Study Design

This was a retrospective real-world study conducted at the Departments of Dermatology of eight university referral centers in Italy (L'Aquila, Firenze, Roma Tor Vergata, Genova, Roma Cattolica, Roma IFO, Roma Sapienza, Ancona). All subjects enrolled in the study received DMF according to local guidelines and the summary of product characteristics.

Ethical Considerations

The investigation was conducted in accordance with the Helsinki Declaration and later amendments, and patients signed a consent form authorizing the use of their clinical records for scientific purposes. Confidentiality and privacy of patient data are assured by internal data protection regulations as well as by the General Data Protection Regulation (GDPR) (EU) 2016/679. The study did not require ethical approval in accordance with national guidelines.

Patients

Patients aged ≥18 years with a diagnosis of moderate psoriasis who underwent DMF treatment for 48 weeks between June 2022 and December 2023, according to standard clinical practice, were enrolled in the study.

Data Collection

Demographic and disease variables, such as age, sex, weight, body mass index (BMI), psoriasis clinical variant, disease duration, and PASI, were collected alongside information about previous treatments and the presence of comorbidities. Data collection was carried out while ensuring the anonymity of the participants.

Statistycal Analysis

The imputation of missing data was performed using the last observation carried forward (LOCF) analysis. A paired Student t-test was used to compare baseline values with those at each time point (weeks 4, 8, 12, 24, and 48). Data are presented as a percentage of patients who achieved PASI 50 or PASI 75 with a PASI score reduction of 50% and 75% (PASI 50, PASI 75) compared with baseline. To estimate the relationship between variables, a binary logistic regression analysis (binary variables) and a multiple regression analysis (continuous variables) were performed. To account for potential confounders, the logistic regression model included the following variables as independent predictors: age, disease duration, BMI ≥ 30, maximum dosage, and number of comorbidities. Statistical analyses were performed using MedCalc® Statistical Software (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2025).

Results

A total of 148 patients were enrolled in the study, of whom 94 (63.5%) were male. The mean PASI was 8.9 (±4.2). The average age was 53.8 (range 19–88), and 18 (12.2%) patients had a BMI ≥30 (Table 1). The most prevalent variant of psoriasis was the plaque type (141 patients, 95.3%), followed by palmoplantar psoriasis (17 patients, 11.5%), inverse psoriasis (five patients, 3.4%), and psoriatic arthritis (two patients, 1.4%). Most of the population had at least one comorbidity (52.7%). Notably, some patients displayed relevant comorbidities, including various types of anamnestic cancer, hepatitis B virus or hepatitis C virus infections, tuberculosis (TB), or multiple sclerosis. Among the study group, 95 patients (64.2%) had not been previously treated for psoriasis. In contrast, 33.8% had received conventional therapies, including acitretin (16 patients, 10.8%), cyclosporin (31 patients, 20.9%), or MTX (18 patients, 12.2%). A smaller proportion (4.7%) had been treated with biological systemic

Table 1. Patient Baseline Characteristics.

Characteristics	N=148
Sex (Male)	94 (63.5)
Age (years)	53.8 (±16.6, 19–88)
Weight (kg)	75.4 (±13.0, 45.0–123.0)
BMI (kg/m^2)	26.6 (±3.8, 17.6–42.6)
BMI ≥30	18 (22.2)
Psoriasis clinical variants	
• Plaque type	141 (95.3)
• Inverse psoriasis	5 (3.4)
• Palmoplantar psoriasis	17 (11.5)
• Psoriatic arthritis	2 (1.4)
Disease duration (years)	16.9 (±14.3, 1–65)
Mean PASI	8.9 (±4.2)
Comorbidities	
• None	70 (47.3)
• 1	31 (20.9)
• 2	26 (17.6)
• 3	12 (8.1)
• >3	10 (6.8)
Comorbidities of interest	
Neoplasms	9 (6.1%)
• Malignant melanoma	3 (2.0%)
• Non-melanoma skin cancer	2 (1.4%)
• Prostate cancer	1 (0.7%)
• Colorectal cancer	1 (0.7%)
• Thyroid cancer	1 (0.7%)
• Parathyroid cancer	1 (0.7%)
Infections or other relevant comorbidities	
• HBV	6 (4.1%)
• HCV	3 (2.0%)
• IgRA TB positive	5 (3.4%)
• Multiple sclerosis	2 (1.4%)
Previous therapy	
None	95 (64.2%)
Conventional systemic therapies	50 (33.8%)
• Acitretin	16 (10.8%)
• Cyclosporin	31 (20.9%)
• Methotrexate	18 (12.2%)
Biological systemic therapies	7 (4.7%)
• TNF inhibitors	5 (3.4%)
• Ustekinumab	1 (0.7%)
• IL-23 inhibitors	1 (0.7%)
Small molecule (apremilast)	7 (4.7%)

Data are presented as mean (±SD, range) or N (%). Abbreviations: BMI: body mass index; HBV: hepatitis B virus; HCV: hepatitis C virus; PASI: Psoriasis Area Severity Index; IgRA TB: interferon gamma release assay test for tuberculosis; TNF: tumor necrosis factor.

therapies: TNF inhibitors in 3.4% (five patients), ustekinumab in 0.7% (one patient), and IL-23 inhibitors in 0.7% (one patient). Additionally, 4.7% (seven patients) had been treated with apremilast (Table 1).

DMF was effective in reducing the mean PASI from baseline at week 4, with efficacy increasing through week 48 (10.0 vs. 1.8, P<0.001, Table 2). The LOCF analysis also showed a significant effect of DMF throughout the observation period, with mean PASI decreasing from 8.9 to 4.3 (P<0.001, Table 2, Figure 1). At 48 weeks, the percentage of patients who achieved PASI 50 was 56.8%, while 36.5% achieved PASI 75 (Table 3, Figure 2). The mean treatment duration was 6.9 (±4.9) months, ranging from 0 to 12 months, reflecting a dropout rate of 62.8%. The main reasons for discontinuing DMF treatment were the appearance of adverse events (61 patients, 41.2%) and inefficacy (28 patients, 18.9%). Most adverse events occurred within the first 12 weeks of treatment (39/61, 63.9% versus 22/6, 36.1% after 12 weeks, P<0.001).

Interestingly, logistic regression analysis showed that the naïve status of patients as well as prior treatments (experienced) did not influence treatment outcomes with DMF, as observed for the mean PASI and PASI 50 and PASI 75 (Table 4). The analysis also showed that a longer duration of psoriasis was associated with a higher frequency of adverse events upon starting treatment with DMF. DMF treatment was significantly more effective in patients with a disease duration of less than five years after 24 and 48 weeks than in patients with a disease duration of 5–10 or more than 10 years (P=0.04 and P=0.032; Table 5). Furthermore, the treatment with DMF was significantly more effective in patients whose disease onset was less than 10 years at 12 (P=0.041), 24 (P=0.011), and 48 weeks (P=0.009) (Table 5, Figure 3). PASI 50 and PASI 75 responses were comparable between biologic/systemic-naïve and previously treated patients at each time point, with no statistically significant difference observed (all p-values of t-test >0.1; Supplementary Table 1). Disease duration, BMI ≥30, maximum dosage, and number of comorbidities did not account for significant differences in achieving PASI 50 or 75 at three months in the logistic regression model.

Discussion

Conventional systemic treatment of psoriasis relies on the use of MTX, cyclosporin, and acitretin [7]. DMF is an FAE that has been used as a first-line systemic treatment for psoriasis in recent years because of its good safety profile for long-term therapy [21]. In contrast to cyclosporin, MTX, and acitretin, which are associated with several contraindications, potentially severe adverse events, and cumulative organ toxicity [22–24], DMF predominantly causes non-

Table 2. Mean PASI Analysis at Each Visit (as observed) and Mean PASI Analyzed using the Last Observation Carried Forward Analysis (LOCF).

PASI analysis	Mean (±SD)		Paired t-test p-value
As observed analysis			
Baseline vs week 4	N=141, 9.0 (±4.2)	N=141, 7.6 (±4.1)	<0.001
Baseline vs week 8	N=82, 9.0 (±4.5)	N=82, 6.4 (±5.0)	<0.001
Baseline vs week 12	N=101, 9.5 (±4.3)	N=101, 5.1 (±4.0)	<0.001
Baseline vs week 24	N=87, 9.6 (±4.2)	N=87, 3.3 (±4.0)	<0.001
Baseline vs week 48	N=54, 10.0 (±4.3)	N=54, 1.8 (±2.3)	<0.001
LOCF analysis			
Baseline vs week 4	8.9 (±4.2)	7.6 (±4.1)	<0.001
Baseline vs week 8	8.9 (±4.2)	6.9 (±4.1)	<0.001
Baseline vs week 12	8.9 (±4.2)	5.7 (±4.1)	<0.001
Baseline vs week 24	8.9 (±4.2)	4.7 (±4.6)	<0.001
Baseline vs week 48	8.9 (±4.2)	4.3 (±4.7)	<0.001

Abbreviations: LOCF: last observation carried forward; PASI: Psoriasis Area Severity Index.

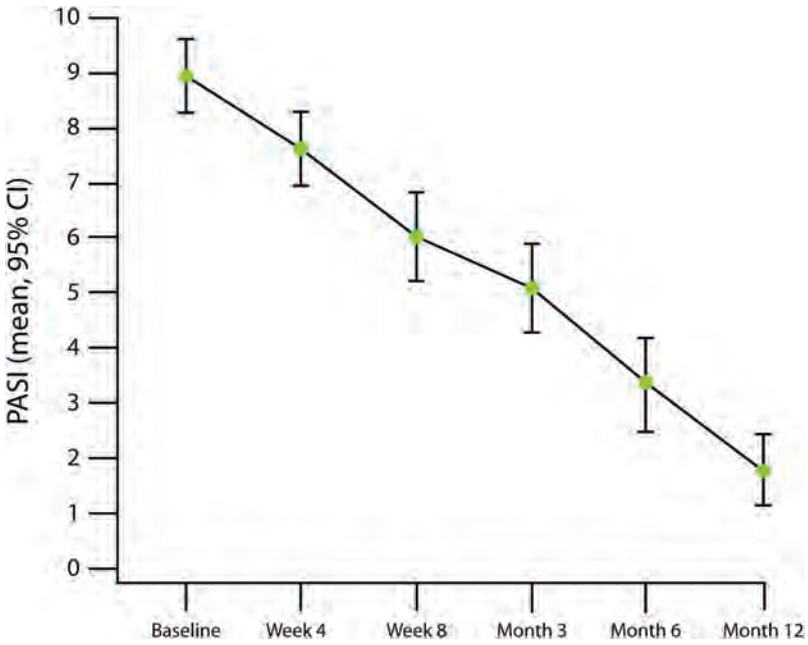


Figure 1. Mean PASI analyzed using the last observation carried forward analysis (LOCF). The figure shows the decline in PASI over follow-up visits.

serious and self-limiting side effects [25]. Mechanistically, DMF inhibits NF-kB translocation in fibroblasts and keratinocytes, thereby downregulating the production of inflammatory cytokines and hindering the inflammatory response. Additionally, DMF increases the proportion of regulatory T cells relative to T-helper lymphocytes 17, induces T-cell apoptosis, and inhibits keratinocyte proliferation [18].

Our study showed that DMF is a valid treatment option for patients with moderate psoriasis, as 36.5% of total patients, representing 70.4% of those still on treatment at the timepoint, achieved PASI 75 at week 48. Notably, these results were observed across both treatment-naïve and previously treated individuals, suggesting consistent therapeutic benefit irrespective of prior systemic exposure. Our findings confirmed that DMF is a slow-acting agent that, although starting to reduce PASI by week 4, achieves its full therapeutic effect only after several weeks of treatment. The dropout rate was high (62.8%), with the primary reason for discontinuation being gastrointestinal issues and flushing. Although these adverse events were mild, they were not tolerated by patients. However, it is important to make a distinction between tolerability and safety. While DMF's adverse events are frequent and may lead to early discontinuation due to the patient's low tolerability, they are generally mild, self-

limited, and reversible upon treatment cessation. Besides this, in patients who endured DMF, the drug exerted remarkable and prolonged efficacy in suppressing disease activity, especially in patients with a disease duration of less than five years. Comorbidities, BMI, or dose variations within the studied range did not significantly impact treatment success, underscoring the utility of DMF in diverse patient populations. Furthermore, the analysis showed that the frequency of DMF-induced adverse events was higher in patients with a longer history of psoriasis. This observation supports the postulation that DMF represents a useful first-line therapy option. Moreover, since the adverse events leading to treatment discontinuation mainly occurred during the first 12 weeks, patients could be promptly switched to other therapies if DMF was not well tolerated. Physicians should inform patients about the frequency and types of adverse events as well as of the possibility of slowly titrating the dosage to minimize them. It is crucial that physicians explain to patients that DMF requires time to exert its clinical effects and that most adverse events are manageable or transient. This proactive approach can help identify patients most likely to tolerate and benefit from long-term DMF therapy [26]. Additionally, our real-life study revealed that DMF is predominantly prescribed for moderate psoriasis. This pattern of use aligns with DMF's favorable safety and tolerability profile and with the need for long-term disease control in patients not requiring or not eligible for biologics.

Compared to MTX, cyclosporin, and acitretin, DMF offers a favorable safety profile. MTX is effective in chronic plaque psoriasis and psoriatic arthritis but requires regular monitoring due to risks of hepatotoxicity and myelosuppression [2,27,28]. Cyclosporin acts rapidly and is suitable for severe or non-plaque forms but is limited by nephrotoxicity and metabolic effects and is recommended for intermittent use for up to one year [29]. Acitretin is more effective in palmoplantar and hyperkeratotic psoriasis and safe for patients with a history of malignancy due to its non-immunosuppressive profile, but its use is limited by

Table 3. Percentages of Patients Achieving PASI 50 and PASI 75 Analyzed using the Last Observation Carried Forward (LOCF) Analysis.

Visit	N=148, N (%)
PASI 50	
4 weeks	9 (6.1%)
8 weeks	14 (9.5%)
12 weeks	46 (31.1%)
24 weeks	75 (50.7%)
48 weeks	84 (56.8%)
PASI 75	
4 weeks	4 (2.7%)
8 weeks	6 (4.1%)
12 weeks	20 (13.5%)
24 weeks	37 (25.0%)
48 weeks	54 (36.5%)

Abbreviations:PASI: Psoriasis Area Severity Index.

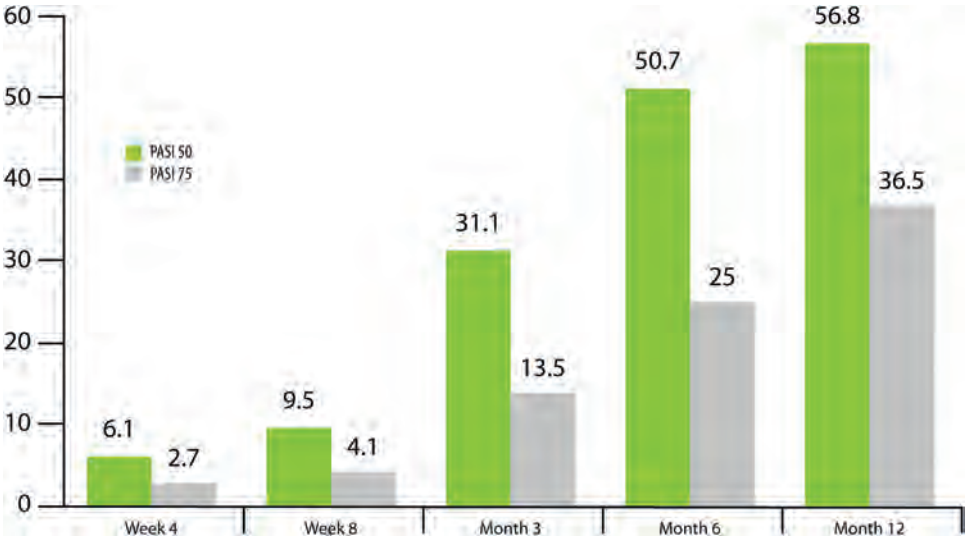


Figure 2. Percentages of patients achieving PASI 50 and PASI 75 analyzed using the last observation carried forward analysis (LOCF). The figure shows the percentages of patients achieving PASI 50 or PASI 75 at different time points during dimethyl fumarate treatment.

Table 4. Mean PASI and Percentages of Patients Achieving PASI 50 and PASI 75 by Visit and Naïve Status Analyzed using the Last Observation Carried Forward Analysis (LOCF).

Visit	Mean PASI (Naïve)	Mean PASI (Exp)	p-value (PASI)	PASI 50 (%) Naïve	PASI 50 (%) Exp	p-value (PASI 50)	PASI 75 (%) Naïve	PASI 75 (%) Exp	p-value (PASI 75)
Baseline	8.6 (±3.9)	9.5 (±4.6)	0.190	–	–	–	–	–	–
4 weeks	7.3 (±3.9)	8.1 (±4.5)	0.228	6.7% (6/89)	5.8% (3/52)	0.820	3.4% (3/89)	1.9% (1/52)	0.619
8 weeks	6.6 (±3.8)	7.4 (±4.5)	0.273	16.3% (8/49)	9.1% (3/33)	0.103	8.2% (4/49)	3.0% (1/33)	0.344
12 weeks	5.4 (±4.0)	6.2 (±4.4)	0.220	41.9% (26/62)	43.6% (17/39)	0.871	22.6% (14/62)	12.8% (5/39)	0.224
24 weeks	4.4 (±4.1)	5.4 (±5.4)	0.209	76.9% (40/52)	77.1% (27/35)	0.981	42.3% (22/52)	34.3% (12/35)	0.455
48 weeks	4.0 (±4.1)	4.7 (±5.6)	0.372	93.9% (31/33)	95.1% (20/21)	0.841	66.7% (22/33)	76.2% (16)	–

Table 5. Mean Psoriasis Area Severity Index by Visit and Disease Duration Analyzed using the Last Observation Carried Forward Analysis (LOCF).

Visit	<5 years (N=33)	5–10 years (N=39)	>10 years (N=76)	p-value (<5/5–10 />10 years)	≤10 years (N=72)	>10 years (N=76)	p-value (≤10 vs >10 years)
Baseline	8.5 (±3.7)	8.7 (±4.6)	9.3 (±4.3)	0.611	8.6 (±4.2)	9.3 (±4.3)	0.336
Week 4	7.0 (±3.5)	7.0 (±4.0)	8.1 (±4.4)	0.314	7.0 (±3.7)	8.1 (±4.4)	0.128
Week 8	6.2 (±3.3)	6.2 (±3.8)	7.5 (±4.5)	0.150	6.2 (±3.6)	7.5 (±4.5)	0.051
Week 12	4.7 (±3.6)	5.2 (±3.8)	6.4 (±4.5)	0.113	5.0 (±3.7)	6.4 (±4.5)	0.041
Week 24	3.6 (±3.7)	3.9 (±3.5)	5.7 (±5.2)	0.040	3.8 (±3.6)	5.7 (±5.2)	0.011
Week 48	3.2 (±3.7)	3.3 (±3.6)	5.3 (±5.4)	0.032	3.3 (±3.6)	5.3 (±5.4)	0.009

mucocutaneous side effects, teratogenicity, and potential hepatotoxicity [14]. In contrast, DMF lacks cumulative organ toxicity and drug–drug interactions, making it suitable for long-term use, especially in patients with comorbidities or when immunosuppression is contraindicated or unwanted [30]. Table 6 summarizes the efficacy, safety, and target populations of DMF based on real-world data and compares them with other conventional systemic treatments for psoriasis.

The main limitation of this study is its retrospective observational nature, which introduces the potential for selection bias, information bias, and confounding variables and does not allow for a direct comparison between DMF treatment and other conventional or biological therapies. Moreover, although the total number of patients enrolled is relatively high, it should be acknowledged that, considering the multicenter design, the sample size could have been larger to enhance the statistical power and generalizability of the findings.

Conclusions

Our study confirms that, when tolerated, DMF represents a valuable first-line systemic therapeutic option for patients with moderate psoriasis as it can induce long-term disease remission while maintaining a good safety profile. DMF should be offered early in the therapeutic journey as this study shows that it is more efficacious and safer for patients with a disease duration of less than five years. DMF is particularly suitable as first-line therapy in cases where immunosuppression is undesired or when patients are on multi-drug

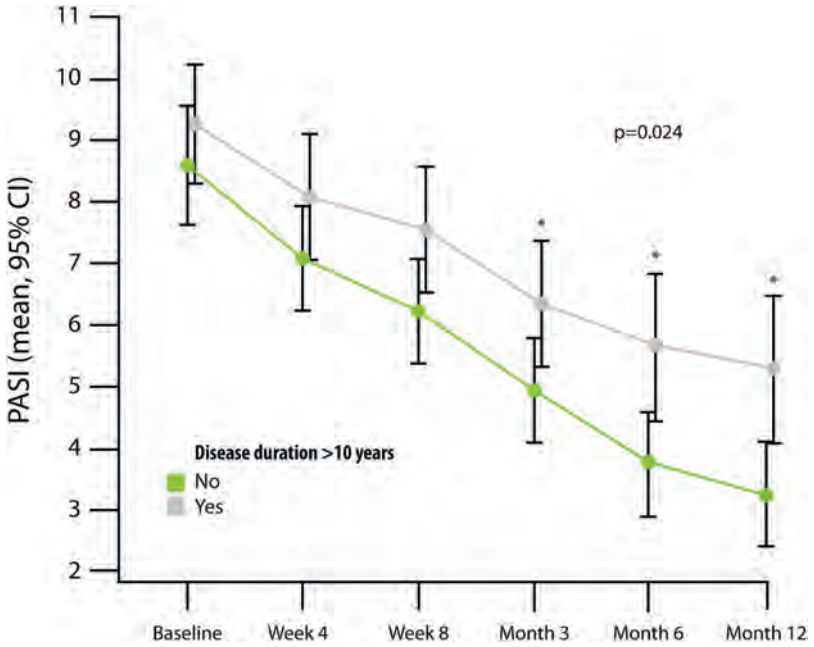


Figure 3. Mean PASI by visit and disease duration analyzed using the last observation carried forward analysis (LOCF).

Table 6. Comparison between these Real-World Data on Dimethyl Fumarate and Efficacy and Safety of other Conventional Systemic Treatments of Psoriasis.

Parameter	Dimethyl fumarate [current study]	Methotrexate [27,28]	Cyclosporin [29]	Acitretin [14]
Efficacy	Moderate efficacy; suitable for long-term management. PASI response lower than methotrexate	Moderate efficacy in chronic plaque psoriasis and PsA	High short-term efficacy; ideal for rapid disease control in severe psoriasis	Moderate efficacy, especially in pustular/ erythrodermic psoriasis; improved with phototherapy
Onset of action	Gradual; improvement over weeks to months	Moderate onset	Rapid onset; ideal for acute flares	Intermediate onset
Tolerability	Generally good; adverse events are mostly early, mild, and reversible (GI upset, flushing); most discontinuations occur early	Requires regular monitoring due to hepatotoxicity, GI effects, and myelosuppression risks	Limited by nephrotoxicity, hypertension, and metabolic issues; requires intermittent short-course use (max ~1 year)	Mucocutaneous AEs common (dryness, cheilitis); lipid/ liver changes require monitoring
Long-term safety	Favorable; lacks cumulative organ toxicity and drug–drug interactions	Risk of liver fibrosis and bone marrow suppression with long-term use	Not recommended beyond 1 year due to renal/metabolic toxicity risks	Teratogenicity (up to 3 years post-therapy), hepatotoxicity, and hyperlipidemia may limit use
Immunosuppressive activity	No	Yes	Yes	No
Best-suited patients	Patients with comorbidities, contraindications to immunosuppressants, or requiring long-term treatment	Patients with extensive plaque psoriasis or joint involvement and no hepatic or hematological contraindications	Patients with rapidly progressive, severe disease requiring fast symptom control	Male or postmenopausal patients with keratinization disorders or pustular/ erythrodermic psoriasis; not for women of childbearing potential

Abbreviations: AE: adverse event; GI: gastrointestinal; PASI: Psoriasis Area Severity Index; PsA: psoriatic arthritis.

therapy as it does not exhibit any drug–drug interaction or cumulative organ toxicities. Further real-world evidence is desiderable to support these findings.

Ethics: The investigation was conducted in accordance with the Helsinki Declaration, and the use of the drug was made according to normal clinical practice and technical data sheet. Patients signed a declaration allowing the use of their clinical records for scientific purposes.

Acknowledgments: The authors acknowledge Lara Vecchi, Valentina Attanasio, and Aashni Shah (Polistudium Srl, Milan, Italy) for editorial assistance and Massimiliano Pianta (Polistudium Srl, Milan, Italy) for graphic support.

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Dermatology Practical & Conceptual

Tildrakizumab as a Potential Option for Early Psoriatic Arthritis in Patients with Metabolic Comorbidities and Psoriasis: a Case Series

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Key words: Tildrakizumab, Psoriatic arthritis, Metabolic syndrome, Psoriasis, Nail psoriasis

Citation: Artosi F, Lanna C, Gaeta Shumak R. Tildrakizumab as a Potential Option for Early Psoriatic Arthritis in Patients with Metabolic Comorbidities and Psoriasis: a Case Series. *Dermatol Pract Concept*. 2025;15(4):5570. DOI: https://doi.org/10.5826/dpc.1504a5570

Accepted: June 12, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Psoriasis is a chronic relapsing inflammatory disease. and approximately 20% of psoriasis patients also develop psoriatic arthritis (PsA).. Interleukin 23 (IL-23) plays a crucial role in maintaining the T-helper (Th) 17 cell population derived from naïve Th1 cells as well as in sustaining inflammation at the enthesis and joints, acting as a pathogenic effector in PsA. Among anti-IL-23 monoclonal antibodies, ustekinumab, guselkumab, and risankizumab are approved in Europe for both psoriasis and PsA for psoriasis and PsA treatment. Tildrakizumab, another IL-23p19 inhibitor, is currently approved only for plaque psoriasis but has shown favorable safety in patients with metabolic comorbidities and potential efficacy in PsA.

Objectives: To retrospectively assess the efficacy of tildrakizumab on psoriatic arthritis manifestations in patients treated according to real-world clinical practice.

Methods: We conducted a retrospective analysis of eight patients affected by psoriasis, early PsA, and metabolic comorbidities, treated with tildrakizumab 100 mg every 12 weeks after induction. Descriptive and inferential statistical analyses were performed. Efficacy and safety were evaluated using standard clinimetric indices over a 28-week follow-up period.

Results: After 28 weeks, a significant mean reduction was observed in Psoriasis Area and Severity Index (-81.3%, P<0.001), Pain Visual Analogue Scale (-85%, P<0.002), Nail Psoriasis Severity Index

(-78%, P<0.002), Dermatology Life Quality Index (-86%, P<0.001), Physician Global Assessment (-73%, P<0.0003), and Disease Activity Index for PsA (-82%, P<0.000023). No adverse events were reported.
Conclusions: Tildrakizumab confirmed its efficacy in reducing signs and symptoms of early PsA, with high safety profile in our psoriasis patients also affected by multiple metabolic comorbidities.

Introduction

Psoriasis is a chronic relapsing inflammatory disease mainly involving the skin. The pathogenesis has not yet been fully understood and includes both immunological cells such as T lymphocytes but also epithelial cells such keratinocytes [1]. Physical, immunological, and infectious factors activate keratinocytes, favoring the release of antimicrobial peptides, DNA, and RNA self recruiting plasmacytoid dendritic cells in the affected skin. After the release of the interferon-α (INFa) by the plasmacytoid dendritic cells (pDC) and the subsequent activation of the dermal dendritic cells (dDCs), the acquired immunity is activated through IL-12 and IL-23. The subsequent differentiation of the T-helper (Th)-naive into Th1, Th17, and Th22 sets the groundwork of psoriatic plaque [1–3]. Keratinocytes contribute to maintaining the inflammatory process over time by promoting angiogenesis and releasing cytokines and chemokines for recruitment of macrophages, neutrophils, and Th17 lymphocytes[1].

Interleukin-23 (IL-23) plays a crucial role in psoriasis; produced by both keratinocytes and dendritic cells, it guarantees the maintenance, expansion, and activation of Th-17 lymphocytes, promotes epidermal hyperplasia, inhibits the function of regulatory T cells, and recalls neutrophils in psoriatic lesional skin with IL-17[2,4].

It is estimated that about 20% of patients with psoriasis are also affected by psoriatic arthritis (PsA), with an annual incidence of about 2% per year[2].

Differently from rheumatoid arthritis (RA), there is no evidence that IL-23 is increased in the synovial fluid in PsA [5]. Histological and molecular studies have shown that IL-23 is expressed within the RA synovium and plays a pro-inflammatory role, inducing both joint inflammation and bone destruction. However, its expression seems to be restricted to highly-inflamed synovial tissue rich in lymphoid aggregates[6]. On the other hand, as for IL-17, a higher concentration in the synovial fluid was found mainly in patients suffering from PsA [7]. Anti-IL-17 antibodies in PsA therapy play a key role but have a different safety profile compared to anti-IL-23 antibodies [8,9].

In order to explain the effectiveness of anti-IL-23 drugs on the arthritic process, some authors have suggested that elevated levels of IL-23 in the synovial fluid of PsA patients may play a key role in the pathogenesis[2, 9–11].

Currently available data support a clear association between nail psoriasis and PsA, with further evidence suggesting that improvement in nail disease correlates with improvement in joint involvement[13]. There is evidence that there is an anatomical continuity between the nail matrix and the entheses of the distal interphalangeal joints extensors, i.e., the most frequently affected site by PsA, confirming that both nail psoriasis and PsA could be considered two different aspects of the same pathogenetic process [14–16].

Currently, three monoclonal antibodies directed against IL-23 (or IL-12 and IL-23) have been approved for the treatment of both psoriasis and PsA, including guselkumab, ustekinumab, and risankizumab[17]. Tildrakizumab, another IL23 inhibitor, approved for plaque psoriasis treatment, is awaiting final approval for PSA. Indeed, phase 2 randomized clinical trials highlight, in patients suffering from PSA, a significant improvement in joint involvement except for dactylitis and enthesitis despite the mean duration of PsA was more than 6 years [18].

Psoriasis, as a systemic inflammatory disease, is closely intertwined with several comorbidities characterized by dysregulated systemic inflammation, with reciprocal influences that contribute to a vicious cycle whose management remains challenging[19]. In this context, it should be emphasized that psoriasis is associated with diabetes mellitus, high abdominal circumference, obesity, hypertension, and insulin resistance favoring progression of metabolic syndrome [19–21]. The therapeutic management of patients with metabolic syndrome requires drugs with high safety profile in terms of blood chemistry parameters and the other co-medications allowed in this class of patients [22,23].

As documented in RCTs, IL-23 inhibitors are a preferred option due to their renowned higher efficacy and better safety profile for psoriatic patients suffering from metabolic syndrome [19,21,23,24]. In a post hoc analysis of the ReSURFACE 1 and ReSURFACE 2 randomized trials, among patients with metabolic syndrome treated with tildrakizumab 100 mg, mean reductions were observed in fasting glucose, triglyceride levels, and systolic blood pressure compared to patients without metabolic syndrome. Similarly, those receiving the 200 mg dose experienced numerical decreases in both systolic and diastolic blood pressure compared to patients

without metabolic syndrome. Notably, patients without metabolic syndrome did not exhibit any increase in metabolic risk factors over the course of the study[23].

According to European guidelines, IL-23 or IL-17 inhibitors should be preferred in all psoriatic patients without contraindications to systemic agents or when they are ineffective [24]. Apremilast is considered a second-line treatment when biological therapies are contraindicated, and in this context, it should be favored over other agents in patients with metabolic comorbidities as it has demonstrated significant benefits in this population [22,24,25].

A case series of patients affected by moderate-to-severe psoriasis, early PsA, and metabolic disorders treated with tildrakizumab was carried out. After 28 weeks of treatment, patients achieved complete or partial resolution of both psoriasis and articular disease.

Methods

We enrolled eight patients with moderate-to-severe psoriasis and early PsA who were treated at the Dermatology Unit of Tor Vergata University Hospital with tildrakizumab 100 mg at baseline (T0), after four weeks, and with a maintenance dose of 100 mg every 12 weeks. All patients signed the informed consent for clinical data collection.

Exclusion criteria were patients <18 years old and those who refused to sign the informed consent for the collection of clinical data.

The following data were collected for each patient at baseline and after 28 weeks of follow-up: demographic data, psoriasis area and severity index (PASI), Pain Visual Analogue Scale (PAIN VAS) score, Nail Psoriasis Severity Index (NAPSI), the Patient Global Assessment (PGA), the Disease Activity in Psoriatic Arthritis (DAPSA) [26], and the Dermatology Life Quality Index (DLQI) [27].

Data on previous treatments for psoriatic and/or arthritic disease, comorbidities, and related drugs were also collected.

The diagnosis of PsA followed the CASPAR classification criteria for PsA [28,29].

The presence of PsA was suspected in each patient with a positive anamnesis of specific signs and symptoms such as morning stiffness lasting more than 30 minutes, joint tenderness, pain worse after rest and relieved by exercise, current or reported presence of swelling joint, dactylitis, limited joint mobility, and joint deformity [17,21]. All patients had a confirmatory color Doppler ultrasound and/or magnetic resonance imaging of the hands and/or feet to evaluate the presence of synovitis, dactylitis, tenosynovitis, erosions, bone edema, and/or enthesitis [29].

All patients received tildrakizumab therapy administered with 100 mg subcutaneous injections, with a dosage established according to the technical data sheet (induction and maintenance) for at least 28 weeks [23].

Statistical Analysis

Descriptive and inferential analyses were performed. The results are expressed as means or percentages, considering the type of each analyzed variable. To analyze the differences in terms of PASI, DLQI, and other indexes or parameters of interest before and after treatment at different timepoints (weeks), the t-test or ANOVA was used, followed by the Bonferroni correction ad hoc test. Differences of $P<0.05$ were considered statistically significant. All statistical analyses were performed using the SPSS 20.0 statistical package (SPSS Incorporated, Chicago)[21].

Results

Eight patients affected by psoriasis and early PsA were enrolled to start Tildrakizumab 100 mg treatment in the period between March 2022 and December 2023. The patients' demographics and clinical data are reported in Table 1. The mean duration of PsA at baseline was less than one year. No patient had PsA with axial involvement.

Five patients (62.5%) were male, and the mean age was 56 years. The mean PASI at T0 was 14.13. In six patients CRP values were found to be beyond the normal upper limit for the laboratory cutoff (1 mg/dl). The mean baseline PAIN VAS was ≃50.

Five (62.5%) patients had nail involvement, with a mean hand NAPSI score of 30/80. Mean DLQI value at T0 was 16.4. Patients N. 2 and N. 3 interrupted their previous treatment with biological drugs due to secondary therapeutic ineffectiveness. Patient N. 5 interrupted the treatment with dimethyl fumarate due to the onset of daytime flushing and diarrhea. Patients N. 1 and N. 7 interrupted the cyclosporine due to an increase in mean blood pressure. In all other cases, the previous treatments were suspended due to primary or secondary therapeutic ineffectiveness. All patients were affected by oligoarticular PsA, with a prevalent involvement of the distal interphalangeal joints. The mean patient PGA value at baseline of treatment with tildrakizumab was 6.5; Mean DAPSA value at T0 was 20.75.

Although just patient N. 1 and patient N. 7 had a diagnosis of metabolic syndrome, each patient had at least one metabolic comorbidity treated with multiple drugs (Table 1). One patient also had active bowel diverticulitis undergoing treatment with antibiotics, whilst another patient had been diagnosed with benign prostatic hyperplasia and had been treated with dutasteride. The distribution of comorbidities is reported in Figure 1.

Table 2 shows patient's clinimetric score after 28 weeks of treatment with tildrakizumab 100 mg. PASI at T28 was

Table 1. Characteristics of Enrolled Patients.

PATIENTS	Comorbidities/therapies	Previous treatments for psoriasis/psoriatic arthritis	T0 Pasi	T0 CRP (mg/dl)	T0 PAIN VAS	T0 Hand NAPSI	T0 DLQI	T0 Patient PGA	DAPSA
N. 1 - Male, 52 years old	Hypertension, diabetes, hypercholesterolemia/Olmesartan, metformin, rosuvastatin	Topicals, methotrexate, cyclosporin, methylprednisolone	10	2.31	60	40	14	7	31
N. 2 - Female, 79 years old	Hypertension, hypercholesterolemia/ Bisoprolol + furosemide, lovastatin	Topicals, acitretin, brodalumab	13	1.2	50	0	11	6	19
N. 3 - Male, 63 years old	Hypercholesterolemia/Rosuvastatin + ezetimibe	Topicals, certolizumab pegol	15	0.26	50	40	10	5	14
N. 4 - Male, 49 years old	Hypertension, colon diverticulitis/ Amlodipine/rifaximine	Topicals	20	3.8	40	33	18	9	17
N. 5 - Male, 53 years old	Hypercholesterolemia/ lovastatin	Dimethyl fumarate	10	<0.40	60	20	10	6	17
N. 6 - Female, 54 years old	Hypertension, mixed connective tissue disease/ ramipril + amlodipine	Topicals, cyclosporine	18	1.8	70	0	23	8	32
N. 7 - Female, 62 years old	Hypertension, diabetes, obesity/ metformin, enalapril, nicotinamide	Topicals, dimethyl fumarate, cyclosporine	7	2	30	20	30	4	14
N. 8 - Male, 38 years old	Hypercholesterolemia, obesity, benign prostatic hypertrophy/ Atorvastatin, dutasteride	Topicals	20	4.2	50	0	15	7	22

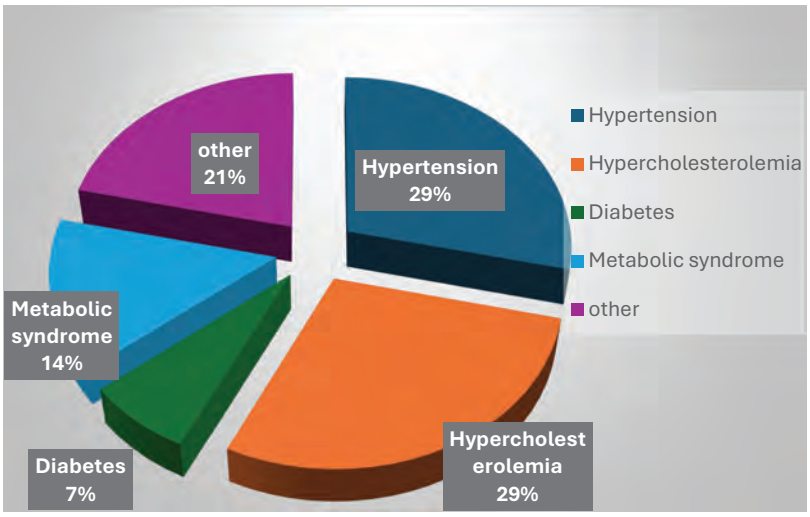


Figure 1. Distribution of comorbidit

Table 2. Evaluation of Clinimetric Scores at Baseline and after 28 Weeks of Treatment.

PATIENT	T28 Pasi	T28 CRP (mg/dl)	T28 PAIN VAS	T28 Hand NAPSI	T28 DLQI	T28 patient PGA	T28 DAPSA
1	0	0.6	0	8	0	0	2
2	3	0.9	0	0	3	2	2
3	3	0.75	0	4	4	1	1
4	12	0.51	0	10	10	7	1
5	3	<0.40	20	0	0	2	9
6	0	1	0	0	0	0	2
7	0	<0.40	0	4	1	1	1
8	0	3.1	10	0	0	1	12

about 2.63, reduced by 81.3% from baseline (P<0.001; Figure 2A). C-reactive protein at T28 remained above the normal limit in only one patient, showing a statistically significant mean value reduction of 66% in all patients (P<0.01; Figure 2B). After 28 weeks only two patients reported still having residual arthritic symptoms, though reduced in severity compared to baseline, with a mean PAIN VAS among all patients of 3.75; the PAIN VAS mean reduction was 85% (P<0.002; Figure 2C). Four patients had residual nail involvement, with a mean NAPSI of 6.5/80, showing a statistically significant reduction (P<0.001; Figure 2D) in the mean value from T0 of ≃ 78%. The DLQI at T28 was 2.25, with a mean reduction of 86% compared to T0 (P<0.001; Figure 2E). The mean patient PGA at T28 was 1.75, with a statistically significant reduction of 73% (P<0.001; Figure 2F).

Mean DAPSA index value at T28 was 3.75, and we also highlight a statistically significant reduction of 82% index between T0 and T28 (t-test P<0.000023; Figure 3).

The monitoring of metabolic parameters did not reveal any abnormality during study protocol in treated patients.

Discussion

The role of IL-23 is crucial to maintaining the Th17 population from Th-1 naïve cells being a central effector involved in the pathogenesis also of PsA. Therefore, it is possible to attribute a primary role to dermal dendritic cells and IL-23 producing keratinocytes, different in terms of "cytokine hierarchy" compared to that of Th17. As the data currently available show the proven efficacy of other IL-23 inhibitors other than tildrakizumab in reducing the signs, symptoms, and progression over time of PsA, they have been approved by both the EMA and the FDA for this indication. Despite the current lack of a valid pharmacodynamic rationale and/or any evidence of ineffectiveness, clinicians cannot yet prescribe tildrakizumab as an on-label treatment for PsA, unlike with other IL-23 inhibitors. The documented efficacy of tildrakizumab on different PsA domains could allow clinicians to promptly intervene on patients suffering from severe psoriasis and metabolic comorbidities by acting early on co-occurring PsA symptoms. In fact, the opportunity of early PsA treatment

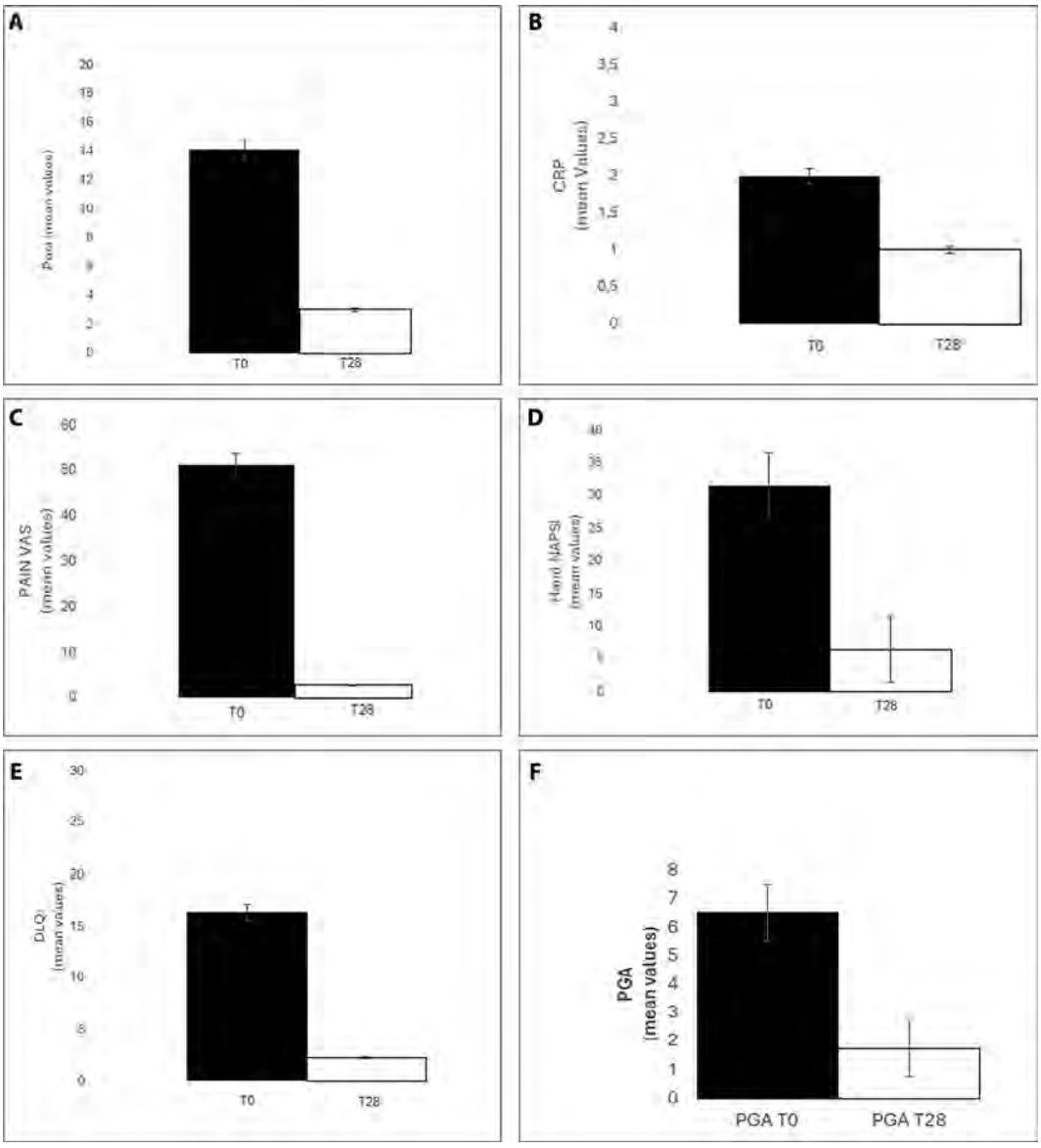


Figure 2. A. Mean PASI values at T0 and T28 (14.13 and 2.63, respectively). Mean reduction: 81.3% (pP<0.001); B. C-reactive protein mean levels at T0 and at T28 (1.95 mg/dl and 0.86 mg/dl, respectively, pP<0.1). We assigned a value of "0" when CRP value was under the lower cut-off limit.; C. Mean PAIN VAS values at T0 and T28 (50 and 3.75, respectively, Pp <0.002); D. Mean HAND NAPSI values at T0 and T28 (30 and 6.5, respectively). Reduction in the mean value from T0 of ≃ 78%, pP<0.001.; E. Mean DLQI values at T0 and T28 (16.4 and 2.25, respectively), mean reduction of 86% compared to T0 (pP<0.001).; F. Mean PGA values at T0 and T28 (6.5 and 1.75, respectively) t-test, pP<0.001.

is now clear, as it can reduce its progression and joint damage, as has been documented in real life studies even in bio-naïve patients [21,30].

Tildrakizumab appears to be safe in patients with cardiovascular comorbidities, including metabolic syndrome, without affecting metabolic parameters.

Dermatologists must also consider the issue of metabolic cardiovascular risk in PsA patients, as shown by our data as well [21]. In fact, some authors have recognized metabolic comorbidities as a possible pathogenetic link with the onset of PsA and not just as a statistically associated disease [31].

Considering biochemical parameters, C-reactive protein is a valid non-specific marker useful to monitoring the progression of joint disease activity, positive in 33–89% of PsA cases, mainly in the early stages of enthesitis [32] but not altered in some active PsA patients[19]. Even in our case series, 25% of patients with active PsA did not show increased CRP values at T0. However, our results also show that only one patient exhibited elevated CRP levels at T28, which remained lower than those recorded at T0. This patient also reported residual, mild arthritic symptoms at T28.

It is noteworthy that the mean PASI at baseline (T0), slightly above 14, did not indicate severe psoriasis. However, the involvement of special sites such as the hands, feet, nails, and genitals accounted for a relatively high mean DLQI at T0 (16.4). After 28 weeks of treatment, PASI was reduced

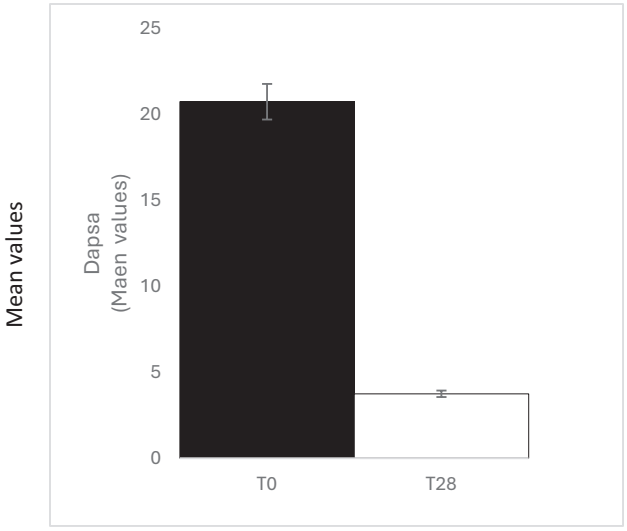


Figure 3. Bar graphs showed statistically significant differences recorded between T0 and T28 for DAPSA score (20.75 and 3.75, respectively). t-test; $P<0.000023$.

by more than 80%, confirming that tildrakizumab can lead to a substantial reduction in disease severity, which was paralleled by a marked improvement in quality of life, as measured by the DLQI.

Nail involvement has been reported in up to 62.5% of psoriatic patients, a finding confirmed in our cohort [16]. The observed improvement in NAPSI was remarkable (approximately 78%), with one patient achieving complete remission of nail psoriasis after 28 weeks. The pathogenesis of nail psoriasis is more closely associated with psoriatic arthritis than with cutaneous psoriasis, and its clinical improvement may reflect better control of joint involvement [16].

Patient PGA assessed by means of VAS is a reliable tool related to both arthritic and cutaneous disease activity [33]. Thus, we decided to evaluate it in order to more accurately highlight the overall trend of the psoriatic pathology over time in each patient. As reported in the results, tildrakizumab was able to strongly reduce the burden of both joint and skin pathology, as reported by the patients, during the 28 weeks of treatment.

The composite DAPSA score is a good tool to assess overall arthritis disease activity as it reflects multiple aspects of affected patients. Our patients obtained a statistically significant reduction in their DAPSA mean score, thus reflecting a better disease course of PsA. It is important to point out that mean baseline score of DAPSA reflected just a mild or moderate activity of PsA.

Anti-TNF-α or anti-IL-17 antibodies are generally prescribed to patients with axial involvement of psoriatic arthritis. Accordingly, no patient with axial disease was treated with tildrakizumab or included in this study. In our clinical practice, our choice of therapeutic option considers firstly anti-IL-17 or anti-TNF-α drugs in patients with a history of psoriatic arthritis of more than one year's duration. These treatment decisions are based on the existing literature, which indicates superior efficacy of these biologics classes compared to anti-IL-23 agents such as tildrakizumab [34].

Psoriasis and PsA are diseases deeply linked to metabolic comorbidities, all having a substrate of chronic systemic inflammation that may play a self-maintaining role [35]. As of March 2025, a dermatologist in Europe can choose the systemic drug for each psoriasis patient from a pool of 18 different therapies, in addition to biosimilars [36]. Among the approved biological drugs for PsA, the ones directed against TNFα show the weakest safety profile, having demonstrated a lower efficacy in obese patients than in normal-weight patients and an association with weight gain in treated patients [37].

Inhibitors of IL-17, while not associated with weight gain in treated patients, have a weaker response in obese patients than in normal-weight patients and are also associated with an increased risk of candidiasis, exacerbated in patients with diabetes mellitus [37,38].

Anti-IL-23 antibodies do not seem to affect glycolipid metabolism or exhibit a different clinical response in obese patients [37]. Recently, tildrakizumab has become available also in a dosage of 200 mg, which is useful in patients weighing over 100 kg and/or with a high disease burden, maintaining the same safety profile compared to the standard dose of 100 mg [39,40]. In light of the RCT tildrakizumab data [23] and based on our real-life clinical experience [21], we consider tildrakizumab to be an effective therapeutic option for psoriasis patients with metabolic comorbidities and signs and symptoms of early PsA who are candidates for biologics to intercept long-term complications such as bone erosions and joint deformities [32].

Conclusions

Awareness of the efficacy of tildrakizumab in PsA could allow clinicians to promptly intervene in patients suffering from severe skin psoriasis and metabolic comorbidities by acting early on co-occurring arthritic symptoms [30].

Further real-life studies are warranted to confirm the role of tildrakizumab in PsA, but our results could be considered a clue of the biological likelihood linked to the treatment of PsA with an IL-23 inhibitor. Our patients achieved complete remission, or at least a dramatic improvement in PsA symptoms after 28 weeks of treatment, together with an almost complete resolution of the skin and nail lesions confirmed by DLQI.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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Dermatology Practical & Conceptual

Unveiling Infantile Hemangiomas: A Comprehensive Study of Patterns, Presentations, and Complications

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Key words: Infantile hemangiomas, Clinical patterns, Presentations, Pediatric complications, Morphology

Citation: Jaiswal P, Singh J, Dua A, Sirohi A, Ashraf F. Unveiling Infantile Hemangiomas: A Comprehensive Study of Patterns, Presentations, and Complications. *Dermatol Pract Concept*. 2025;15(4):5515. DOI: https://doi.org/10.5826/dpc.1504a5515

Accepted: July 1, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Background: Infantile hemangioma is the most common vascular tumor in infants, affecting 4% to 10% of this population. It typically appears as a solitary cutaneous hemangioma but can also be multifocal or segmental. The condition progresses through rapid growth, a plateau phase, and gradual involution. Key risk factors include low birth weight, prematurity, female sex, multiple gestations, and family history. Clinical presentation varies among individuals.

Objective: This study aimed to analyze the clinical characteristics of patients with infantile hemangioma at our hospital, focusing on age at onset, presentation, location, size, type, and complications.

Methods: A retrospective analysis of medical records of infants diagnosed with infantile hemangioma was conducted. Data were collected for statistical analysis on demographics, lesion characteristics, and complications.

Results: The study reviewed 694 hemangiomas in 500 patients, with 50% having a precursor lesion at birth. A significant female predominance (72%) was noted, with most patients (72%) delivered at term. The strawberry mass was the most common morphology (74%), primarily located in the head and neck (42%). Of the hemangiomas, 45% were superficial, and 88% showed progressive growth. Ten patients with periocular hemangiomas experienced amblyopia, while other complications included PHACES syndrome, ipsilateral breast hypertrophy, and arteriovenous malformations.

Conclusion: This study highlights the diverse manifestations, anomalies, and risk factors associated with infantile hemangioma in a tertiary care setting.

Introduction

Infantile hemangiomas (IH) represent the most frequently observed benign tumors in infants, with an incidence rate ranging from 4% to 10% [1]. These tumors originate from a benign proliferation of vascular endothelial cells (VECs) within the mesoderm and can manifest anywhere on the body [2]. The natural progression of infantile hemangiomas is characterized by a triphasic pattern, which includes a rapid growth phase, a plateau phase, and a subsequent slow involution phase. This distinct progression differentiates them from vascular malformations [3]. Nonetheless, certain severe cases of proliferative IH may lead to functional or organic complications such as bleeding, infections, ulcers, external ear obstruction, and airway obstruction [4]. While IH is typically not present at birth, approximately one third of cases can be detected at that time. In 40% of instances, the tumor appears early in infancy, specifically between two to seven weeks of age, while the remaining third develops by six months of age [5]. The proliferation phase lasts from four to 18 months, followed by a gradual involution over three to nine years, often resulting in a fibrofatty remnant in 50% to 70% of cases, along with telangiectasia and excess skin. Key risk factors for IH include female sex, prematurity, low birth weight, European ancestry, multiple gestations, maternal progesterone therapy, and a family history of the condition [4]. Various antenatal factors have also been linked to an elevated risk of IH, including maternal vaginal bleeding during the first trimester, progesterone use, preeclampsia, advanced maternal age, placenta previa, and in vitro fertilization [6]. In contrast, a study examining the incidence of IH in monozygotic and dizygotic twins found no significant difference between the two groups, suggesting that environmental factors may play a more substantial role [7].

Most individuals experience regression without the necessity of intervention; however, around 10%, which can vary by site, may lead to significant complications that necessitate treatment. Complications associated with IH can be classified into several categories: life-threatening, obstructive, ulcerative, or disfiguring. Life-threatening complications encompass airway and hepatic IHs. Functional complications that obstruct essential structures or hinder functionality include periocular, nasal, labial, parotid, auricular, and breast IHs. Local complications typically result from ulceration or occur in areas that are cosmetically sensitive [8].

Infantile hemangiomas (IHs) can be associated with several syndromes, particularly when large or segmental hemangiomas are present. These include PHACES syndrome, an acronym for Posterior fossa malformations, Hemangioma, Arterial anomalies, Cardiac defects, Eye abnormalities, and Sternal clefting or supraumbilical raphe. It is associated with large, segmental hemangiomas, particularly those on the face and neck [9]. Other syndromes involving the lower body are LUMBAR, PELVIS and SACRAL syndrome [2]. LUMBAR stands for lower body hemangioma and other cutaneous defects, Urogenital anomalies, Myelopathy, Bony deformities, Anorectal malformations, and Renal anomalies. PELVIS syndrome [10] stands for Perineal Hemangioma, External genital malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus, and Skin tag. SACRAL syndrome stands for Spinal dysraphism, Anogenital anomalies, Cutaneous hemangioma, Renal anomalies, and Angioma of Lumbosacral localization [11].

Objective

The objective of our study was to analyze the demographic and clinical characteristics such as age at onset, clinical presentation, site, size, type (based on depth), and associated complications in patients who visited our hospital retrospectively and also to compare our data with those obtained from the literature.

Materials and Methods

Study Design

This hospital-based retrospective observational cross-sectional study was conducted in the Department of Dermatology at a tertiary care pediatric hospital. The study reviewed medical records of patients with infantile hemangiomas (IH) treated in the outpatient clinic.

Study Population

The study population comprised patients aged less than 6 years at the time of enrollment who presented with one or more infantile hemangiomas at any stage of evolution. Inclusion criteria involved all patients with clinically diagnosed hemangiomas regardless of size, number, or anatomical location. Patients with other types of vascular anomalies were excluded.

Sample Size

A total of 500 patients were enrolled, and 694 hemangiomas were documented and analyzed.

Study Period

The data were collected retrospectively from medical records from the years 2013 to 2023

Data collected included demographic details, birth history, age at onset, lesion characteristics, and any associated complications.

The primary variables measured included:

- Age at onset and presentation of the hemangiomas
- Lesion characteristics: morphology (papule, macule, plaque, nodule), site (head and neck, trunk, genitalia, limbs, mucosal involvement), size, and number of hemangiomas
- Progression of hemangiomas: gradual, rapid, or stable
- Complications: ulceration, erythema, soft tissue hypertrophy, bleeding, and associations like PHACES syndrome and amblyopia
- Birth history: term or preterm delivery and birth weight
- Associated conditions: amblyopia, PHACES syndrome, and arterio-venous malformations

All clinical assessments were conducted in the outpatient dermatology department by dermatologists trained in pediatric dermatology. Initial evaluations were performed by one of three senior consultants, and data were retrospectively extracted from their standardized clinical documentation. To ensure consistency in diagnosis, a departmental protocol was followed for classifying hemangiomas based on established dermatological descriptors such as lesion depth (superficial, deep, mixed) and morphology (e.g., strawberry vs. bluish lesions).

In cases where classification was ambiguous, diagnostic decisions were refined through consensus discussions held during routine departmental clinical meetings. Although efforts were made to maintain uniformity, we acknowledge that no formal inter-rater reliability testing or use of standardized diagnostic checklists was undertaken, given the retrospective nature of the study.

In patients with large segmental facial hemangiomas, evaluation for PHACES syndrome was guided by the 2009 consensus criteria by Metry et al. [12] Screening investigations included MRI/MRA of the brain and neck, echocardiography, and ophthalmologic examination. PHACES syndrome was diagnosed when a segmental facial hemangioma >5 cm was accompanied by one major or two minor anomalies across the defined domains. Genetic testing and multidisciplinary review were not routinely employed

Statistical Analysis

Data were analyzed using software SPSS 28.0.1. Descriptive statistics were used to summarize demographic data and clinical features. Categorical variables are expressed as frequencies and percentages, while continuous variables are summarized using means or medians as appropriate. Associations between variables were evaluated using chi-square tests or Fisher's exact test. A p-value of <0.05 was considered statistically significant.

Results

A total of 694 hemangiomas were observed in 500 patients recruited from Out Patient Department In 50% (250) of patients, their guardians reported a precursor lesion presenting at birth, while in 46 % (230) of patients, the precursor lesion appeared by three months of age. In the remaining 4% (20), lesions appeared by six months of age at the latest. The majority (44%) of patients presented to the hospital within three months of developing lesions (Figures 1–2).

In our study population, most of the patients 72% (N=360) were born at term, while 25% (N=125) were preterm. Of the 500 patients recruited, 72% (N=360) were females, and the remaining 28% (N=140) were males (Figure 3). Twenty-three percent (N=115) of newborns had low birth weight.

In majority of the patients, the precursor lesion was papule (56%), followed by macule (34%), plaque (6%), nodule (4%).

Head and neck were found to be most common sites (42%), followed by the trunk (15%), genitalia (11%), upper limb (10%), lower limb (7%), and mucosa (5%). Multiple sites were involved in 7% patients (Figure 4).

Forety-four percent (N=305) of hemangiomas ranged in size from 2–5 cm, while 40% (N=277) hemangiomas were <2 cm. Large hemangiomas (>5 cm) were seen in 16% (N=111) of patients. Majority of the patients (87%, N=435) had a solitary hemangioma. Two percent (N=10) of patients had >5 hemangiomas (Figure 5).

The most common morphology observed was strawberry mass (74%, N=514 lesions); bluish discoloration was seen in 28% (N=194) of patients. Twenty-eight percent (N=194) of lesions were ulcerated. On stratified analysis, ulceration was most commonly observed in mixed-type hemangiomas (45.9%, 118/257), compared to superficial (20%, 62/312) and deep (13.6%, 17/125) lesions. Anatomically, facial hemangiomas had the highest incidence of ulceration (31%, 91/294), followed by extremities (28%, 50/180) and trunk (22%, 23/105) (Figure 6). Erythema was seen in 17% (118) of hemangiomas. Associated soft tissue hypertrophy was seen in 12% (N=83) of patients, while bleeding was present in 6% (N=42).

Out of 694 hemangiomas, 45% were superficial (N=312), 18% were deep (N=125), and 37% (N=257) were mixed hemangiomas. The majority of hemangiomas were sessile (89%). Localized hemangiomas were the most common (78%), followed by multifocal (15%) and segmental (7%).

Amblyopia was noted exclusively in patients with periocular hemangiomas, affecting 10 out of 25 patients. On detailed examination, three patients with large segmental hemangiomas over the face were found to have PHACES syndrome. Three patients had associated arterio-venous malformation. A single patient with hemangioma over the chest had associated ipsilateral breast hypertrophy.



Figure 1. Clinical pictures of IH patients showing varied clinical presentations.

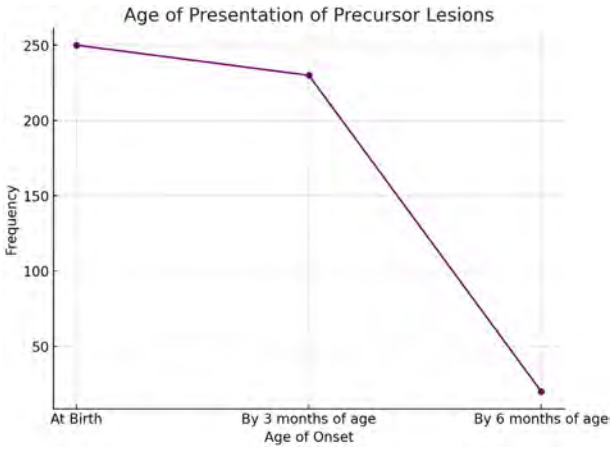


Figure 2. Age at presentation of precursor lesions of infantile hemangioma in the study.

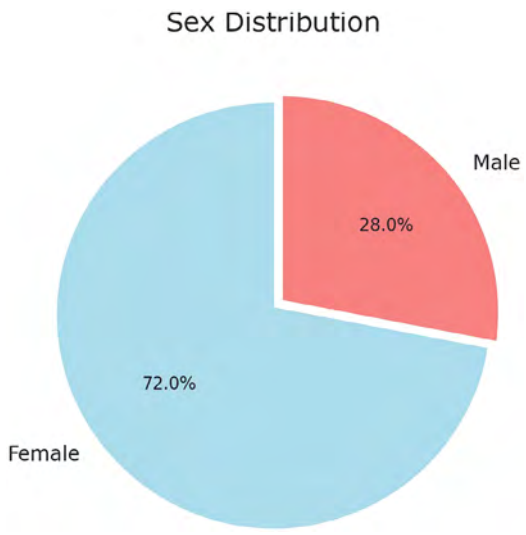


Figure 3. Showing sex distribution: Female (72%) (Blue) vs Male (28%) Red.

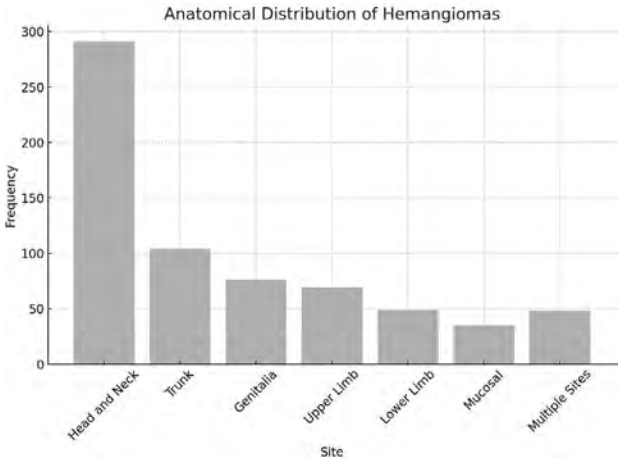


Figure 4. Anatomical sites of distribution of infantile hemangioma found in the study.

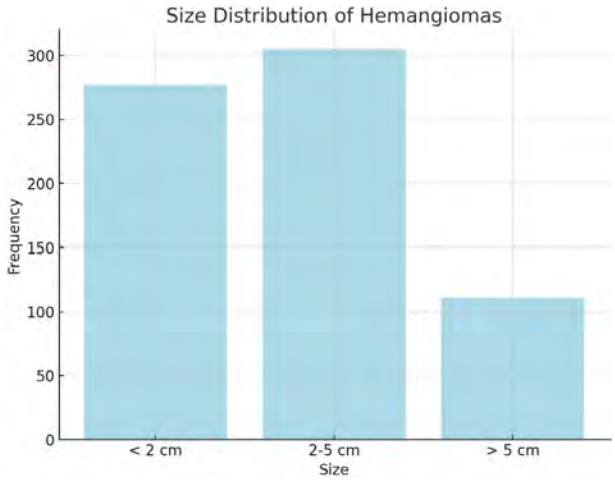


Figure 5. Size distribution of infantile hemangioma in the study.

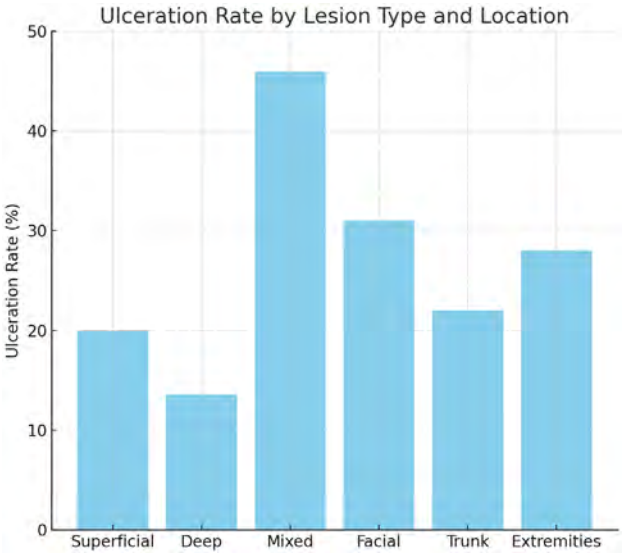


Figure 6. A bar chart showing ulceration rates across lesion types and anatomical locations.

Discussion

This retrospective cross-sectional observational study comprehensively analyzed the demographic and clinical characteristics of infantile hemangiomas of 500 patients. The findings reveal significant insights into the age at onset, clinical presentation, and associated complications of these vascular lesions, contributing to the existing literature on this prevalent condition.

Our findings reveal a predominance of female patients (72%) ,which is consistent with the findings of the study done by Munden et al. [3], with 53% of female and 47% of male infants presenting with infantile hemangioma. This sex bias is likely influenced by hormonal factors, although the exact mechanisms remain unclear. However in a study done by Sandru et al. [13], more male patients with hemangioma were identified than females (57.14% vs. 42.85%).

In our study, 50% of patients exhibited a precursor lesion at birth, while 46% developed the lesion by age three months. This finding is consistent with findings from a prior study done by Chang et al. that highlighted the early onset of infantile hemangiomas by three months of age, indicating a crucial period for observation and possible intervention [14]. Furthermore, in our study, 44% of patients sought hospital care within three months of lesion appearance, which emphasizes the urgency often felt by caregivers regarding these vascular anomalies. This finding is also consistent with the finding from Chang et al., where the mean age at the first visit was five months.

The correlation between infantile hemangiomas (IH) and prematurity has been extensively established, with numerous studies demonstrating a greater occurrence of IH in preterm infants relative to those born at term. One such study is by Suzen Orhan et al., who found IH in 26.6% of preterm infants [15]. We also found a significant portion of preterm infants (25%) developing infantile hemangioma. This connection is believed to arise from common pathophysiological processes, especially those related to hypoxia and vascular growth factors. The case-control study done by Chehad et al. [16], on clinical and epidemiological risk factors for infantile hemangioma indicates that the occurrence of infantile hemangioma (IH) is significantly elevated in low birth weight (LBW) infants, with odds ratios suggesting a 4.5-fold increased risk for LBW infants in comparison to those of normal weight. This finding is congruous with our study, where a significant 23% of newborns with low birth weight developed IH.

In our study, most patients (56%) with IH presented with papule as precursor lesion, followed by macules (34%), plaques (6%), and nodules (4%). These findings are consistent with the previous study done by Lydiawati et al., who also noted that macules were the most frequent skin lesions

(35.36%), with about 28.13% of patients exhibiting a combination of macular and nodular lesions [17]. These findings suggest that the majority of cases begin with a papular stage, highlighting the importance of early recognition and monitoring of these precursor lesions in infants.

Head and neck were found to be the most common sites (42%), followed by the trunk (15%), genitalia (11%), upper limb (10%), lower limb (7%), and mucosa (5%). Multiple sites were involved in 7% of patients in our study. This corroborates with the study by Otaibi et al., who found that the most common site of hemangioma was the face (36.4%), followed by the upper limbs (18.3%), lower limbs (12.7%), chest (12.7%), and scalp (9.1%). The site preference could be justified by the anatomical factors as well as by the timing of vasculature development of different sites. It has been found that the head and neck are the most common sites as they have a higher density of blood vessels, making them more susceptible to vascular tumors like IH. It can also be seen that IHs typically manifests within the first few weeks of life, which coincide with the rapid vascular development in the head and neck areas [18].

The size distribution of hemangiomas in our study, with 44% ranging from 2–5 cm^2 and 16% exceeding 5 cm^2, is consistent with the findings of the study done by Lydiawati et al. [17], with 14.29% of IH in their study being ≥5 cm^2. The size of the lesion is an important factor to observe since it can determine the likelihood of the complications. The predominance of focal hemangiomas (87%), with 15% multifocal and 7% segmental in our study, is in accordance with the findings from the study done by Hung et al.[19] and Chiller et al.[5].In this study we observed that 45% of lesions were superficial (N=312) and 18% lesions were deep (N=125); 37% (N=257) were mixed hemangiomas, among which 74% were strawberry mass and 28% were bluish discoloration, morphologically. This is in accordance with the existing literature by Sturb et al.[20], who found that the most common presentation was superficial hemangiomas characterized by bright red or "strawberry mass" that involves the upper dermis. While deep lesions have a more bluish hue, mixed lesions have both characteristics.

The observation that 88% of hemangiomas exhibited progressive growth, with a notable 40% showing rapid progression, raises important considerations for clinical practice. The growth patterns of hemangiomas can significantly influence management strategies, as rapid growth may necessitate early intervention to prevent complications [21]. The stable size observed in 12% of cases may suggest a subset of hemangiomas that can be monitored without immediate treatment, emphasizing the importance of individualized patient assessment.

Our post hoc stratified analysis revealed that mixed-type hemangiomas had the highest rate of ulceration (45.9%), followed by superficial (20%) and deep lesions (13.6%). This aligns with the findings of Mariani et al., who reported increased complication rates in mixed and larger hemangiomas due to their rapid proliferative phase and greater tissue involvement, which can predispose to breakdown and ulceration [8]. Among anatomical sites, facial lesions showed the highest ulceration rate (31%), consistent with a study by Chang et al. highlighting that hemangiomas in exposed or high-motion areas (such as the face and extremities) are at higher risk of mechanical irritation and breakdown [14].

Moreover, periocular hemangiomas were strongly associated with amblyopia, observed in 100% of cases (10/10). This supports earlier studies by Haggstrom et al. and Frieden et al., who emphasized the importance of early ophthalmologic evaluation in infants with periocular hemangiomas due to the risk of visual axis obstruction, astigmatism, and anisometropia [22,23]. Our findings reinforce the need for clinicians to monitor mixed-type and facial hemangiomas closely for early signs of ulceration and to promptly refer periocular hemangiomas for ophthalmologic evaluation, ideally within the first few weeks of life.

Additionally, we observed associations with syndromic conditions such as PHACES syndrome and arteriovenous malformations in three patients, along with ipsilateral breast hypertrophy noted in one patient with infantile hemangioma located on the chest. These findings echo the concerns raised in a previous study done by Haggstrom et al. regarding the potential for IH to be associated with significant morbidity, particularly when located in critical areas [23]. The incidence of ulceration (28%) and bleeding (6%), which corroborate the findings of Sun et al. [18], further emphasizes the need for comprehensive management strategies to address both the aesthetic and functional implications of IH.

Limitations

This study has several limitations inherent to its retrospective design. First, no a priori power calculation was performed. The sample size of 500 patients was based on feasibility and represents a consecutive cohort over a 10-year period at a single tertiary care center. While adequate for descriptive analysis, the study is likely underpowered to detect statistically significant associations for rare outcomes such as PHACES syndrome or amblyopia. A post hoc estimate suggests a larger sample size would be required to detect these events reliably. Future studies should incorporate prospective power planning.

Second, the referral bias associated with conducting the study at a tertiary care pediatric hospital may have led to an overrepresentation of severe, atypical, or treatment-resistant infantile hemangiomas. This could limit the generalizability of findings to general pediatric or primary care settings. We recommend that future research include community-based

populations or birth cohorts to provide a more representative epidemiological profile of infantile hemangiomas across clinical contexts.

Third, while lesion assessments were performed by dermatologists following a standardized departmental protocol, evaluations were conducted by multiple providers over the study period. Although diagnostic classification relied on established morphological descriptors and consensus discussions were held for ambiguous cases, we acknowledge that no formal inter-rater reliability testing or structured diagnostic checklist was used. This introduces the potential for inter-observer variability in lesion classification and complication reporting.

Lastly, due to the retrospective nature of the study, imaging and diagnostic protocols (e.g., MRI, echocardiography for PHACES syndrome) were selectively applied to patients with clinical indications (e.g., large segmental facial hemangiomas). While we adhered to the 2009 PHACES diagnostic consensus guidelines for these cases, the absence of uniform screening limited our ability to comment on true syndrome prevalence in the cohort.

Conclusion

In conclusion, our study provides a comprehensive analysis of the demographic and clinical characteristics of infantile hemangiomas, contributing valuable data to the existing literature. The findings underscore the need for heightened awareness among healthcare providers regarding the presentation and management of IH, particularly in vulnerable populations. Future research should focus on longitudinal studies to better understand the long-term outcomes of IH and the impact of early intervention on associated complications.

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Dermatology Practical & Conceptual

Association Between Altered Gut Microbiota and Acne Vulgaris: A Comparative Study of Trimethylamine N-Oxide Levels in Patients and Healthy Controls

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Key words: Acne vulgaris, Gut microbiota, Trimethylamine N-oxide, Dysbiosis, Inflammation

Citation: Bal Bayazıtlı EC, Aksoy Saraç G, Uzdoğan A, et al. Association Between Altered Gut Microbiota and Acne Vulgaris: A Comparative Study of Trimethylamine N-Oxide Levels in Patients and Healthy Controls. *Dermatol Pract Concept*. 2025;15(4):5486. DOI: https://doi.org/10.5826/dpc.1504a5486

Accepted: July 1, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Microbiota refers to the microorganisms inhabiting specific environments, while the microbiome encompasses these organisms, their metabolites, and environmental factors. Variations in microbiota composition across body regions influence physiological processes, including metabolism, immunity, and skin health. Trimethylamine N-oxide (TMAO), a metabolite linked to gut dysbiosis, inflammation, and systemic diseases, has not been previously investigated in acne patients.

Objective: We aimed to investigate the potential relationship between gut dysbiosis and acne vulgaris by assessing serum TMAO levels in acne patients compared to healthy controls.

Methods: This case-control, cross-sectional study involved 70 acne patients and 70 age- and sex-matched healthy controls. Serum TMAO levels were measured, and acne severity was graded using the Global Acne Grading System (GAGS). Statistical analysis was performed using SPSS 20.0, with p-values <0.05 considered significant.

Results: Acne patients exhibited significantly higher serum TMAO levels (16.74 ± 10.10 ng/ml) compared to controls (13.11 ± 4.28 ng/ml, *P*=0.007). While no significant correlation was found between TMAO levels and acne severity, a weak negative trend was observed (*P*=0.062). Similarly, TMAO levels showed no significant correlation with body mass index (BMI) (*P*=0.933).

Conclusion: This study identified elevated serum TMAO levels in acne vulgaris patients, suggesting a potential link between gut dysbiosis, diet, and acne pathogenesis. While these findings emphasize the role of systemic inflammation and microbiota, further research is necessary to establish causal relationships and to evaluate the impact of dietary and microbial interventions in acne management.

Introduction

The term microbiota refers to microorganisms such as bacteria, fungi, and viruses present in a given environment, while the term microbiome encompasses these microorganisms along with microbial elements, metabolites, and environmental conditions as a whole. The components of microbiota vary across different regions of the body, with distinct compositions observed in areas such as the gut and skin [1]. Studies have shown that the microbiome plays a role in vital physiological processes such as energy balance, metabolism, gut epithelial health, immune activities, and neurobehavioral development [2]. Changes in the microbiome have been associated with diseases such as inflammatory bowel disease, type 2 diabetes, psoriasis, and Parkinson's disease [3].

Trimethylamine N-oxide (TMAO) is a metabolite produced in the liver from trimethylamine (TMA), which is generated by the gut microbiota through the metabolism of dietary nutrients such as choline, betaine, and L-carnitine [4-6]. In the liver, TMA is oxidized to TMAO primarily by flavin monooxygenase (FMO) enzymes, with FMO-3 acting as the rate-limiting enzyme in this process [7]. TMAO has been implicated in promoting oxidative stress and low-grade chronic systemic inflammation, which are key contributors to various chronic diseases [8]. Elevated TMAO levels have been associated with high dietary intake of choline and L-carnitine as well as gut dysbiosis [9,10].

Studies have shown that gastrointestinal health and skin balance are closely linked through the regulation of both the innate and adaptive immune systems. While this regulation is mainly mediated by the gut microbiota, the skin microbiota is also important to maintaining skin immune balance. A disruption of this balance can lead to weakened skin barrier function. This connection has also been implicated in dermatologic conditions such as hidradenitis suppurativa (HS) and acne vulgaris [11].

In the dermatological context, hidradenitis suppurativa (HS), a chronic inflammatory skin disorder affecting the pilosebaceous unit and sharing pathogenic mechanisms with acne vulgaris, has been linked to increased circulating TMAO levels, which correlate with disease severity [4,12].

Acne vulgaris is a common chronic inflammatory disease. While genetic and hormonal factors are known to play a role in its development, the relationship between diet and acne remains unclear. Studies suggest that a high glycemic index diet, dairy products, and chocolate consumption may trigger or exacerbate acne vulgaris [13,14]. Research has shown a bidirectional interaction between gut microbiota and skin homeostasis through immune system regulation. However, the relationship between acne and microbiota has not yet been fully elucidated [15,16].

Objective

TMAO levels, an indirect marker of gut dysbiosis and inflammatory processes, were investigated in this study in patients with acne vulgaris. The aim was to explore the potential role of gut dysbiosis in acne development by comparing patients with a healthy control group.

Methods

This case-control, cross-sectional, observational study was conducted between September 2023 and April 2024 at the Dermatology and Venereal Diseases outpatient clinic. Ethical approval was obtained from the Ethics Committee for Clinical Research at Ankara Bilkent City Hospital (approval number: E1-23-3868). All participants were verbally informed about the study, and detailed written informed consent was obtained.

The study included 140 volunteers: 70 patients with acne vulgaris and 70 healthy individuals as controls. The control group was matched to the patient population in terms of age and sex. The inclusion criteria were volunteers aged 18 years or older, no known systemic disease, and first-time hospital admission for acne. The control group consisted of volunteers aged 18 years or older with no history of acne vulgaris or any known systemic disease. Patients diagnosed with seborrheic dermatitis, polycystic ovary syndrome, rosacea, or inflammatory bowel disease were excluded. Patients who had previously been treated for acne with antibiotic therapy within the preceding six months or who were smokers were also excluded.

For eligible participants, demographic data, height, and weight were recorded. Disease severity was assessed using the Global Acne Grading System (GAGS), a standardized tool developed by Doshi et al. (1997), and the corresponding scores were recorded. [17]. Blood samples were collected to evaluate TMAO levels.

Descriptive data are presented as frequencies, percentages, means, standard deviations, and minimum-maximum values. The normality of the data distribution was assessed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Differences in distribution between the two groups were analyzed using the chi-square test. Differences between two group means were evaluated using the Student's T-test, while differences among three group means were analyzed using the one-way ANOVA test. Relationships between two numerical values were assessed using Pearson's correlation test. A p-value of <0.05 was considered statistically significant. Data analysis was performed using SPSS 20.0 software.

Results

The study included 70 acne patients and 70 healthy volunteers matched to the patients in terms of age and sex. The mean age of the acne group was 21.6 ± 3.77 years, while that of the control group was 20.76 ± 3.26 years. Females accounted for 67% of the acne group and 48% of the control group. The mean BMI in the acne group was 22.16 ± 4.43, compared to 22.02 ± 3.58 in the control group, with no statistically significant difference between them. The mean serum TMAO level in the acne group was 16.74 ± 10.10 ng/ml, compared to 13.11 ± 4.28 ng/ml in the control group; this difference was statistically significant (*P*=0.007; Table 1) and is illustrated in Figure 1.

Acne patients were evaluated using GAGS and categorized into three groups: mild, moderate, and severe. Although serum TMAO levels tended to be higher in patients with mild acne (19.75 ± 10.45 ng/ml) and lower in those with severe acne (16.67 ± 10.89 ng/ml), the difference was not statistically significant (*P*=0.062; Table 2). The correlation between TMAO levels and GAGS scores was weakly negative and did not reach statistical significance (*P*=0.084). Similarly, the correlation between TMAO levels and BMI was also weakly negative and not statistically significant (*P*=0.933).

Discussion

This study investigated serum TMAO levels in patients with acne vulgaris, providing insight into the potential involvement of gut dysbiosis in acne pathogenesis. The results indicate that serum TMAO levels, which have been linked to inflammation and cardiovascular risk and are considered a marker of gut dysbiosis [6], were significantly higher in acne patients compared to healthy controls. These findings suggest a possible association between gut microbiota alterations and the development of acne vulgaris.

Similarly, increased TMAO levels have also been observed in hidradenitis suppurativa (HS), a disease of the pilosebaceous unit like acne. In a study by Barrea et al., a correlation was identified between TMAO levels and disease severity. Elevated TMAO, considered a marker of inflammation, may also reflect increased systemic inflammation in HS patients [4]. In this study, while TMAO levels were found to be elevated in acne patients compared to the control group, no significant relationship was observed between acne severity and TMAO levels.

Recent evidence indicates that certain probiotics and prebiotics may reduce systemic TMAO levels by modulating gut microbiota composition. Strain-specific effects have been observed, particularly with *Lactobacillus rhamnosus* GG and *Lactiplantibacillus plantarum* ZDY04, which were shown to lower TMAO concentrations in both animal and limited human studies [18,19]. These findings suggest a potential role for microbiota-targeted interventions in reducing TMAO-mediated inflammation, which may be relevant in acne pathogenesis.

Table 1. Demographic Characteristics, TMAO Levels, and Acne Severity in Compared Groups.

Characteristics	Case	Control	p-value
Number of participants	70	70	
Age (year) (mean ± SD)	21.61 ± 3.77	20.76 ± 3.26	0.153
Sex [N (%)]			
Male	24 (34.3)	22 (31.4)	0.719
Female	46 (65.7)	48 (68.6)	
BMI (mean ± SD)	22.16 ± 4.43	22.02 ± 3.58	0.840
TMAO (mean ± SD)	16.74 ± 10.10	13.11 ± 4.28	**0.007**
GAGS (mean ± SD) (min-max)	21.90 ± 8.65 (8-42)		

SD: standard deviation; GAGS: Global Acne Grading System; BMI: body mass index; TMAO: Trimethylamine N-oxide.

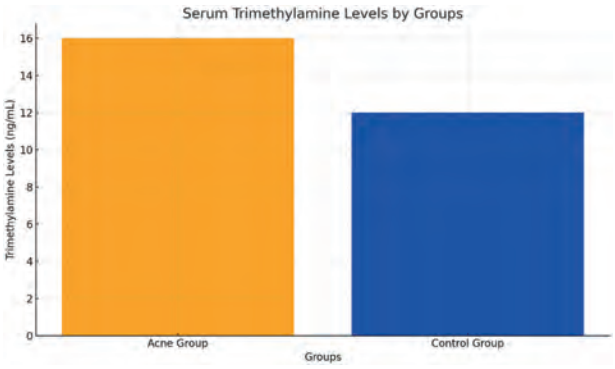


Figure 1. Comparison of mean serum trimethylamine N-oxide (TMAO) levels between the acne group and the control group. TMAO levels were significantly higher in the acne group (P=0.007).

Table 2. Demographic Characteristics, TMAO Levels, and Acne Severity by Severity Groups.

Characteristics	Severe	Moderate	Mild	p-value
Number of participants	16	25	29	
TMAO (mean ± SD)	16.67 ± 10.89	13.28 ± 8.29	19.75 ± 10.45	0.062

Diet plays a significant role in shaping the microbiota, which has been associated with various systemic diseases. Research has shown that dietary changes can significantly alter microbiota composition within 24 hours [20]. For example, a red meat-based diet increases *Bacteroides* and *Clostridia spp.*, while reducing *Bifidobacterium spp.* In contrast, a plant-based protein diet promotes *Bifidobacterium* and *Lactobacillus* growth, while reducing *Bacteroides* and *Clostridium* populations. Similarly, diets rich in saturated and unsaturated fatty acids or high in carbohydrates also influence microbiome composition [21]. Foods rich in choline and carnitine, such as red meat, eggs, milk, and cheese, promote TMA production by *Firmicutes* and *Proteobacteria* [22].

Moreover, short-chain fatty acids (SCFAs) such as acetate and butyrate, produced by beneficial gut microbes, are recognized for their anti-inflammatory properties and roles in maintaining gut epithelial integrity. In acne patients, dysbiosis has been linked to reduced acetate levels and a decline in SCFA-producing bacteria like *Fecalibacterium* spp., which may contribute to systemic inflammation and increased intestinal permeability [23,24]. These findings further support the relevance of gut-derived metabolites in acne and suggest new directions for microbiota-based therapeutic approaches.

This study has several limitations. First, its case-control design restricts causal inferences regarding the role of TMAO in acne pathogenesis. Although significantly higher TMAO levels were observed in acne patients compared to healthy controls, no significant association was found between TMAO levels and acne severity; this may be attributed to the limited sample size, which could have reduced statistical power. While the study discusses gut dysbiosis, no microbial profiling was performed, preventing identification of specific TMA-producing or SCFA-reducing bacterial taxa. Additionally, dietary intake was not recorded, despite the known influence of red meat, eggs, and fish on TMAO production. Other potentially influential factors such as probiotic use, menstrual status, stress, sleep, and physical activity were not systematically assessed. Finally, inflammatory markers such as CRP or IL-6 were not measured, limiting direct confirmation of systemic inflammation.

Conclusion

In this study, serum TMAO levels, an indirect marker influenced by diet and gut microbiota, were found to be elevated in patients with acne vulgaris, suggesting that dietary factors may contribute to acne pathogenesis. Previous research has reported associations between high glycemic index diets, dairy consumption, and acne development, which may support a potential link between diet, gut-derived metabolites such as TMAO, and acne [25,26].

This study investigated TMAO levels in acne vulgaris patients. Further research is warranted to clarify the potential role of gut microbiota and diet in acne pathogenesis.

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Dermatology Practical & Conceptual

Spontaneous Regression of Well-Differentiated Squamous Cell Skin Cancer Following Partial, Diagnostic Biopsy: Retrospective Cohort in Queensland

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Key words: Squamous Cancer, Spontaneous Resolution

Citation: Wilkinson D, Sottovia J, Hoogstad S. Spontaneous Regression of Well-Differentiated Squamous Cell Skin Cancer Following Partial, Diagnostic Biopsy: Retrospective Cohort in Queensland. *Dermatol Pract Concept*. 2025;15(4):5632. DOI: https://doi.org/10.5826/dpc.1504a5632

Accepted: June 26, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Well-differentiated squamous cell skin cancer (WDSCC) is common in sun-exposed populations. Guidelines promote active treatment, with excision preferred. Isolated cases of spontaneous regression (SR) have been reported. Having observed multiple patients with apparent SR following partial, diagnostic biopsy, we did a retrospective cohort study to explore this further.

Objectives: We sought to report frequency of SR of WDSCC following partial biopsy by a general practitioner (GP) in a primary care setting and referral to a public hospital general surgery service for excision, to report patient characteristics, and to estimate the time interval between biopsy and SR.

Methods: Retrospective cohort study (22 months) of patients in Queensland, Australia, with a diagnosis of WDSCC following a partial biopsy by a GP. SR was defined as no clinical or dermoscopy evidence of squamous cell carcinoma (SCC).

Results: Among 153 consecutive patients with WDSCC referred for excision, 51 showed SR at consultation (33.3%, 95% CI: 25.6–41). There was no significant difference in age or sex of the SR and

non-SR groups. In almost all patients with SR (N=49, 96.1%), lesions were located below the knee, compared with 90 (88.2%, *P*=0.042) without SR. Average interval between biopsy and surgical consultation was 13.6 weeks (range 2.7–24.7 weeks).

Conclusions: WDSCC may spontaneously resolve following partial, diagnostic biopsy more often than previously reported. These preliminary observations may have implications for treatment options, especially among frail patients with comorbidities.

Introduction

Squamous cell carcinoma (SCC) of the skin is the second most common type of skin cancer worldwide. It typically develops in sun-exposed parts of the body, particularly in older people with fair skin. The primary risk factor is cumulative ultraviolet (UV) radiation exposure. Other risk factors include chronic immunosuppression, previous radiation therapy, and chronic wounds. While SCC has a favorable prognosis when detected early, it has the potential for local invasion and metastasis, particularly in high-risk anatomical sites on head and neck. The global incidence is rising, due to ageing populations, increased sun exposure, and improved detection [1].

SCC represents a significant public health burden in Australia, with the highest rates of skin cancer in the world. Due to the combination of high UV exposure, predominantly fair-skinned population, and outdoor lifestyle, Australia's incidence rates of SCC are more than five times those seen in other Western countries, and Queensland reports the highest rates in Australia [2]. The economic impact is substantial, with skin cancers (including SCC) costing the Australian healthcare system over $1.5 billion annually. While mortality rates remain relatively low, the sheer volume of cases creates a significant burden on healthcare resources [3].

While actinic keratosis typically resolves spontaneously when UV exposure is reduced, and the natural history of keratoacanthoma (considered a form of SCC by many but not all) is characterized by spontaneous resolution, SCC does not resolve spontaneously [4]. We observed apparently spontaneous resolution among several patients referred to a general surgical service for SCC excision following partial, diagnostic biopsy by their general practitioner (GP). We therefore designed a retrospective cohort study to explore this further.

Objectives

1. To report the frequency of SR of WDSCC following partial, diagnostic biopsy by a general practitioner (GP) in a primary care setting and referral to a public hospital general surgery service for excision.
2. To report characteristics of patients showing SR, and compare these with patients not showing SR.
3. To estimate the time interval between biopsy and spontaneous resolution, using the interval between biopsy and surgical consultation (with patient reports) as a proxy.

Methods

We used the STROBE checklist [5].

Study Design

A retrospective cohort study was conducted over a 22-month period between December 2022 and September 2024.

Setting

Sunshine Coast Universityospital and Health Service (SCHHS), Sunshine Coast, Queensland, Australia. The health service serves approximately 500,000 people from the heavily populated coast, through more rural farming areas into remote, smaller settlements [6]. GPs typically biopsy suspicious skin lesions in their clinics using a punch biopsy technique (or less often, a shave biopsy). Most GPs then refer patients for treatment, depending on the size and location of the lesion, patient characteristics and comorbidities, and their own procedural skill level.

Referral guidelines are provided via HealthPathways [7]. and patients are referred for excision to either the General Surgery Service (lesions below the head and neck) or Plastic Surgery Service (lesions on the head and neck). All GP referrals are made centrally to the SCHHS and are reviewed and allocated to services and clinics there. The written referral (not the patient) is reviewed by a clinical nurse and a surgeon and allocated to the waiting list, according to urgency. WDSCC are usually considered non-urgent (category 3), with specialist consultation recommended within 365 days, or semi-urgent (consultation recommended within 90 days) [8].

Participants

Consecutive patients with a histological diagnosis of WDSCC following a partial, diagnostic biopsy of a suspicious

lesion, conducted by the patient's GP in a primary care at Maleny Hospital, part of the SCHHS. All other subtypes of SCC were excluded.

Variables

Age, sex, diagnosis, time interval between biopsy and surgical consultation, spontaneous resolution or not of the biopsied lesion.

Spontaneous resolution (SR) was defined as the absence of any clinical or dermatoscopic evidence of SCC and the presence of a flat scar clinically, with dermoscopy consistent with a scar.

Data Sources

All data were extracted from the patients' electronic medical record by DW and SH. Ethical approval was granted by Metro South Health Human Research Ethics Committee (HREC/2024/QMS/106985) on 2 September 2024.

Bias

This was minimized by including all consecutive patients with a diagnosis of WDSCC who attended this general surgery clinic.

Study Size

A total of 153 consecutive patients with a confirmed pathological diagnosis of WDSCC following partial, diagnostic biopsy of a suspicious lesion by the patient's GP.

Quantitative Variables

We report the number of patients with WDSCC, the number (%, and 95% confidence intervals [CI]) with SR, age and sex, and lesion location, comparing SR with non-SR patients and time interval between biopsy and surgical consultation.

Statistical Methods

Statistical analysis was performed using Microsoft Excel 2010. Descriptive statistics were used to summarize the data, with categorical variables expressed as frequencies and percentages. CI for proportions were calculated using the normal approximation method (SAS/STAT software, Version 9.4 (SAS Institute Inc., Cary, NC). Data visualization, including tables and figures, were generated using Excel charts to illustrate findings.

Results

Over the 22-month study period, 153 consecutive patients with biopsy-proven WDSCC were consulted at the general surgery clinic. Seven patients had more than one WDSCC, representing 160 lesions in all.

Of the 153 patients (with 160 lesions, Table 1), 51 patients (with 54 lesions) exhibited spontaneous resolution at the time of surgical consultation, corresponding to 33.3% (95% CI: 25.6–41) of patients and 35.3% (95% CI: 27.7%–42.9) of lesions. Mean and standard deviation (SD) of the age of the SR group was not statistically significantly different from the non-SR group: 73.7 (8.5) years vs 75.2 (6.3) (P=0.18). In almost all patients (N=49, 96.1%) with SR, lesions (N=51, 94%) were mainly located below the knee; in non-SR patients the proportion below the knee was 90/102 (88.2%, P=0.042). Average interval between biopsy and surgical consultation was 13.6 weeks (range 2.7–24.7 weeks), with no difference between SR and non-SR groups (Figure 1).

Discussion

These preliminary observations suggest that WDSCC may have relatively high rates of spontaneous resolution following a partial diagnostic biopsy over a period of a few weeks. Our findings suggest that this may occur in approximately

Table 1. Characteristics of SR and non-SR Groups.

	SR	Non-SR
Number of patients (%)	51 (33.3)	102 (66.7)
Number of lesions (%)	54 (33.8)	106 (66.2)
Age at point of biopsy years, mean (SD)	73.7 (8.5)	75.2 (6.3)
Sex, number of patients (%)		
Male	29 (56.9)	58 (56.9)
Female	22 (43.1)	44 (43.1)
Location, Number of lesions (%)		
Lower leg (below the knee)	49 (94.4)	90 (88.2)
Forearm	2 (5.6)	12 (11.8)

Abbreviations: SR: spontaneous regression.

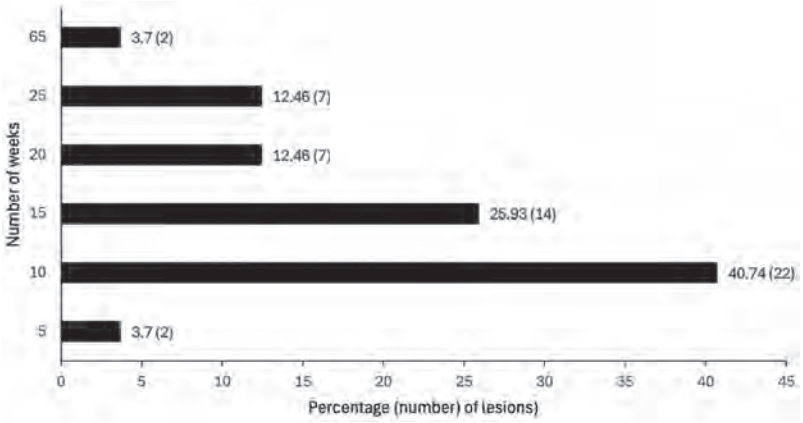


Figure 1. Distribution of time interval between biopsy and surgical consultation.

one third of patients, noting that our retrospective cohort was restricted largely to patients with lesions below the head and neck. Most patients with spontaneous resolution (SR) had lesions on the lower leg below the knee, and at a higher proportion than those without SR. There was no significant difference in age or sex between the two groups.

Caution needs to be applied when estimating the time taken for SR to occur. The data we have were for the interval between biopsy and surgical consultation. Spontaneous resolution inevitably occurred prior to the consultation, so the time to SR was shorter than the time to consultation. Most patients with SR reported that the biopsy took 1–2 weeks to heal and that the lesion itself then slowly and steadily disappeared over the next 3–4 weeks. Several patients with SR started their consultation with us by saying, "I think I am wasting your time; the cancer seems to have gone." Ideally, future studies will carefully monitor lesions following biopsy to determine the precise timelines for healing and any SR (or not) over perhaps a 2- to 3-month period.

Spontaneous resolution of SCC, without any procedure, is very rare [9], while rapid evolution and subsequent resolution of keratoacanthoma (widely regarded as a type of SCC is the norm [10] and resolution of actinic keratosis (a precursor of SCC) is also typical [11]. Furthermore, multiple case reports exist of spontaneous resolution of other cancers [12,13]. It is also well documented that in basal and squamous cancers that are incompletely excised, many (40% of SCC and 20% of BCC in one study [14]) show no residual tumor on re-excision, implying that some form of immune response as part of wound healing often leads to eradication of the tumor.

Our search of the literature did not find any report of studies like ours that explored rates of spontaneous resolution following partial, diagnostic biopsy.

These findings are preliminary, and some limitations do apply. This was a single site study, and while there was no selection bias in patients selected for surgical consultation at this clinic, it will be essential to replicate the study in other clinics and settings. It is important to affirm that all referrals to the public hospital service from all GPs across this large population are sent to a single central site at the university hospital for review, triage, and surgical outpatient clinic allocation. Our study was made possible by the inherent timelines that occur when a GP refers a patient with WDSCC to this public hospital general surgery service, where the referral is reviewed, triaged, and allocated to a general surgical outpatient clinic for consultation (and then surgical intervention, as required). This process typically takes a few weeks, and when patients are allocated as category 2 or 3, as is typical for WDSCC, these timelines can easily become a few months [8]. These realities allowed us to explore the rates and timelines of spontaneous resolution following partial, diagnostic biopsy.

It is important to stress that the procedure done by the GP was in almost all cases a punch biopsy (usually a 3 mm punch), and only occasionally a shave biopsy. In all cases the biopsy was partial (with peripheral margins involved) and diagnostic and was not an excisional biopsy. We do not have data on original lesion size as this was usually not recorded by the GP in the referral. Any further studies should be designed to include this information, and it would be useful to estimate what proportion of the lesion is removed by a diagnostic, partial biopsy.

The diagnosis of WDSCC was provided by the pathology report presented to the patient's GP. GPs choose their preferred private pathology service in Queensland, and most specimens were reported by the four major pathology providers in the area. The literature recognizes some variation in accuracy of reporting of WDSCC and other skin cancers [15]. We were limited, in this preliminary study, to the pathology reports provided to the GP and included in the referral. Future studies could usefully include standardized reporting, either from a single dermatopathologist or with blinded review of at least a sample

of slides to provide greater confidence in diagnostic accuracy. It is possible, for example, that some of the lesions in our study exhibited features of keratoacanthoma but were not reported as such, and hence were more likely to spontaneously resolve. It would be appropriate to capture immunosuppression status also.

Conclusion

If these findings are confirmed and extended, what are the possible implications? We work in a setting with very high levels of skin cancer, and large numbers of older patients (often with comorbidities) present with WDSCC on the lower leg, often repeatedly. Treatment can be challenging, as although typically clinically indolent, guidelines do recommend active treatment usually by surgical excision or other destructive means [16]. Furthermore, diagnosis is essential, and most patients do want these often ugly and irritating lesions treated. However, treatment-fatigue among patients with multiple recurrent lesions is common. Surgical excision below the knee is often challenging due to poor skin quality, tight skin, and restricted arterial circulation [17]. Flaps or grafts are often needed, with healing not assured, and poor healing with chronic ulceration is not uncommon and can be very debilitating.

A period of close clinical observation following diagnostic biopsy could be appropriate in selected patients. If gradual spontaneous resolution is observed and complete healing is documented, patients could then be followed carefully with regular skin examinations and review. Such an approach has been advocated for selected cases of low-risk basal cell cancer [19]. A similar approach is also adopted for lower risk cases of prostate cancer, with active surveillance preferred to immediate intervention [19].

Our study provides novel insights into the natural history of WDSCC following a partial, diagnostic biopsy and adds to the literature reporting resolution of incompletely excised SCC and BCC as well as to the literature on spontaneous resolution of other cancers. Further studies to clarify, confirm, and expand on our observations are warranted.

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Dermatology Practical & Conceptual

Dupilumab: an Additional Arrow in the Quiver for Prurigo Nodularis? Data From a Real-Life Setting

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Key words: Prurigo nodularis, Real-life setting, Dupilumab, Antidepressants

Citation: Di Caprio R, Caccavale S, Di Brizzi EV, et al. Dupilumab: An Additional Arrow in the Quiver for Prurigo Nodularis? Data From a Real-Life Setting. *Dermatol Pract Concept*. 2025;15(4):5639. DOI: https://doi.org/10.5826/dpc.1504a5639

Accepted: July 20, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Prurigo nodularis (PN) management remains a significant challenge due to its chronicity, treatment resistance, and scarcity of approved treatments and to its impact on patients' quality of life.

Objective: The aim of this study was to assess PN therapeutic management in a real-life setting.

Methods: In this prospective observational study, 90 patients diagnosed with moderate-to-severe PN were included. Patients were each prescribed therapies available for PN according to symptom severity, consistent with treatment guidelines; only those undergoing systemic therapies were included. Disease severity was evaluated through the measurements of Investigator's Global Assessment (IGA) score, Numeric Rating Scale (NRS) for pruritus, and Dermatology Life Quality Index (DLQI) at the beginning of the study (week 0 – W0) and after a 6-month period of treatment (W24).

Results: At W0, patients were prescribed antidepressants (41.0%), dupilumab (34.0%), antihistamines (23.0%), phototherapy (4.0%) or nemolizumab (2.0%). At W24, patients on dupilumab achieved an IGA score of 0 or 1 and a ≥4-point NRS reduction, more than those on antidepressants (44.5% vs 16.7% and 54.4% vs 16.7%, respectively). The average DLQI score was reduced by 14 points in the dupilumab group, compared to a 6-point reduction in the antidepressant group.

Conclusions: Our findings reflect the real-world practice of treating PN and support the use of dupilumab as a new effective treatment option, with significant improvements in pruritus, quality of life, and disease severity compared to antidepressant therapy, suggesting its potential as a preferred therapeutic option for PN.

Introduction

Prurigo nodularis (PN) is an inflammatory skin condition with highly pruritic, hyperkeratotic papules or nodules arising in the setting of chronic pruritus, which can greatly impact patients' quality of life [1,2]. These nodules, often resulting from a relentless itch-scratch cycle, can lead to significant skin thickening and lichenification [3]. The prevalence of PN is not well documented, but it is known to affect both sexes and all races, with a slight predominance in middle-aged and elderly individuals [1]. PN pathogenesis is multifactorial and not yet fully understood. It is thought to involve a complex interplay between neurogenic, immunologic, and psychogenic factors. Neurogenic factors include increased nerve growth factor expression, and increased nerve fiber density in pruritic skin, which can lead to heightened itch perception. Immunologic factors involve elevated levels of circulating and skin-resident Th2 cells, mast cells, and eosinophils, which contribute to inflammation and pruritus. Psychogenic factors such as stress and anxiety can also exacerbate pruritus and scratching behavior, leading to a vicious itch-scratch cycle [4-6].

PN management remains a significant challenge due to the chronic nature of the disease, treatment resistance, and its substantial impact on patients' quality of life [7]. Traditional treatments consist of topical corticosteroids (TCS) and selective topical calcineurin inhibitors (TCI) administered either alone or with antihistamines, followed by phototherapy and other systemic treatments (gabapentin, antidepressants, corticosteroids, or immunosuppressants) [8]. However, these treatments often provide incomplete relief and can have undesirable side effects, such as skin atrophy caused by the long-term topical corticosteroid use and sedation caused by antihistamines [9].

Dupilumab, a fully human monoclonal IgG4 antibody, has recently emerged as a promising new treatment option for PN. It blocks interleukin (IL)-4 and IL-13 signaling by specifically binding to IL-4 receptor alpha subunit shared by both IL-4 and IL-13 receptor complexes and has demonstrated good efficacy and safety in a variety of diseases with type 2 inflammation, like atopic dermatitis and asthma [10,11]. Based on favorable results from clinical trials substantiating type 2 cytokines IL-4 and IL-13 implication in steering the pathogenesis of PN, dupilumab has been approved by the U.S. Food and Drug Administration (FDA) as the first specific drug for the treatment of PN [12]. However, data on dupilumab efficacy from real-world studies are lacking, and the range and degree of the disease burden and how it impacts treatment satisfaction in patients with PN remains not well investigated.

Objective

Our aim was to conduct a prospective observational study to assess the therapeutic management of PN in a real-life setting.

Methods

Study Design

This prospective observational study was conducted over a 27-month period (October 2021–December 2023) and involved 90 consecutive patients diagnosed with PN at the Dermatology Unit, University of Campania Luigi Vanvitelli, Naples, Italy. Patient demographic details are shown in Table 1.

Inclusion criteria were: males or females aged 18–80 years at the time of signing the informed consent, a minimum of 10 PN lesions in total on both legs, and/or both arms and/or trunk at screening visit, and patients with PN who are inadequately controlled on topical prescription therapies or when those therapies are not advisable.

Moreover, as regarded patients scheduled with dupilumab, those who did not respond to or showed contraindications

Table 1. Clinical and Demographic Patient Characteristics.

	N	%
Population	90	100
Sex		
male	35	39
female	55	61
Age, y		
≤ 18	1	1
> 18≤35	5	6
> 35≤65	44	49
> 65	40	44
Comorbidities		
Diabetes	15	16.7
Dyslipidemia	23	25.5
Hypertension	33	36.7
Heart diseases	4	4.4
Others	27	30
IGA		
1	22	24.4
2	36	40
3	19	21.2
4	13	14.4
NRS		
0-5	17	18.9
6-10	73	81.1
DLQI		
≤2	9	10
>2≤10	45	50
>10	36	40

Abbreviations: DLQI: Dermatology Life Quality Index; IGA: Investigator's Global Assessment score; NRS: Numeric Rating Scale.

or side effects to at least one conventional systemic therapy according to Italian law were included.

Exclusion criteria were: active chronic or acute infection (except well-controlled HIV infection), PN secondary to medications or medical conditions, such as neuropathy or psychiatric disease, known or suspected immunodeficiency, severe renal conditions, moderate-to-severe atopic dermatitis (AD) within six months before the screening visit, or documented diagnosis of moderate-to-severe AD from screening visit to randomization visit, active malignancy or history of malignancy within five years of baseline.

At enrollment, clinical and demographic data, including sex, age, comorbidities, and previous treatments, were collected. To date, guidelines for the treatment of PN have been published only by the Japanese Dermatological Association (JDA) and by the International Forum for the Study of Itch (IFSI) [13]. Both recommend a step-by-step treatment approach (step 1: TCS, TCI, and H1 antihistamines; step 2: topical capsaicin, intralesional corticosteroids, and UV therapy; step 3: gabapentin, pregabalin, or antidepressants in case of predominating neuropathic characteristics versus cyclosporine or methotrexate in cases of predominant inflammation; step 4: neurokinin 1 receptor (NK1R) antagonist, μ-opioid receptor antagonists, dupilumab, nemolizumab (currently under investigation) [8]. Enrolled patients could be prescribed any of the aforementioned available therapies, according to symptom severity, consistent with treatment guidelines. The entry into the study did not influence the therapeutic decision.

Clinical response was closely monitored throughout the treatment period to aid in the evaluation of the therapy efficacy. For all patients, disease severity was evaluated through the measurements of Investigator's Global Assessment (IGA) score [14], Numeric Rating Scale (NRS) for pruritus [15], and Dermatology Life Quality Index (DLQI) [16], at the beginning of the study (week 0 [W0]) and after 6-month period of systemic treatment (W24). The IGA score is a 5-point scale used to rate the severity of the disease. The NRS is a patient-reported outcome measure used to assess the severity of itching. The DLQI, because of its self-explanatory questions, is one of the most commonly used tools for the assessment of health-related quality of life (HRQoL) in dermatology. The DLQI score ranges from 0 to 30 points, with a lower score indicating better HRQoL. According to the classification of DLQI score proposed by Hongbo et al. [17], 0 to 1 point indicates normal QoL, 2–5 points indicate slightly, 6–10 points severely, 11–20 points very severely, and 21–30 extremely severely impaired HRQoL.

The baseline characteristics (e.g., IGA, NRS, DLQI, comorbidities) between the two subgroups treated with dupilumab or antidepressants were similar and quite comparable.

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided informed consent before participating in the study.

Statistical Analysis

The data are expressed in the form of mean for continuous variables, while categorical variables are presented as numbers and percentages. Data that passed the normality test were analyzed using a two-tailed t-test; otherwise, the Mann-Whitney test was used to calculate statistical differences. Statistical significance was established at $P<0.05$. Bonferroni test correction for multiple comparisons was applied for the analysis of IGA improvement, ≥4 points NRS, and DLQI reduction from baseline between patients on dupilumab and patients on antidepressant treatment. Statistical analyses were performed using GraphPad Prism 6.0 (GraphPad Software Inc, La Jolla, CA, USA) or SAS software v 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

In all, 90 patients, 35 (39%) males and 55 (61%) females, aged 18–80, were enrolled into the study. Among the participants, 15 (16.7%) patients had diabetes, 23 (25.5%) dyslipidemia, 33 (36.7%) hypertension, and four cardiovascular diseases (4.4%). Other comorbidities were present in 27 (30%) of the patients. Baseline demographic and clinical data are summarized in Table 1. PN was diagnosed in 73% of cases by clinical evaluation only, while the remaining 27% by a combination of clinical and histological examinations. The distribution of the pruritic nodules varied among the patients, with the upper limbs 59 (66%), lower limbs 51 (57%), and trunk 48 (53.3%) being the most commonly affected areas. The back (N=17, 18.9%) and face (N=13, 14.4%) were less commonly affected.

Regarding disease severity indices, at baseline (W0), 22 (24.4%) patients presented Grade 1 IGA Score, 36 (40.0%) had Grade 2, 19 (21.2%) had IGA 3, and 13 (14.4%) had IGA4. Moreover, 17 (18.9%) patients had NRS itching score between 0–5, while the remaining 73 (81.1%) between 6–10, suggesting a moderate-to-very severe level of pruritus. The mean DLQI score at baseline was 16.2, indicating a very large effect of the disease on patients' life. In detail, DLQI ≤2 was observed in nine (10%), DLQI >2≤10 in 45 (50%), and DLQI >10 in 36 (40%) patients(Table 1).

All patients had previously under gone various treatments for PN, including topical corticosteroids (N=55, 61.1%), antihistamines (N=40, 44.4%), antidepressants (N=49, 54.4%, of whom 94% amitriptyline, 4% mirtazapine, and 2% escitalopram), systemic corticosteroids (N=9, 10.0%), and other immunosuppressants (N=7, 7.8%). At W0, patients

were prescribed as follows: 37 (41.0%) antidepressants, 30 (34.0%) dupilumab, 21 (23.0%) antihistamines (57.0% sedating and 43.0% non-sedating), four (4.0%) phototherapy, and two (2.0%), nemolizumab (Figure 1). The latter were two patients referred by the dermatologist to participate in a clinical trial evaluating the efficacy and safety of nemolizumab for the treatment of PN (NCT04921345). Thus, since 75% of patients were in treatment with antidepressants or dupilumab, the subsequent analysis was performed on this subpopulation. At W24, after six months of treatment, IGA 0–1 was attained by 14 (44.5%) patients on dupilumab, indicating clear or almost clear skin, compared to six (16.7%) of those on antidepressants (Figure 2; $**P<0.01$).

Furthermore, 16 (54.4%) patients receiving dupilumab had a ≥4-point NRS reduction compared to six (16.7%) patients on antidepressant therapy (Figure 3; $**P<0.01$) [14]. In terms of the impact on quality of life, the average DLQI score at W24 was reduced by 14 points in the dupilumab group, compared to a 6-point reduction in the antidepressant one (Figure 4, $***P<0.1$). Patients withdrawing from the study were defined as non-responders according to the non-responder imputation method.

Discussion

In this prospective observational study, we assessed the therapeutic management of PN in a real-world setting since it still poses considerable challenges for both patients and physicians. Indeed, until FDA approval of dupilumab as the first specific biologic agent for the treatment of PN, these patients were often treated with a multimodal, long-term regimen of both topical and systemic therapies; however, treatment effectiveness was poor [7-9]. When treating PN, the primary goal is to reduce pruritus and break the itch-scratch cycle, thereby allowing the skin to heal. In support of this, first, a correct diagnostic approach is mandatory to identify dermatological or systemic diseases associated with PN and to choose the best therapy for the patient. The approval of dupilumab has changed the scenario of PN management [19]. Data from recent clinical trials have demonstrated its effectiveness in alleviating both itching and nodule development

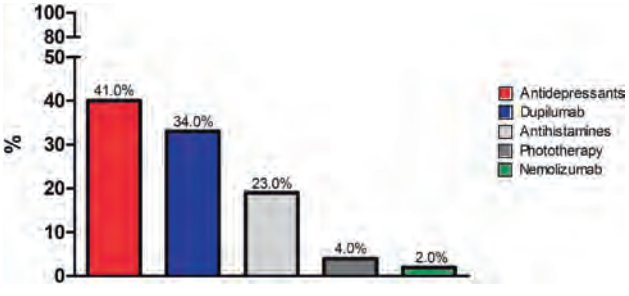


Figure 1. Percentage of patients receiving different systemic therapies at week 0.

as well as in enhancing overall quality of life. Indeed, in two parallel phase 3 trials of similar design, LIBERTY-PN PRIME and PRIME2, dupilumab resulted in a ≥4-point Worst Itch (WI)-NRS reduction in 60% and 18% of patients (PRIME) or 57.7% and 19.0% (PRIME2) at week 24, in the dupilumab and placebo arms, respectively [12]. Moreover, IGA of clear-to-almost clear (0–1) was achieved in 48% vs 18.4% as well as in 44.9% *vs* 15.9% in the two trials, respectively. Dupilumab-treated patients also had significant improvements in QoL, as measured by mean change in DLQI score from baseline to week 24: PRIME, -12.0; PRIME2, -13.2. [12]. Thus, these data confirmed the involvement of an activated Th2 cytokine pathway in PN pathogenesis. However, although randomized controlled trials allow assessing treatment efficacy, their applicability is restricted to ideal conditions, and this limits their ability to portray what happens in the real world. Moreover, as strict inclusion and exclusion criteria might limit generalizability and applicability of trial results to the broader PN population, disease treatment remains difficult and unsatisfactory. In our real-life setting, 40.0% of patients presented Grade 2 and 21.2% Grade 3 IGA scores at baseline; 81.1% had an NRS itching score between 6–10, suggesting a moderate-to-severe disease with a very high level of pruritus.

In line with the literature, topical corticosteroids, antidepressants, and antihistamines were the treatments most frequently used previously. At W0, patients enrolled in the study were prescribed with antidepressants (41.0%), dupilumab (34.0%), antihistamines (23.0%), phototherapy (4.0%), or nemolizumab (2.0%). We therefore decided to verify the improvement of the selected study indices in the two most represented treatment groups (antidepressants and dupilumab). Our results demonstrated a significantly greater reduction in all disease parameters in the patients treated with dupilumab compared to those treated with antidepressants. In particular, after 24 weeks of treatment, 44.5% of dupilumab-treated patients achieved an IGA score of 0 or 1, indicating clear or almost clear skin, vs 16.7% of those on antidepressants. Moreover, regarding pruritus and scratching, 54.4% of patients receiving dupilumab had a ≥4-point NRS reduction compared to 16.7% of patients on antidepressant therapy. As expected, pruritus relief greatly improved patients' QoL. Indeed, the mean DLQI score at W24 was reduced by 14 points in the dupilumab group, compared to the 6-point reduction we found in the antidepressant group. These findings are partially in line with previous studies.

In a real-world observational study, Zhang et al. demonstrated a significant reduction in IGA score, mean NRS Itch Intensity (NRSI), and DLQI, from 3.75, 8.625 and 15.13 to 1.50, 1.563, and 4.625, respectively, in eight adult patients diagnosed with PN after 16 weeks of treatment

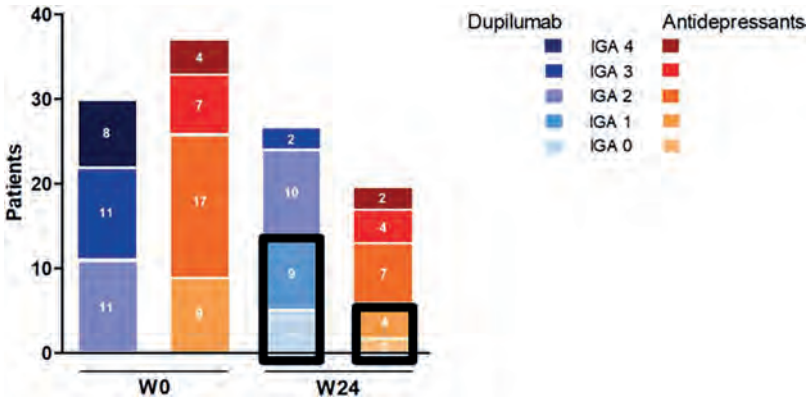


Figure 2. Improvement in IGA and IGA activity score at week 24 (W24). Statistical analysis was performed using the Mann-Whitney test (with Bonferroni correction) between the two most represented treatment groups (antidepressants and dupilumab), ***P*<0.01. The rectangles highlight patients achieving IGA0–1 in both dupilumab (5+9=14 patients) and antidepressants (2+4=6 patients) groups.

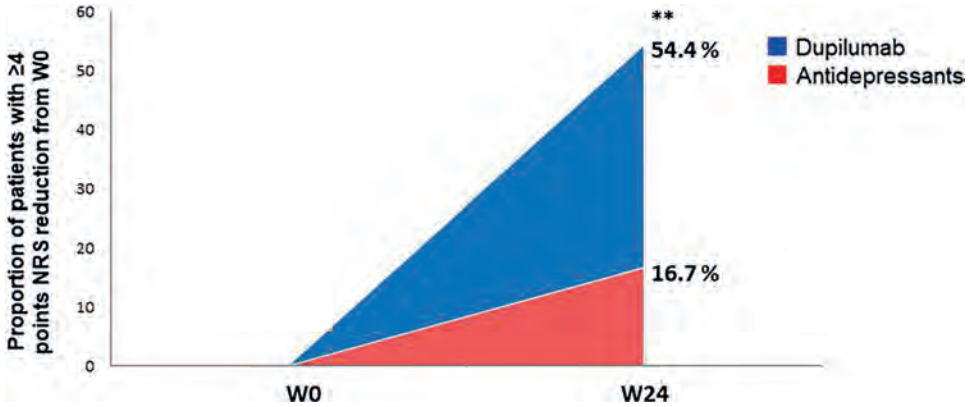


Figure 3. Percentage of patients who achieved NRS improvement (reduction) by ≥4 points from baseline (W0) at week 24 (W24), respectively. Statistical analysis was performed using the Mann-Whitney test (with Bonferroni correction) between the two most represented treatment groups (antidepressants and dupilumab), ***P*<0.01.

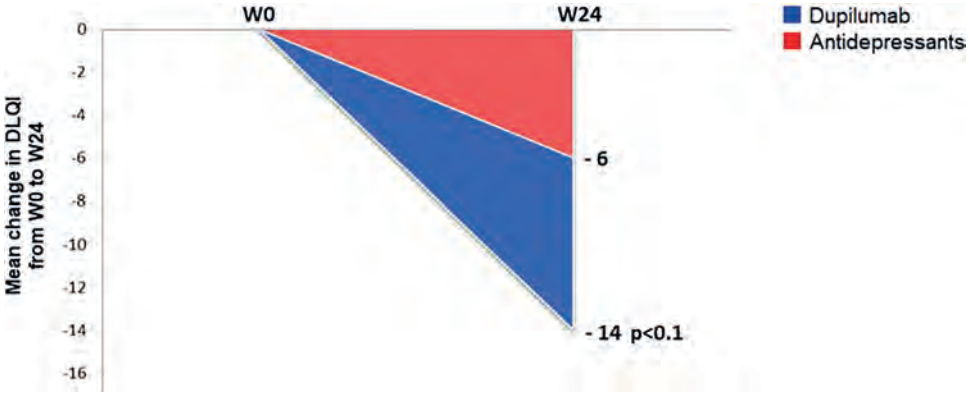


Figure 4. Mean DLQI reduction from baseline (W0) at week 24 (W24), respectively. Statistical analysis was performed using the Mann-Whitney test (with Bonferroni correction) between the two most represented treatment groups (antidepressants and dupilumab), ****P*<0.1.

with dupilumab [20]. Similarly, Chiricozzi et al. reported a reduction in IGA for at least 2 grades in 82.6% of the patients after 16 weeks of treatment [21]. In a retrospective cohort study, Pruritus Peak (PP)-NRS and DLQI significantly improved in all the 45 enrolled patients from baseline to 16 weeks after dupilumab treatment ($P< 0.001$ for both [22]. Moreover, compared to antidepressants, dupilumab has been proven to elicit fast and notable symptom reduction in PN patients. Zhai et al. observed a mean NRSI reduction of 7.89 points after only two weeks of dupilumab, whereas Beck et al. reported a pruritus improvement to nearly 0 in terms of NRSI in 12 weeks of treatment [23,24]. In addition, beyond clinical symptom relief, patients' mental health and quality of life also saw subjective improvements after biological therapy. Conversely, antidepressants' effects on chronic pruritus are variable and may appear modest in patients with PN. Kouwenhoven et al. showed that systemic treatment with gabapentin and/or antidepressants decreased the median average pruritus NRS score from 7.0 to 5.5 in 31 patients with severe chronic pruritus after 4 weeks and remained stable with up to 24 weeks of treatment [25]. However, the common side effects of antidepressants result in considerable rates of discontinuation. After initiation of gabapentin and/or antidepressants, vertigo and drowsiness were most frequently and particularly present in the first few days of treatment [26]. Moreover, even if previous clinical trials for gabapentin in neuropathic pain did not find a higher incidence of these adverse reactions in older adults, clinicians should be careful in these patients with preexisting dizziness or somnolence, with adjusted dosing, patient instructions, and close follow-up [27].

Limitations

Our study presents some limitations. First, the sample size of the enrolled patients, although higher than others, was relatively small, which may limit the generalizability of the findings and results. Second, the study was conducted over a 6-month period, which may not be sufficient to evaluate the long-term efficacy and safety of the treatments. In this regard, Paganini et al. have recently demonstrated the effectiveness of dupilumab in all the parameters considered for the disease, up to week 84 of treatment [19].

Conclusion

Our findings reflect the real-world practice of treating PN and support the use of dupilumab as a new effective treatment option, with significant improvements in pruritus, quality of life, and disease severity compared to antidepressant therapy. However, further large-scale, longer-term studies are needed to confirm these findings and to evaluate the long-term efficacy and safety of dupilumab in the management of PN.

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Dermatology Practical & Conceptual

Dermoscopy as a Predictor of Photodynamic Therapy Outcomes in Actinic Keratoses and Bowen's Disease: Prospective Study in Solid Organ Transplant Patients

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Key words: actinic keratoses, bowen's disease, photodynamic therapy, dermatoscopy, transplant recipients

Citation: Bernal Masferrer L, Gracia Cazaña T, Álvarez-Salafranca M, et al. Dermoscopy as a Predictor of Photodynamic Therapy Outcomes in Actinic Keratoses and Bowen's Disease: Prospective Study in Solid Organ Transplant Patients. *Dermatol Pract Concept*. 2025;15(4):5645. DOI: https://doi.org/10.5826/dpc.1504a5645

Accepted: June 17, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Solid organ transplant recipients (SOTRs) have a significantly higher risk of developing cutaneous squamous cell carcinoma. Identifying predictive markers for response to non-surgical treatments such as photodynamic therapy (PDT) may help optimize management strategies.

Objectives: To evaluate the association between dermatoscopic features in actinic keratoses (AK) and Bowen's disease (BD) and response to PDT in SOTRs.

Methods: A prospective observational study was conducted, including 35 SOTRs with clinically and histologically confirmed AK or BD treated with methyl aminolevulinate-PDT. Thirteen dermatoscopic features were analyzed to assess their correlation with treatment response.

Results: Response rates were 62.5% for AK and 89.47% for BD. Among the dermatoscopic features evaluated, white structureless areas in AK and rosettes in BD were significantly associated with resistance to PDT.

Conclusions: Dermoscopy may serve as a valuable tool to predict PDT response in SOTRs with AK and BD, potentially improving patient selection and treatment outcomes.

Introduction

Actinic keratoses (AK) and in situ squamous cell carcinoma (SCC) are considered precursor lesions of invasive cutaneous squamous cell carcinoma (cSCC). Their development is influenced by cumulative exposure to ultraviolet (UV) radiation, advanced age, immunosuppression, and other factors [1-3]. Given their high incidence linked to an ageing population and prolonged sun exposure, early treatment is essential to prevent progression to invasive cSCC [4].

Solid organ transplant recipients (SOTRs) represent a particularly complex group, with a 65-fold increased risk of developing cSCC [1]. This heightened risk is intrinsically linked to immunosuppression and the use of specific treatments for transplant maintenance such as calcineurin inhibitors. Therefore, early diagnosis and effective treatment are especially crucial for this population [2].

Photodynamic therapy (PDT) has emerged as a valid, effective, and repeatable treatment for AK and Bowen's disease (BD) or in situ cSCC. Compared to cryotherapy, PDT offers the added advantage of treating the cancerization field [2,3]. However, PDT's indirect immunomodulatory action may be less effective in transplant patients, potentially reducing its efficacy and explaining the lower success rates observed compared to immunocompetent patients [2].

In this context, diagnostic tools like dermoscopy not only aid in the early and accurate recognition of lesions but may also provide valuable insights into the effectiveness of treatments such as PDT, particularly in patients with unique clinical characteristics like transplant recipients.

Dermoscopy is a non-invasive technique that has become an essential tool for clinicians in identifying these lesions. Dermoscopic patterns associated with AK and BD have been shown to increase diagnostic sensitivity, and their disappearance has been correlated with lesion resolution [4,5]. However, only one study has investigated the possible relationship between dermoscopic signs of AK and response to PDT [6], while another focused on basal cell carcinoma (BCC) [7]. To our knowledge, no study has explored these correlations in BD or in SOTRs.

The aim of this study was to identify dermoscopic signs associated with the response to conventional PDT in BD and daylight PDT in AK in SOTRs.

Materials and Methods

A prospective observational clinical practice study was conducted. The study population consisted of SOTRs referred from the Nephrology and Cardiology Transplant Clinics to the specialized transplant skin cancer unit at Miguel Servet University Hospital between January 2022 and December 2023. Patients had to meet the following inclusion criteria: aged 18 years or older; solid organ transplant recipient; diagnosed with at least five Grade I or II Olsen AKs within a field of cancerizations or histologically confirmed in situ SCC; eligible for treatment with MAL-PDT and having provided informed consent to participate (Annex II); no hypersensitivity to any component of Metvix®; no photodermatosis diagnosis.

Exclusion criteria were: allergic to any treatment component; refused treatment with PDT; did not provide consent to participate in the study; unable to complete treatment or follow-up; had undergone treatment for non-melanoma skin cancer (NMSC) within the previous three months.

A baseline biopsy was performed for all patients to confirm clinical diagnoses, accompanied by clinical and dermoscopic photography (DermLite Handyscope 2020). The study was approved by the Ethics Committee of the Autonomous Community of Aragon (CEICA) EPA22/0007.

Treatment Protocols

For BD patients, two sessions of conventional PDT were conducted. Lesions were first curetted, followed by application of 16% methyl aminolevulinate (MAL, Metvix®, Galderma). After three hours of occlusive incubation, the area was illuminated using a red diode device (Aktilite CL 128, Galderma Nordic AB, Sweden) at 37 J/cm² for eight minutes from a distance of 10 cm. The second session was conducted 7–14 days later [8]. For AK patients, one session of daylight PDT was conducted. Lesions were curetted, followed by MAL 16% application. Patients were then exposed to sunlight for two hours, after which the photosensitizer residue was removed [9].

Outcome Measures

Three months post-treatment, lesion biopsies were repeated to confirm histological clearance or persistence. Dermoscopic evaluations were conducted by a blinded observer (M.A.S) using pre-treatment dermoscopic photographs. The evaluated dermoscopic signs included superficial scales, thick white-yellow scales, white circles, white structureless areas, erythema, rosettes, red pseudonetwork or perifollicular vessels, strawberry pattern, glomerular vessels, hairpin vessels, irregular linear vessels, erosions, and ulcerations [4].

Treatment response was assessed clinically and histologically three months post-treatment. Follow-up visits were conducted over the subsequent 12 months, with persistent lesions excised.

Statistical Analysis

Qualitative variables are presented as absolute numbers and percentages. Chi-squared tests (Chi^2) were used for group comparisons, with statistical significance defined as $P<0.05$. Statistical analyses were performed using SPSS® software (version 25.1).

Results

A total of 35 patients were included in the study: 16 with at least five Grade I or II Olsen AKs and 19 with BD, all with histopathological confirmation. Complete response rates were 62.5% for AK and 89.47% for BD.

Among the dermoscopic features analyzed, only the absence of rosettes in BD and the absence of white structureless areas in AK were significantly associated with response to PDT. No other dermoscopic structure showed a statistically significant correlation with treatment response. The statistical analysis of all dermoscopic structures is summarized in Tables 1 and 2.

Discussion

Photodynamic therapy (PDT) is considered the most effective treatment for actinic keratoses (AK) in solid organ transplant recipients (SOTRs) [10]. Our study achieved similar results in terms of clinical and histological effectiveness.

Table 1. Statistical Analysis of Dermoscopic Structures in Bowen's Disease and Response to Photodynamic Therapy.

Variable	Response	No response	p-value
Superficial scales			
Yes	7 (41.2%)	1 (50%)	1.00
No	10(58.8%)	1 (50%)	0.81
White-yellow scales			
Yes	10 (58.8%)	1 (50%)	1.00
No	7 (42.1%)	1 (50%)	0.81
White circles			1.00
Yes	1 (5.3%)	0 (0%)	0.72
No	16 (94.1%)	2 (100%)	
White structureless areas			0.38
Yes	3(17.6%)	1 (50%)	0.28
No	14 (82.4%)	1 (50%)	
Erythema		2 (100%)	1.00
Yes	16 (94.1%)	0 (0)	0.72
No	1 (5.3%)		
Rosettes			
Yes	0 (0%)	1 (50%)	0.10
No	17 (100%)	1 (50%)	**0.003**
Red pseudonetwork			
Yes	5 (31.6%)	1 (50%)	1.00
No	12 (70.6%)	1 (50%)	0.55
"Strawberry pattern"			
Yes	4 (23.5%)	1 (50%)	0.46
No	13 (76.5%)	1 (50%)	0.42
Glomerular vessels			
Yes	8 (47.1%)	1 (50%)	1.00
No	9 (52.9%)	1 (50%)	0.93
Hairpin vessels			1.00
Yes	2 (11.8%)	0 (0)	0.60
No	15 (88.2%)	2 (100%)	
Linear irregular vessels			
Yes	1 (5.3%)	0 (0)	1.00
No	16 (94.1%)	2 (100%)	0.72
Erosions			
Yes	1 (5.3%)	0 (0)	1.00
No	16 (94.1%)	2 (100%)	0.72
Ulceration			-
Yes	0 (0)	0 (0)	
No	17 (100%)	2 (100%)	

Table 2. Statistical Analysis of Dermoscopic Structures in Actinic Keratoses and Response to Photodynamic Therapy.

Variable	Response	No response	p-value
Superficial scales			
Yes	6 (60%)	2(33.3%)	0.60
No	4 (40%)	4(66.7%)	0.30
White-yellow scales			
Yes	3 (30%)	3 (50%)	0.60
No	7 (70%)	3 (50%)	0.42
White circles			-
Yes	0 (0%)	0 (0%)	
No	10 (100%)	6 (100%)	
White structureless areas			
Yes	0(0%)	2(33.3%)	0.12
No	10 (100%)	4(66.7%)	**0.05**
Erythema			
Yes	9 (90%)	6 (100%)	1.00
No	1 (10%)	0 (0)	0.42
Rosettes			
Yes	2 (20%)	0 (0%)	0.50
No	8 (80%)	6 (100%)	0.24
Red pseudonetwork			
Yes	6 (60%)	2(33.3%)	0.60
No	4 (40%)	4(66.7%)	0.30
"Strawberry pattern"			
Yes	3 (30%)	1(16.7%)	1.00
No	7 (70%)	5(83.3%)	0.55
Glomerular vessels			
Yes	1 (10%)	0 (0%)	1.00
No	9 (90%)	6 (100%)	0.42
Hairpin vessels			-
Yes	0 (0%)	0 (0)	
No	10 (100%)	6 (100%)	
Linear irregular vessels			-
Yes	0 (0%)	0 (0)	
No	10 (100%)	6 (100%)	
Erosions			-
Yes	0 (0%)	0 (0)	
No	10 (100%)	6 (100%)	
Ulceration			-
Yes	0 (0)	0 (0)	
No	10 (100%)	6 (100%)	

Dragieva et al. conducted a prospective study involving 17 SOTRs with 129 AK lesions. The patients received two consecutive treatments (one with methyl aminolevulinate [MAL] and the other with placebo), resulting in complete resolution in 13 patients and partial response in three others [11]. The clinical response of some patients is summarized in Figure 1.

For Bowen's disease (BD), Antonetti et al. conducted a systematic review, reporting clinical response rates of 88–100% with MAL-PDT in immunocompetent patients. They hypothesized that efficacy could be maintained in immunosuppressed individuals, which aligns with our findings, though current evidence remains limited [12].

Our study analyzed dermoscopic signs in AK and BD lesions in SOTRs and their association with PDT response. Rosettes correspond histopathologically to hyperkeratosis within follicular openings interspersed with a normal peripheral stratum corneum [13]. Meanwhile, white structureless areas represent hyperkeratosis and parakeratosis overlying dysplastic epidermis [4]. Both features are indicators of lesion keratinization and hyperkeratosis, potentially

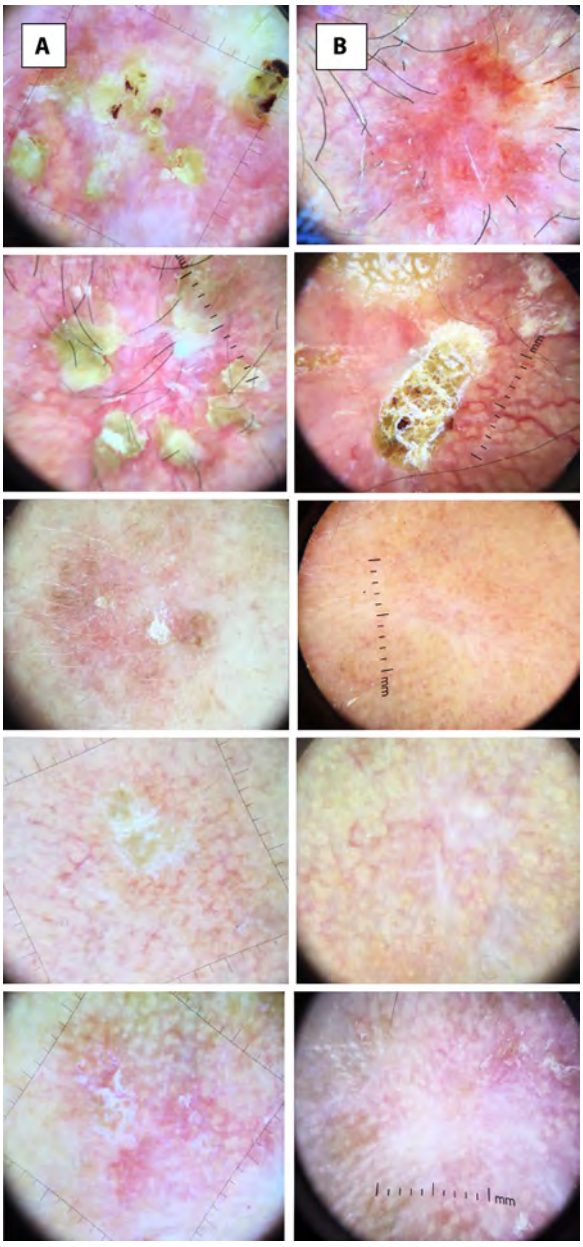


Figure 1. Photographs of the lesions before the treatment with MAL-PDT (A) and after three months of the treatment (B). In the first two pictures we can see the white structureless areas associated with the lack of response to PDT.

hindering photosensitizer penetration and reducing treatment effectiveness.

Zalaudek et al. proposed that white structureless areas could also signal lesion progression to invasive SCC, with vertical growth increasing lesion thickness and complicating dermal penetration. Lesion thickness is a key predictor of resistance to PDT [14].

In a study by Lee et al. [5], the most frequent dermoscopic findings in AK lesions were superficial scales (79.4%) and red pseudonetwork pattern (73.5%). Following treatment with PDT, imiquimod, or cryotherapy, most dermoscopic structures disappeared in tandem with histological clearance. However, superficial scales persisted in 20.6% of cases and red pseudonetwork pattern in 14.7%, even when histological atypia was absent. Similarly, Mun et al. concluded that the disappearance of vascular patterns in BD lesions correlated with treatment success, while their persistence indicated histological disease presence [15].

Wang et al. identified red pseudonetwork pattern as positive predictors of PDT response in AK, whereas microerosions and white structureless areas were negatively associated. However, their findings are not fully comparable to ours due to methodological differences, including the use of cryotherapy or CO2 laser as neoadjuvant treatments, higher photosensitizer concentrations (20% aminolevulinic acid vs. 16% MAL in our study), and fluences exceeding three times the standard (100–120 J/cm² vs. 37 J/cm²). Nevertheless, both studies identified white structureless areas as predictors of treatment resistance [6].

This study has some limitations, including a relatively small sample size from a single center, which may affect generalizability. Moreover, dermoscopic evaluation was performed by a single observer, which may introduce observer bias or limit the reproducibility of the findings. Despite these limitations, the prospective design and histological confirmation strengthen the reliability of the findings.

Conclusions

To summarize, photodynamic therapy (PDT) is an effective treatment for actinic keratoses (AK) and Bowen's disease (BD) in solid organ transplant recipients (SOTRs), with response rates of 62.5% and 89.47%, respectively. Among the dermoscopic features evaluated, the presence of rosettes in BD and white structureless areas in AK were negatively correlated with treatment response. These findings suggest that dermoscopy may serve as a useful tool for predicting PDT outcomes in this specific patient population.

Further research with larger cohorts is needed to confirm these results and to better understand the factors influencing treatment response and the utility of dermoscopy in this clinical context.

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Dermatology Practical & Conceptual

All Eyes on Dermoscopy: Features of Benign Conjunctival Melanocytic Lesions

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Key words: Dermoscopy, Conjunctiva, Melanocytic Lesion, Ocular Pigmentation, Nevus

Citation: Sgouros D, Theofilogiannakou P, Pappa G, et al. All Eyes on Dermoscopy: Features of Benign Conjunctival Melanocytic Lesions. *Dermatol Pract Concept*. 2025;15(4):5596. DOI: https://doi.org/10.5826/dpc.1504a5596

Accepted: July 17, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Conjunctival nevi (CN) represent the majority of benign conjunctival melanocytic lesions (CML), followed by complexion-associated melanosis (CAM). Noninvasive methods like dermoscopy could be of importance to increase diagnostic accuracy in this biopsy-sensitive area. Because of the unique anatomy of the conjunctiva, dermoscopic findings differ significantly compared to the skin or other mucosae.

Objective: Our objective was to analyze epidemiological, clinical, and dermoscopic characteristics of benign conjunctival melanocytic lesions and to explore their correlation to total body nevus count (TBNC).

Methods: This retrospective study involved the collection and analysis of demographic data, patient information, and clinical and dermoscopic images from individuals with long-standing, stable, pigmented conjunctival lesions.

Results: A total of 30 benign conjunctival melanocytic lesions in 28 patients (female/male :18/10) with a median age of 32 (range 16–68) years were evaluated. The prevalent dermoscopic pattern was a mixed, globular, homogeneous pattern (36.6%). Clear cysts were identified via dermoscopy in 60% of the lesions, and a reticular pattern was observed in all cases involving cysts (P<0.05). The presence of benign CML was associated with a low TBNC (<10) in 64.3%.

Conclusions: The present study provides a detailed overview of the clinical and dermoscopic characteristics of benign CML. It highlights consistent patterns such as cyst-associated reticular features and a low TBNC among affected individuals. These findings support the clinical utility of dermoscopy as a noninvasive tool for differentiating between benign and suspicious conjunctival lesions. The observed association with low TBNC may warrant increased vigilance during ocular examination in patients with few cutaneous nevi. Prospective studies with larger cohorts are needed to confirm and extend these observations.

Introduction

Benign melanocytic conjunctival lesions consist mainly of melanocytic nevi of the conjunctiva, which account for 23–29% of conjunctival tumors [1,2] and 52% of conjunctival melanocytic lesions (CML) [3-5]. Conjunctival nevi (CN) tend to form or become evident as they acquire pigmentation during the first two decades of life [2]. Clinically, they are congenital or acquired, well-demarcated, pigmented, elevated lesions, commonly associated with intralesional cysts and intrinsic vasculature or feeder vessels [2,6,7]. They are usually located on the bulbar conjunctiva and most commonly near the limbus [2,4,8]. Localization in the fornices or palpebral conjunctiva raises suspicion of malignancy and warrants biopsy [9,10]. Less than 1% of CN has the potential to undergo malignant transformation into conjunctival melanoma [4], whereas cutaneous nevi exhibit an even lower risk of progression, of less than 0.0005% annually [11]. The differential diagnosis includes a spectrum of benign and premalignant or malignant conditions. Complexion-associated melanosis (CAM) is also a common, bilateral condition of flat and usually multifocal pigmentation observed mainly in darker-skinned individuals. Other conditions to be considered are pigmentation associated with systemic pathologies, primary acquired melanosis (PAM) with or without atypia, ocular melanocytosis, and conjunctival melanoma (CM). Management typically involves periodic observation with photographic documentation.

Dermoscopy is a fast, non-invasive imaging technique that significantly improves the diagnostic accuracy in melanocytic lesions when performed by trained dermatologists [12,13]. Dermoscopic criteria have been described for most cutaneous tumors as well as for mucosal lesions for most anatomical sites. However, the dermoscopic characteristics of benign conjunctival proliferations have not been described extensively. This disparity may contribute to the observed differences in the rates of malignant transformation between the two.

Objectives

The unique anatomical and functional characteristics of the conjunctiva present distinct diagnostic and clinical management challenges. By utilizing dermoscopy, this study aimed to address the gap in understanding the dermoscopic features of CML, an area where the existing literature remains limited. The primary objective of this study was to describe the epidemiological, clinical, and dermoscopic characteristics of benign CML and to explore their association with total body nevus count (TBNC), contributing to a more comprehensive understanding of these lesions.

Methods

Twenty-eight patients with thirty CML were included in this retrospective observational cohort study conducted by the 2nd Department of Dermatology-Venereology of "Attikon" General University Hospital of Athens between 1 May 2021 and 31 December 2022. An institutional scientific board and ethics committee approval was obtained (98/17-02-2023). All subjects provided signed informed consent. The inclusion criteria included patients with a long-standing, stable course of pigmented conjunctival lesions, defined as a duration of at least five years. The exclusion criteria were: i) age <15 years old; ii) patients with new or changing lesions; iii) history of ocular malignancy; iv) recurrent lesions following previous interventions; v) patients who did not consent to data collection for the purposes of this study. Patients age <15 years were excluded as childhood nevi often have unique histological features, complicating malignancy exclusion [14]. Three subjects were excluded based on these criteria. All selected patients underwent total body skin and ocular dermoscopic examination. Demographic and clinical characteristics were evaluated and recorded, including age, sex, Fitzpatrick skin type (FST I-VI), TBNC (categorized as <10 nevi, 10-50 nevi, >50 nevi), global dermoscopic pattern of cutaneous nevi

(reticular, globular, homogeneous, or multicomponent), history of conjunctival lesion (in years), anatomic localization of the tumor (juxtalimbal, other bulbar, palpebral, forniceal, plica semilunaris, caruncular, or multifocal) and quadrant when juxtalimbal or other bulbar (temporal, nasal, superior, inferior, or multifocal), primary morphology (flat or elevated), lesion color (light brown, dark brown, black, or amelanotic), and the presence or absence of intralesional cysts (clear, cystic structures of various size and distribution among the lesion) and/or feeder vessels. Additionally, a detailed history was obtained, including sun exposure habits (occupational and recreational sun exposure, sunburns before the age of 18 years, solarium use), personal and family history of skin cancer, and any previous ocular pathology or trauma. Clinical and dermoscopic images of the lesions were captured using a Nikon J1 camera (Tokyo, Japan) and a handheld DermLite Hybrid II dermatoscope (DermLite Inc., San Juan Capistrano, CA, USA). The polarized mode enabled contactless visualization and documentation. Two authors evaluated all the dermoscopic images (DS and PT) for specific characteristics based on pattern analysis method. Dermoscopic features analyzed for each lesion included the dermoscopic pattern (reticular, globular, or homogeneous), the number of patterns, the lesion color (light brown, dark brown, or black), the number of colors, and the presence or absence of intralesional cysts [15, 16]. Statistical analysis was performed with Stata/IC version 15.1 (StataCorp, Lakeway Drive, TX, USA). For continuous variables, the mean and standard deviation (SD) are reported for normally distributed data, while the median, 25th and 75th percentiles are used for non-normally distributed data. The range is reported for all variables. For categorical variables the frequencies and percentages were calculated. The continuous variables were tested for normality using a Shapiro-Wilk test. Chi-squared and Fisher's exact tests were applied for the comparison of categorical variables. Where appropriate, 95% confidence intervals (CI) were calculated to provide an estimate of precision. A p-value <0.05 was considered to be statistically significant.

Results

Our sample consisted of 28 patients with 30 CML, of whom 18 (64.3%, 95% CI: 44.07–81.36) were females and 10 (35.7%, 95% CI: 18.64–55.93) were males. In our cohort, we observed a higher incidence of females, with a female-to-male ratio of 1.8:1. The age of patients ranged from 16 to 68 years, and the median age at observation was 32 years (range: 23.5–51.5). All patients presented with solitary lesions, except for two patients who were diagnosed with two lesions each. All lesions were self-detected by the patients. The distribution of Fitzpatrick Skin Types (FST) was as follows: FST II (21.4%, N=6; 95% CI: 8.30–40.95), FST III (50.0%, N=14; 95% CI: 30.65–69.35), and FST IV (28.6%, N=8; 95% CI: 13.22–48.67), with no case of FST I, V, or VI observed.

Notably, none of the patients presented with a total body nevus count (TBNC) >50. The majority, 64.3% (N=18; 95% CI: 44.07–81.36), had a TBNC <10, while 35.7% (N=10; 95% CI: 18.64–55.93) had a TBNC between 10 and 50. Recreational sun exposure was reported by 85.7% (N=24; 95% CI: 67.33–95.97) of participants, and 17.8% (N=5; 95% CI: 6.06–36.89) reported chronic occupational sun exposure. Additionally, 46.4% (N=13; 95% CI: 27.51–66.13) experienced at least one sunburn (grade 2 or higher) during childhood or adolescence, and 10.7% (N=3; 95% CI: 2.27–28.23) reported solarium use. A personal history of cutaneous melanoma (MM) was identified in 7.1% (N=2; 95% CI: 0.88–23.50) of participants, while another 7.1% (N=2; 95% CI: 0.88–23.50) reported a history of non-melanoma skin cancer (NMSC). Family history revealed cutaneous MM in 14.3% (N=4; 95% CI: 4.03–32.67) and NMSC in 17.9% (N=5; 95% CI: 6.06–36.89). Notably, no participant reported a prior history of ocular pathology (Table 1).

The mean duration of the conjunctival lesion was 20 years (SD: 10.72, range: 5–50).

Clinical Findings

Benign CML were most frequently located in the juxtalimbal area (53.3%, N=16; 95% CI: 34.33–71.66) and the temporal quadrant (60%, N=18; 95% CI: 40.60–77.34). No lesion was observed in the palpebral or forniceal conjunctiva. Morphologically, the majority of the lesions were flat (60%, N=18; 95% CI: 40.60–77.34), with the remainder being partly elevated (40%, N=12; 95% CI: 22.66–59.40). All lesions were pigmented, and regarding color variations, the coexistence of light and dark brown was mostly observed (46.6%, N=14; 95% CI: 28.34–65.67). Intralesional cysts were clinically identified in 13.3% of the cases (N=4). Additional features (intralesional cysts or vessels) were absent in 63.3% of the cases (N=19; 95% CI: 43.86–80.07). A summary of all clinical parameters is shown in Table 2.

The differential diagnosis for these lesions, depending on clinical history and lesion characteristics, included conjunctival nevi or CAM. Definite clinical diagnoses were determined unanimously by two investigators (DS and PT), considering factors such as age at presentation, FST, multifocality, lesion color, lesion thickness, and the presence of cysts. The diagnoses were 93.3% (N=28; 95% CI: 77.93–99.18) nevus and 6.7% (N=2; 95% CI: 0.82–22.07) CAM.

Prevalent Dermoscopic Features

All dermoscopic characteristics studied are reported in Table 3. Most conjunctival lesions displayed a mixed globular and homogeneous pattern (36.70%, N=11; 95% CI:

Table 1. Descriptive Statistics of Patient Demographics and Lesion characteristics.

Characteristics	N (%)	95% Confidence interval
Sex		
Male	10 (35.71)	18.64 –55.93
Female	18 (64.29)	44.07– 81.36
Fitzpatrick skin type		
I	0	0 – 12.34*
II	6 (21.43)	8.3 – 40.95*
III	14 (50)	30.65 – 69.35*
IV	8 (28.57)	13.22 – 48.67*
Total body nevus count		
<10	18 (64.29)	44.07 – 81.36
10-50	10 (35.71)	18.64 – 55.93
>50	0 (0)	
Personal history of cutaneous melanoma		
Yes	2 (7.14)	0.88 – 23.5
No	26 (92.86)	76.5 – 99.12
Personal history of NMSC		
Yes	2 (7.14)	0.88 – 23.5
No	26 (92.86)	76.5 – 99.12
Family history of cutaneous melanoma		
Yes	4 (14.29)	4.03 – 32.67
No	24 (85.71)	67.33 – 95.97
Family history of NMSC		
Yes	5 (17.86)	6.06 – 36.89
No	23 (82.14)	63.11 – 93.94
Sunburns (grade >2) before 18 years old		
Yes	13 (46.43)	27.51 – 66.13
No	15 (53.57)	33.87 – 72.49
Occupational sun exposure		
Yes	5 (17.86)	6.06 – 36.89
No	23 (82.14)	63.11 – 93.94
Recreational sun exposure		
Yes	24 (85.71)	67.33 – 95.97
No	4 (14.29)	4.03 – 32.67
Solarium use		
Yes	3 (10.71)	2.27 – 28.23
No	25 (89.29)	71.77 – 97.73
Ocular pathology		
Yes	0 (0)	0 – 12.34*
No	28 (100)	87.66 – 100*

NMSC, non-melanoma skin cancer.
* One-sided 97.5% confidence interval.

19.93–56.14), followed by homogeneous (26.70%, N=8; 95% CI: 12.28–45.89), reticular (13.30%, N=4; 95% CI: 3.76–30.72), and mixed reticular and homogeneous patterns (13.30%, N=4; 95% CI: 3.76–30.72). One lesion (3.30%, N=1; 95% CI: 0.08–17.22) exhibited a reticular and globular combination. Each lesion displayed either one or two dermoscopic patterns: 46.70% (N=14; 95% CI: 28.34–65.67) had a single pattern, while 53.30% (N=16; 95% CI: 34.33–71.66) showed two. No lesion exhibited more than two dermoscopic patterns.

In terms of pigmentation, all lesions exhibited brown coloration. Specifically, 30% (N=9; 95% CI: 14.73–49.40) were light brown, 10% (N=3; 95% CI: 2.11–26.53) were dark brown, and 50% (N=15; 95% CI: 31.30–68.70)

Table 2. Clinical Characteristics of Benign Conjunctival Melanocytic Lesions.

Clinical Characteristics	N (%)	95% Confidence interval
Eye		
Right	14 (46.67)	28.34 – 65.67
Left	16 (53.33)	34.33 – 71.66
Anatomical location		
Juxtalimbal	16 (53.33)	34.33 – 71.66
Bulbar	12 (40)	22.66 – 59.4
Bulbar/Multifocal	2 (6.67)	0.82 – 22.07
Palpebral	0 (0)	
Forniceal	0 (0)	
Quadrant		
Temporal	18 (60)	40.6 – 77.34
Nasal	5 (16.67)	5.64 – 34.72
Superior	3 (10)	2.11 – 26.53
Inferior	2 (6.67)	0.82 – 22.07
Multifocal	2 (6.67)	0.82 – 22.07
Primary morphology		
Macule	18 (60)	40.6 – 77.34
Papule or partly elevated	12 (40)	22.66 – 59.4
Color		
Light brown	10 (33.33)	17.29 – 52.81
Dark brown	5 (16.67)	5.64 – 34.72
Black/light brown	1 (3.33)	0.08 – 17.22
Light/dark brown	14 (46.67)	28.34 – 65.67
No pigment	0 (0)	
Additional features		
Intralesional Cysts	1 (3.33)	0.08 – 17.22
Feeder vessels	7 (23.33)	9.93 – 42.28
Intralesional cysts/ feeder vessels	3 (10)	2.11 – 26.53
Absent	19 (63.33)	43.86 – 80.07
Clinical diagnosis		
Nevus	28 (93.33)	77.93 – 99.18
Complexion-associated melanosis	2 (6.67)	0.82 – 22.07

showed both light and dark brown. Additionally, black pigmentation was noted in 10% (N=3; 95% CI: 2.11–26.53) of cases. None of the lesions demonstrated more than three colors. Uniform pigmentation with a single color was observed in 40% (N=12; 95% CI: 22.66–59.40) of lesions.

Intralesional cysts were dermoscopically identified in 60% (N=18; 95% CI: 40.60–77.34) of lesions, whereas 40% (N=12; 95% CI: 22.66–59.40) showed no cyst (Figure 1). Notably, all lesions with a reticular dermoscopic pattern exhibited cysts, indicating a statistically significant association (P<0.05; Figure 2).

Regarding the global dermoscopic pattern of cutaneous nevi, the reticular pattern was most frequent (46.70%, N=14; 95% CI: 28.34–65.67), followed by globular (23.30%, N=7; 95% CI: 9.93–42.28), multicomponent (16.70%, N=5; 95% CI: 5.64–34.72), and homogeneous (13.30%, N=4; 95% CI: 3.76–30.72) patterns.

Discussion

Our findings regarding demographics and clinical characteristics are comparable to a relevant previous extensive study on 410 conjunctival nevi conducted by Shields et al. [2]. The mean age at the time of initial diagnosis was specified as 32 years in both studies, with a mean history of 10 years reported by Shields et al. and 20 years in our population. In our sample, 40% of the lesions were located on the bulbar conjunctiva, with 53.3% being juxtalimbal. In comparison, Shields et al. reported a bulbar location in 72% of cases, including lesions near the limbus. Gerner et al., in their series of 343 conjunctival nevi in Denmark, reported bulbar lesions in 33% of cases and juxtalimbal lesions in 27% [7]. Temporal (60%) and nasal (16.7%) quadrants were involved more than were the superior and inferior, consistent with previously published findings [2,16]. No lesion was identified in

Table 3. Dermoscopic Characteristics of Benign Conjunctival Melanocytic Lesions.

Dermoscopic Characteristics	N (%)	95% Confidence interval
Dermoscopic pattern		
Globular	2 (6.67)	0.82 – 22.07
Homogeneous	8 (26.67)	12.28 – 45.89
Reticular	4 (13.33)	3.76 – 30.72
Globular & homogeneous	11 (36.67)	19.93 – 56.14
Reticular & homogeneous	4 (13.33)	3.76 – 30.72
Reticular & Globular	1 (3.33)	0.08 – 17.22
Number of patterns		
1	14 (46.67)	28.34 – 65.67
2	16 (53.33)	34.33 – 71.66
Color		
Light brown	9 (30)	14.73 – 49.4
Dark brown	3 (10)	2.11 – 26.53
Light/dark brown	15 (50)	31.3 – 68.7
Black/light/dark brown	3 (10)	2.11 – 26.53
Number of colors		
1	12 (40)	22.66 – 59.4
2	15 (50)	31.3 – 68.7
3	3 (10)	2.11 – 26.53
Intralesional cysts		
Yes	18 (60)	40.6 – 77.34
No	12 (40)	22.66 – 59.4
Global dermoscopic pattern		
Reticular	14 (46.67)	28.34 – 65.67
Globular	7 (23.33)	9.93 – 42.28
Homogeneous	4 (13.33)	3.76 – 30.72
Multicomponent	5 (16.67)	5.64 – 34.72

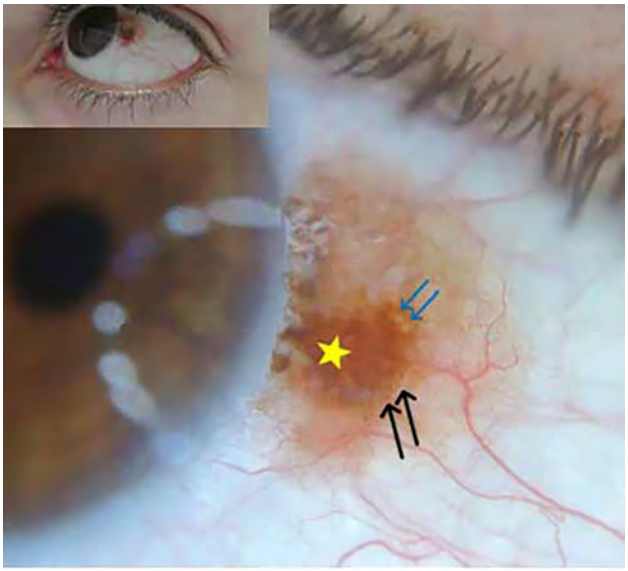


Figure 1. Conjunctival nevus with characteristic intralesional cysts (blue arrows) and mixed dermoscopic pattern: homogeneous (yellow asterisk) and globular (black arrows).

the palpebral or forniceal conjunctiva, nor did any show corneal involvement, features suggestive of the benign nature of the studied sample [9,10].

Different acquired conjunctival nevi types include junctional, compound, and subepithelial nevi, similar to the classification of the cutaneous nevi [8]. CN are constantly evolving with age. Junctional nevi, emerging in childhood and adolescence, originally derive from a benign proliferation of melanocytes in the junction of the epithelium [17]. During the second and third decades of life, the nevus cells begin to recede to the underlying stroma, causing the elevation of the lesions. Parts of the epithelium, including squamous and goblet cells, are driven downwards as well, protruding in the substantia propria and forming the clear cysts [8,18]. The compound nevus stage is achieved when nevus cells are located in both the epithelial and subepithelial tissues. A subepithelial nevus, corresponding to cutaneous intradermal nevus, arises when the intraepithelial component is eliminated [8,18]. Intralesional cysts represent

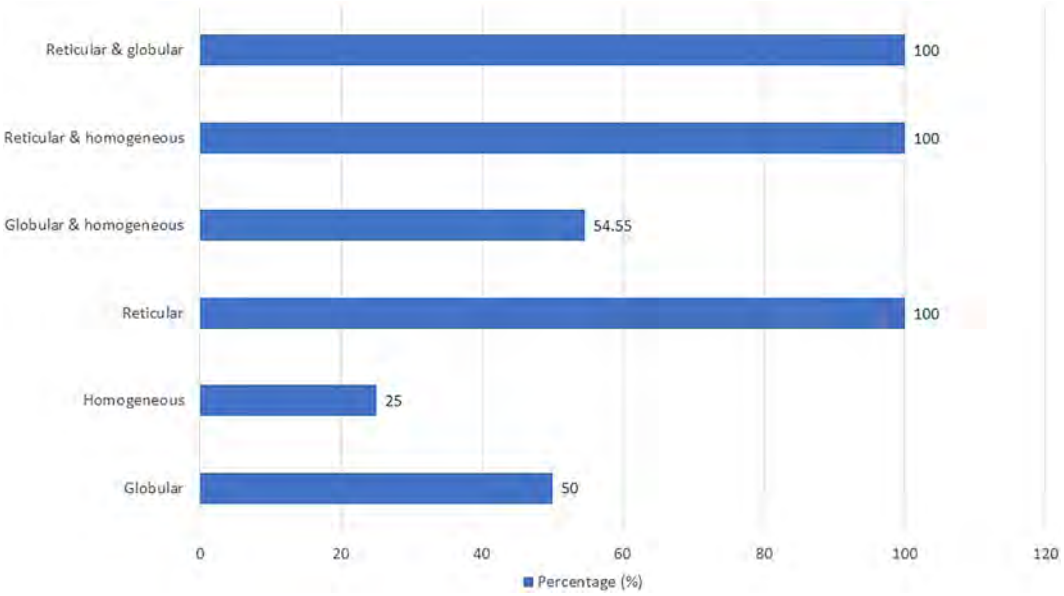


Figure 2. Presence of intralesional cysts across various dermoscopic patterns.

an important benign feature of CN, particularly compound nevi, and are extremely rare in PAM or CM [8]. In our study, cysts were recognized clinically in 13.3%, in contrast with previously published studies, which describe a higher incidence, in 50–65% of cases [2,16,19].

In our cohort, we identified patients with benign CML to present with a low TBNC. This observation is, to the best of our knowledge, reported for the first time and raises the hypothesis that these lesions may arise from a different genetic background compared to those of cutaneous origin. Although molecular data are limited, studies indicate that up to 50% of conjunctival nevi harbor BRAF V600E mutations [20]. This is directly comparable to acquired cutaneous nevi [20]. Accordingly, the possible pathway leading to the development of CML and their potential parallels with the development of acquired cutaneous melanocytic nevi remains to be elucidated in the future. Furthermore, increased awareness should be raised regarding ocular examination and follow-up for these individuals, who are less likely to be under dermatological surveillance due to their low number of cutaneous nevi.

Limited literature relevant to the dermoscopy of conjunctival lesions is available, and no previous study has examined the features of benign CMLs alone. The small number of published reports and the unique anatomy of conjunctival mucosa makes the terminology and dermoscopic criteria quite perplexing. Cinotti et al. were the first to publish a dermoscopic analysis of 147 conjunctival tumors of both benign and malignant nature [21]. Kaçar et al., in their study, explored the utility of dermoscopy in a more limited sample size of 20 conjunctival infiltrations [22]. Two more recent publications from Dębicka-Kumela et al. mainly concern the malignant dermoscopic characteristics and an algorithm for the differentiation between CM and other CML [23,24].

As far as the dermoscopic pattern is concerned, our findings align with those of Cinotti et al. [21], with the mixed pattern being the most prevalent in the nevi group. However, a direct comparison of specific mixed pattern variations is not possible, as Cinotti et al. did not report exact incidences [21]. A homogeneous (structureless) pattern was identified in 76.7% of our cases, closely matching the 83% reported by Cinotti et al. [21], making it the most frequently observed pattern, either alone or in combination with others. While no reticular pattern was noted in the cohort of Cinotti et al. [21], we observed it in 29.9% of the lesions in our sample. This might be explained by the unique conjunctival anatomy, which includes a flat stromal-epithelial junction, unlike the rete ridge pattern of the epidermis seen in cutaneous nevi. From our point of view, the reticular pattern observed in conjunctival lesions likely emerges from the alternation of pigmented areas, forming a grid of thin brown lines and clear intralesional cysts, appearing as hypopigmented holes (Figure 3). Interestingly, all the cases in our study that exhibited a reticular pattern also presented with cysts ($P<0.05$), further supporting this hypothesis.

In accordance with Cinotti et al. [21], dermoscopic examination substantially contributed to revealing the presence

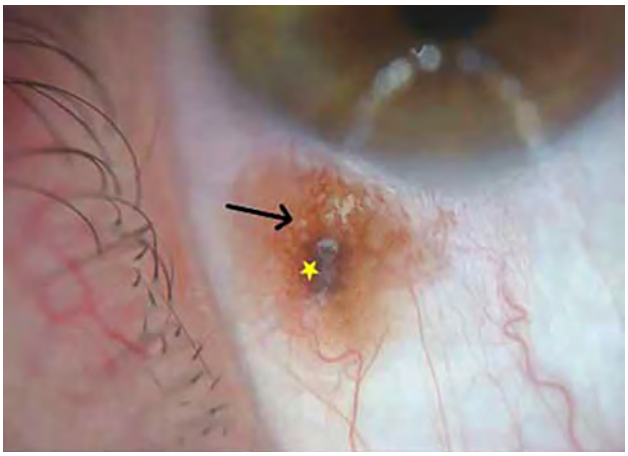


Figure 3. Conjunctival nevus with clear cysts and reticular pattern (black arrow) combined with homogeneous pattern in the center of the lesion (yellow asterisk).

of the benign epithelial cysts in 60% of the lesions, versus 13.3% observed with naked eye examination in our cases. This observation probably suggests the increased accuracy of the method and the diagnostic importance of structures identified via dermoscopy.

Regarding lesion color, all lesions in our study displayed brown or black pigmentation, likely due to the studied population being over 15 years of age, a stage when these lesions had probably achieved full pigmentation. In contrast, Shields et al., who included both pediatric and adult patients (age range 2–93 years), reported 16% of their sample to be completely amelanotic, which could be attributed to the fact that an estimated 30% of conjunctival nevi can remain amelanotic before puberty [5]. In terms of color variability, all lesions in our sample exhibited brown pigmentation, consistent with the findings of Cinotti et al. [21], although fewer color variations were observed. Notably, gray pigmentation, strongly associated with conjunctival melanoma (CM) in more than 60% of suspicious lesions by Cinotti et al. and Kaçar et al. [21, 22], was absent in our cases. Additionally, 10% (N=3) of lesions in our cohort displayed three colors (light brown, dark brown, and black), consistent with observations in nevi groups from previous studies. In contrast, colors linked to malignancy, such as blue, white, or red, were not identified in our sample.

Both PAM, a potentially premalignant condition, and CM tend to exhibit a dermoscopic pattern characterized by brown or black dots, irregularly distributed and often confluent into a peripheral structureless pattern, as consistently described by all study groups [21-24]. No case in our study displayed similar morphologic characteristics. Furthermore, studies investigating the malignant features of pigmented CML have described significant heterogeneity and plurality in both dermoscopic patterns and color variations [21-24]. More specifically, malignant and premalignant lesions were associated with the presence of ≥ two patterns and/or more than two colors. In contrast to these observations, none of the lesions in our study exhibited more than two patterns, with a single-pattern morphology identified in 46.7% (N=14) of the cases. Dębicka-Kumela et al. reported that 87.5% of CMs in their study exhibited two or more dermoscopic patterns [23]. Notably, none of the lesions in our study showed the presence of black dots throughout the lesion, a feature strongly associated with malignancy in former reports [21].

CML are predominantly assessed by ophthalmologists using tools such as slit-lamp biomicroscopy, anterior segment optical coherence tomography, and ultrasound biomicroscopy, which provide detailed insights into lesion depth, thickness, and potential intraocular invasion. However, our study highlights the value of dermoscopy, a practical, non-invasive tool that allows dermatologists to accurately identify hallmark features of benign lesions through detailed surface-level assessment. This capability not only reduces unnecessary referrals to ophthalmologists but also minimizes the need for invasive procedures such as biopsies in benign cases. Additionally, dermoscopy facilitates longitudinal monitoring through photographic documentation, making it a valuable tool for ongoing evaluation and follow-up in clinical practice.

Limitations

While our study provides valuable insights into the clinical and dermoscopic features of benign CMLs, several limitations must be acknowledged. The relatively small sample size and number of analyzed lesions may restrict the generalizability of our findings. Additionally, the lack of histopathological validation limits the strength of our conclusions. As a retrospective cohort study, follow-up data and patient outcomes were unavailable, preventing any assessment of the natural progression of these lesions. Last, the homogeneity of the study population and the lack of a control group made it challenging to identify meaningful correlations between different subgroups. These limitations highlight the need for future studies with prospective study design, larger samples, and comprehensive follow-up to validate and expand upon our findings.

Conclusions

Our findings indicate that benign conjunctival melanocytic lesions are more commonly observed in individuals with a low total body nevus count and are dermoscopically characterized by either a single or mixed pattern, with the homogeneous pattern being the most prevalent. Fewer than three colors were identified in all cases, and brown pigmentation was the most frequent. Another indicator of benignity was

the presence of intralesional cysts in more than half of the cases and their correlation with a reticular pattern.

Dermoscopy, when combined with clinical characteristics and patient history, may serve as a valuable tool for the identification and monitoring of benign conjunctival melanocytic lesions. A closer collaboration between ophthalmologists and dermatologists could lead to optimization of the management of these lesions, yet larger additional studies are needed to establish the present findings and standardize site-specific dermoscopic criteria.

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Dermatology Practical & Conceptual

Real-World Safety of Oral Isotretinoin in Patients During Sunny Months: Retrospective Cohort Study

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Key words: Oral isotretinoin, Acne, Seasonality, Safety, Sun Exposure

Citation: Marzola E, Pedarzani E, Valpiani G, Fraternale S, Toni G, Bettoli V, et al. Real-World Safety of Oral Isotretinoin in Patients During Sunny Months: Retrospective Cohort Study. *Dermatol Pract Concept*. 2025;15(4):5612. DOI: https://doi.org/10.5826/dpc.1504a5612

Accepted: June 28, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: There is a widespread clinical practice of avoiding oral isotretinoin administration during the sunny season due to its purported photosensitizing effect. However, this approach is not supported by solid evidence.

Objective: The aim of this study was to assess the safety and effectiveness of administering oral isotretinoin at a reduced daily dosage during the sunny period in a real-world clinical setting.

Methods: This retrospective cohort study included all acne patients treated with oral isotretinoin at our Acne Clinic (January 2014 - December 2023) who had received the drug between June and September, when UV index exceeds a threshold of 6. Conventionally, oral isotretinoin daily dosage is reduced by approximately half during these four sunny months and then increased again. We compared the occurrence of side effects or treatment discontinuation between sunny and non-sunny periods. The therapeutic response was explored in relation to the daily dosage.

Results: 359 patients (61.3% males, with a mean age of 19.0 years, standard deviation (SD) 6.7) were included. Adverse events were reported by 39.2% and 28.3% of patients during the non-sunny and sunny months, respectively. The incidence of treatment discontinuation was negligible. The reduction in acne severity was independent of the daily dosage of oral isotretinoin.

Conclusions: The study results support the lack of any necessity to suspend or refrain from administering oral isotretinoin during sunny seasons. The preventive reduction of its daily dosage during sunny periods does not negatively affect the drug's effectiveness. Oral isotretinoin can be taken, at a slightly reduced dosage, during sunny months.

Introduction

Oral isotretinoin is the most effective therapeutic option for acne by virtue of its broad spectrum of action [1,2]. According to European guidelines, it is typically reserved for severe papulopustular or moderate nodular acne as well as for acne that has not responded to oral antibiotics and topical treatments [3].

Despite its efficacy, dermatologists are often hesitant to prescribe oral isotretinoin due to its well-documented side effects. The most significant, and not dose-dependent, extracutaneous side effect is teratogenicity, necessitating the use of effective contraception in females of childbearing age, along with monthly pregnancy tests [4]. Common and dose-dependent cutaneous side effects include dryness of the skin, lips, and eyes, which may cause discomfort and require the use of moisturizers or eye drops [5].

Photosensitivity is listed as a potential side effect in the technical data sheets, recommending limited exposure to ultraviolet (UV) radiation and the use of protective measures such as long clothing, hats, and high SPF sunscreen along with the personalization of the dosage. However, the available evidence on isotretinoin photosensitivity is outdated and often contradictory. Only a few cases, a long-time ago, reported phototoxic [6,7] or photoallergic [8] mechanisms. Immediate-type hypersensitivity with IgE involvement has been suggested [9]. Attempts to confirm the allergic mechanism through phototesting have not demonstrated sunlight as the primary cause of erythema in patients taking oral isotretinoin [10]. Moreover, studies have shown no significant changes in the ultraviolet A and B minimal erythema dose (MED) in patients using the drug [11].

Despite that, there is a widespread clinical practice of avoiding its administration during the sunny season or temporarily suspending treatment during ongoing therapy. This approach lacks solid evidence to support it, as no study has addressed the use of oral isotretinoin in the summer or in seasons with high UV indices. Therefore, there is no concrete evidence to suggest that more frequent or severe side effects occur during the sunny season compared to other times of the year.

Objectives

In our clinical practice, we do not suspend or delay the initiation of oral isotretinoin treatment during the sunny months. However, we have found that reducing its daily dosage can be beneficial. This precaution is based on oral isotretinoin's effect on the skin, including the reduction of the lipid film and thinning of the stratum corneum, which may increase its vulnerability to external factors, including solar radiation.

The aim of this study was to assess the safety of using oral isotretinoin, at a reduced daily dosage, during the sunny season in a real-world clinical setting.

Methods

Study Design and Objectives

This study was designed as a single-center, retrospective cohort study to analyze the use of oral isotretinoin in acne patients during the sunny months of the year, when administered at a reduced daily dosage. The study was conducted in a geographic region where the UV index typically exceeds a threshold of 6 during June, July, August, and September. Specifically, the objectives of the study were to assess the safety of oral isotretinoin administration during the aforementioned four sunny months and to evaluate the effectiveness of a reduced daily dosage regimen of oral isotretinoin, tailored to the sunny season.

This was an observational study conducted without external funding. All patients treated at our outpatient clinic adhered to the ethical principles outlined in the Declaration of Helsinki (1975, revised 2013). The study was approved by the Comitato Etico Area Vasta Centro della Regione Emilia-Romagna (CE-AVEC) (protocol number 395/2024/Oss/AOUFe, approval date: 18/07/2024) and by the ethics committees at all participating sites. Written informed consent was obtained from all patients. A waiver of informed consent was granted for patients who could not be traced and for whom obtaining consent was not feasible. Adherence to the STROBE checklist for observational studies is summarized in Table S1.

Study Patients

In our clinical practice, acne patients are offered treatment with oral isotretinoin when they fail to respond to prior conventional combined therapies, which typically include a systemic antibiotic and a topical agent, or in cases of acne relapse after discontinuation of first-line treatments.

All acne patients treated with oral isotretinoin between January 2014 and December 2023 at the Acne Clinic of the Dermatology Unit at the University Hospital of Ferrara (located in northeastern Italy) were retrospectively considered for inclusion. Patients were eligible if they had received oral isotretinoin for at least four weeks between June and September, regardless of when the treatment was initiated or its overall duration. Age, acne severity, and whether the treatment was the first or a subsequent course were not used as inclusion criteria. For recruitable patients who underwent multiple cycles of oral isotretinoin, only the first in chronological order was taken into consideration. The only exclusion criteria were refusal to participate or incomplete demographic or clinical data.

Study Procedures and Assessments

At our Acne Clinic, the mean daily dosage of oral isotretinoin is between 0.2 and 0.3 mg/kg [12]. Initially, a daily dose of <0.2 mg/kg is administered to reduce the potential for acne flare-ups [13,14], and this is gradually increased over the first four weeks of treatment. Conventionally, the daily dosage is reduced by approximately half during the four sunny months, then increased again in October and the following months.

Oral isotretinoin is never suspended a priori during the sunny season.

The severity of acne is assessed using the Leeds Revised Acne Grading System [15], both at baseline and at subsequent control visits, which are scheduled at 12-week intervals. Liver function tests and lipid profile are evaluated for all patients prior to treatment initiation and again at six weeks after treatment begins. These tests are repeated as needed throughout the treatment course. For female patients of childbearing potential, a pregnancy test is performed before starting treatment and monthly thereafter, prior to each prescription. Oral contraception is required to be initiated before starting treatment and continued throughout the entire treatment period as well as for four weeks after therapy ends.

All patients receive both verbal and written information on the need to use emollients for their lips and moisturizing products for their skin and to adhere to rigorous photoprotection during the sunny months. Patients can contact the Acne Clinic at any time to report side effects, with a follow-up visit scheduled as necessary.

The following data were collected from the patients' clinical records: i) age and sex; ii) acne severity at baseline, using the Leeds Revised Acne Grading System; iii) acne severity at each control visit; iv) daily dosage of oral isotretinoin for each month of therapy; v) occurrence of clinical side effects or laboratory anomalies, specifying the month of onset or diagnosis; vi) treatment discontinuation for any reason; vii) treatment duration in months. All adverse events which occurred during therapy were taken into account, except for lip xerosis, which was excluded as it is an expected effect.

Sample Size and Statistical Analysis

In the literature, there is no scientific evidence of the seasonal proportion of adverse events in patients receiving oral isotretinoin. For the sample size calculation, historical data of our Acne Clinic were employed: a "seasonal" adverse events proportion (sunny period from June to September and not-sunny period from October to May) of 13.4% and 5.2%, respectively, was registered. A power estimation, based on the comparison of the two proportions, given a level $\alpha = 0.05$ and $1-\beta = 0.8$, allowed a sample size of 182 patients. Despite the fact that 182 is the minimum number of patients to be considered in order to identify a statistically significant difference in terms of seasonal proportion of adverse events, we considered the entire historical cohort of patients treated at our Acne Clinic in the time frame considered.

The Shapiro-Wilk test was used to check the normality assumption of continuous variables. In the presence of symmetry, variables were represented with mean and standard deviation (SD) or, in case of asymmetry with median and quartiles [Q1 Q3]; categorical data are expressed as absolute values and percentages (%).

The Student's t-test or Mann-Whitney test was used to detect possible mean or median significant differences between the two groups. In case of categorical variables, $\chi 2$ or exact Fisher test was used. A scatter plot with an interpolation line is displayed to represent the joint distribution between the differential daily mean dose (x-axis) and the differential Leeds scores (y-axis), for each site (face, back, and chest). The first and last month of treatment values available were used to calculate the differential in daily mean dose. Moreover, differential values in Leeds scores were computed as the difference between baseline and last available observation. All analyses were performed using the software RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/. A p-value of <0.05 was considered statistically significant.

Results

Baseline Study Population Features

A total of 359 patients were included, of whom 61.3% were male (N=220) and 38.7% were female (N=139) (Table 1). The median age of all patients was 17 years (range: 16.0–20.0), with a mean age of 19.0 years (±6.7). Male patients were slightly younger (median age: 17.0 years, range: (15.0–19.0)) compared to female patients (median age: 18.0 years, range: (16.0–23.0)), with a difference in the median ages (P=0.009).

Facial acne was highly prevalent, affecting 98.3% of the entire cohort. The difference between males and females was not significant (P=0.086) as 100% of females and 97.3% of males had facial acne. However, significant sex differences were observed in the distribution of truncal acne. Back acne was present in 74.1% of males compared to 40.3% of females (P<0.001). Similarly, chest acne was more common in males (38.6%) than in females (24.5%) (P=0.008).

The severity of acne assessed using the Leeds Revised Acne Grading System showed no significant difference between sexes on the face (P=0.541), back (P=0.666), or chest (P=0.199). The median duration of oral isotretinoin treatment was 10.0 months [8.0 13.0] for the entire cohort, with no significant difference between male and female patients (P=0.233).

Table 1. Baseline Characteristics of the Study Patients.

	All Patients (N= 359)	Female (N= 139)	Male (N= 220)	*p-value*
Age (years), median [Q1 Q3]	17.0 [16.0;20.0]	18.0 [16.0;23.0]	17.0 [15.0;19.0]	0.009
Age (years), mean (SD)	19.0 (6.7)	19.9 (6.2)	18.5 (6.9)	0.056
Sex, N (%)				
Male	220 (61.3%)	0	220 (100%)	
Female	139 (38.7%)	139 (100%)	0	
Face, presence of acne, N (%)	353 (98.3%)	139 (100.0%)	214 (97.3%)	0.086
Back, presence of acne, N (%)	219 (61.0%)	56 (40.3%)	163 (74.1%)	<0.001
Chest, presence of acne, N (%)	119 (33.1%)	34 (24.5%)	85 (38.6%)	0.008
Face Leeds Revised Acne Grading System, median [Q1 Q3]	3 [2;4]	3 [2;4]	3 [2;4]	0.541
Back Leeds Revised Acne Grading System, median [Q1 Q3]	3 [2;4]	3 [2;4]	3 [2;4]	0.666
Chest Leeds Revised Acne Grading System, median [Q1 Q3]	2 [1;3]	1 [1;2]	2 [1;3]	0.199
Treatment duration (months), median [Q1 Q3]	10.0 [8.0;13.0]	10.0 [8.0;12.0]	10.0 [8.0;14.0]	0.233

[Q1 Q3]: first and third quantiles; SD, standard deviation.

Treatment Effectiveness

The effectiveness of oral isotretinoin treatment was assessed by comparing acne severity scores before treatment and at its completion using the Leeds Revised Acne Grading System (Table 2). A total of 352 patients were evaluated for facial acne severity, 219 for back acne, and 118 for chest acne.

There is a minor discrepancy compared to the total number of enrolled patients, as the number of patients with facial acne and truncal cane was 353 and 119, respectively (Table 1). However, one subject did not have a baseline severity score recorded for the face. Similarly, one patient with chest acne lacked follow-up data for this site. They were therefore excluded from the analyses.

For facial acne, the median severity score significantly decreased from 3 (2–4) at baseline to 0 (0–1) after treatment (P<0.001). Similarly, for back acne, the median score dropped from 3 (2–4) to 0 (0–1) (P<0.001). Chest acne also showed substantial improvement, with the median score decreasing from 2 (1–3) to 0 (0–1) following treatment (P<0.001).

These results show a statistically significant reduction in acne severity across all body areas following oral isotretinoin therapy.

Seasonal Safety of Treatment

The seasonal safety profile of oral isotretinoin was assessed by comparing the daily dosage, occurrence of adverse events, and treatment discontinuation rates between the non-sunny months (October to May) and the sunny months (June to September) (Table 3).

The median isotretinoin dose was significantly lower during the sunny months (10.0 mg; (10.0– 15.0)) compared to the non-sunny months (15.0 mg; (10.0–20.0)) (P<0.001). Adverse events were reported by 39.2% of patients during the non-sunny months, while this figure decreased to 28.3% during the sunny months (P<0.001). The most frequently adverse event recorded was skin xerosis (212 records), followed by epistaxis, and facial dermatitis, reported 136 and 104 times, respectively. Other notable side effects included fatigue (76 records), arthralgia and myalgia (54), conjunctivitis (45), headache (41), and mood disturbances (27). Less common adverse events included xerophthalmia (7), increase in creatine phosphokinase (2), elevated liver enzyme levels (1), and muscle cramps (1).

Treatment discontinuation rates remained consistent across the two periods, with 1.1% of patients discontinuing oral isotretinoin during the non-sunny months and 1.2% during the sunny months (P=0.999). It is worth noting that the treatment was not discontinued due to adverse effects related to the medication but rather due to a temporary suspension for personal reasons and surgical procedures.

Relationship between Daily Dose and Treatment Effectiveness

A further study objective was to assess the therapeutic response based on the daily dosage of oral isotretinoin across the three different skin sites. The relationship between the differential daily dose and the differential Leeds scores, for each site, showed no significant association (Figure 1).

Table 2. Acne Severity Scores by Area, comparing Before and After Treatment. After treatment data have been computed as the median of the last available data for each patient, in each area of interest.

	N	Before treatment	After treatment	*p-value*
Face Leeds Revised Acne Grading System, median [Q1 Q3]	352	3 [2;4]	0 [0;1]	<0.001
Back Leeds Revised Acne Grading System, median [Q1 Q3]	219	3 [2;4]	0 [0;1]	<0.001
Chest Leeds Revised Acne Grading System, median [Q1 Q3]	118	2 [1;3]	0 [0;1]	<0.001

[Q1 Q3]: first and third quantiles

Table 3. Comparison of Oral Isotretinoin Daily Dose, Discontinuation, and Adverse Events Occurrence in Non-Sunny and Sunny Months. Not-sunny period refers to months from October to May while sunny period is between June and September.

	Non-sunny months	Sunny months	*p-value*
Drug daily dose (mg), median [Q1 Q3]	15.0 [10.0 20.0]	10.0 [10.0 15.0]	<0.001
Adverse Events, N (%)			<0.001
none	2,224 (60.8%)	294 (71.7%)	
1 or more	1,434 (39.2%)	116 (28.3%)	
Drug discontinuation, N (%)			0.999
yes	29 (1.1%)	18 (1.2%)	
no	2,488 (98.9%)	1,537 (98.8%)	

[Q1 Q3]: first and third quantiles

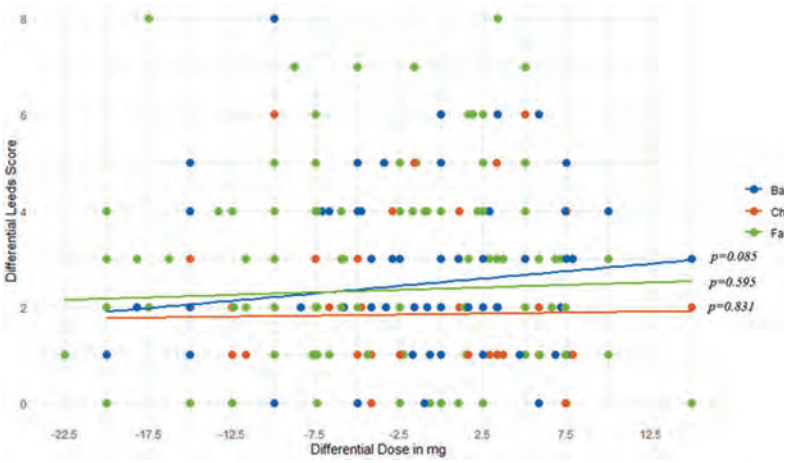


Figure 1. Scatter plot comparing differential values in dose between first versus last month's daily dosage and pre- versus post-treatment Leeds Severity Scoring system by skin site.

Conclusions

The primary objective of this study was to assess the safety of administering oral isotretinoin during sunny seasons. The extensive time frame analyzed retrospectively, along with the high and steady patient attendance at our Acne Clinic, allowed for the inclusion of a greater number of patients than initially estimated through the sample size calculation. The sample included provided a robust opportunity to offer evidence regarding the common belief that oral isotretinoin should be contraindicated during sunny months, either confirming or refuting this assumption.

The patients enrolled represent a typical acne patient cohort receiving oral isotretinoin, both demographically and clinically. Truncal acne was significantly more prevalent in male patients than in females (Table 1), in accordance with existing epidemiological data [16].

Regarding treatment outcomes, a significant reduction in acne severity was observed across all anatomical areas after oral isotretinoin treatment (Table 2). The Leeds Revised Acne Grading System scores showed marked improvement for facial, back, and chest acne, with the median scores dropping to near-zero values post-treatment (Table 2). These results were expected and are consistent with numerous previous studies that have demonstrated the effectiveness of oral isotretinoin in inducing acne remission, even in severe and recalcitrant cases [3,17–20].

The complete or near-complete resolution of acne in most patients is unsurprising given the unique mechanism of action of oral isotretinoin [4]. The consistency of these outcomes across different body sites further supports its broad-spectrum effectiveness. While facial acne is often the primary focus of treatment, acne on the back and chest can be more challenging due to the thicker skin and larger sebaceous glands in these areas [21]. These results reinforce the role of oral isotretinoin as the gold standard in acne treatment, regardless of the affected body site.

The most noteworthy aspect of this study, which was not specifically addressed in previous research, is its primary objective, i.e., assessing the safety of oral isotretinoin when administered during sunny seasons. The rates of adverse events observed during the sunny months were no higher than those recorded during the non-sunny periods. In fact, our experience indicates that the incidence of side effects was lower during the sunny months compared to the rest of the year. This appears to be attributed to the reduced daily dosage of the drug during the sunniest months, as adverse events are known to be dose-dependent.

The absence of an increased rate of drug discontinuation and severe adverse events during the summer months further supports the notion that oral isotretinoin is neither photoallergic nor phototoxic. While patients on oral isotretinoin may experience heightened skin sensitivity, this vulnerability is not limited to sun exposure; it extends to a variety of exogenous irritants at any time of the year. This underscores the importance of advising patients to adopt protective measures year-round, including emollients for the skin and lips, gentle cleansing, and rigorous photoprotection.

Therefore, our data challenge the common practice of delaying oral isotretinoin administration until after the summer or suspending treatment during the sunny months due to concerns about sun exposure. Given that untreated acne can lead to long-term scarring, postponing treatment for several months could result in permanent skin damage [22]. Instead, initiating oral isotretinoin treatment promptly and advising patients on appropriate skin care can help prevent unnecessary delays in achieving acne remission. This approach also addresses the suffering and emotional burden that acne can cause.

The systematic reduction in the daily dosage of oral isotretinoin before the start of the sunny season raises the question of whether this practice affects the treatment's effectiveness. Figure 1 shows the relationship between mean daily dosages (from the start to the completion of treatment) and changes in acne severity. For the back site, a positive trend was found, albeit not significant (P=0.085). Clinically, this suggests that a temporary reduction in daily dosage does not significantly impact the therapeutic efficacy of oral isotretinoin [23].

The study results have several limitations. As a retrospective study, it did not allow for the collection of detailed information on patients' sun exposure habits, including the use of photoprotection. Given the young age of the participants, it is likely that their ultraviolet exposure was primarily recreational rather than occupational, but specific data on this were not available. Additionally, while comparing the four months with the highest UV radiation to the remaining eight months was a rational approach, it was somewhat arbitrary. The findings of this study are specific to the geographical area in which it was conducted and may not be generalizable to regions with different radiation levels. Furthermore, the subjects included were all Caucasian, while other ethnic groups were not represented.

Despite these limitations, this is the first study to specifically address the use of oral isotretinoin during sunny seasons, with a focus on its safety profile. The study suggests that reducing the daily dose of oral isotretinoin during the sunny months may be a reasonable strategy to minimize the occurrence of adverse events. Based on our findings, there is no evidence to support postponing the start of treatment until the fall or suspending it during the summer months. On the contrary, oral isotretinoin can be safely administered during sunny seasons to reduce acne severity, alleviate its emotional burden, and prevent scarring, which can be worsened by delaying appropriate treatment. While reducing the daily dose may help mitigate side effects during sunny months, it does not appear to compromise the drug's therapeutic effectiveness.

In conclusion, this study's results support the use of oral isotretinoin even during high UV radiation seasons, at a slightly reduced daily dosage.

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Dermatology Practical & Conceptual

Supplementary File

Table S1. Adherence to the STROBE checklist for observational studies.

	Item No	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2	The study's design as a retrospective cohort is indicated in the title and abstract.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	The abstract provides a summary of the study's objectives, methods, results, and conclusions.
Introduction				
Background /rationale	2	Explain the scientific background and rationale for the investigation being reported	3	[…] the available evidence on isotretinoin photosensitivity is outdated and often contradictory. Only a few cases, a long-time ago, reported phototoxic or photoallergic mechanisms. Immediate-type hypersensitivity with IgE involvement has been suggested. Attempts to confirm the allergic mechanism through phototesting have not demonstrated sunlight as the primary cause of erythema in patients taking oral isotretinoin. Moreover, studies have shown no significant changes in the ultraviolet A and B minimal erythema dose (MED) in patients using the drug. Despite that, there is a widespread clinical practice of avoiding its administration during the sunny season or temporarily suspending treatment during ongoing therapy. This approach lacks solid evidence to support it, as no study has addressed the use of oral isotretinoin in the summer or in seasons with high UV indices. Therefore, there is no concrete evidence to suggest that more frequent or severe side effects occur during the sunny season compared to other times of the year.
Objectives	3	State specific objectives, including any prespecified hypotheses	4	The aim of this study was to evaluate the safety of using oral isotretinoin, at a reduced daily dosage, during the sunny season in a real-world clinical setting.
Methods				
Study design	4	Present key elements of study design early in the paper	4	This study was designed as a single-center, retrospective cohort study.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	All acne patients treated with oral isotretinoin between January 2014 and December 2023 at the Acne Clinic of the Dermatology Unit at the University Hospital of Ferrara (located in north-east of Italy) were retrospectively considered for inclusion.

Table S1 continues

Table S1. Adherence to the STROBE checklist for observational studies. *(continued)*

	Item No	Recommendation	Page No.	Relevant text from manuscript
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5	All acne patients treated with oral isotretinoin between January 2014 and December 2023 at the Acne Clinic of the Dermatology Unit at the University Hospital of Ferrara (located in north-east of Italy) were retrospectively considered for inclusion. Patients were eligible if they had received oral isotretinoin for at least 4 weeks between June and September, regardless of when the treatment was initiated or its overall duration. Age, acne severity, and whether the treatment was the first or a subsequent course were not used as inclusion criteria. For patients who underwent multiple cycles of oral isotretinoin, among those that met the inclusion and exclusion criteria, only the first in chronological order was taken into consideration. The only exclusion criteria were refusal to participate or incomplete demographic or clinical data.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6	The following data were collected from the patients' clinical records: i) age and sex, ii) acne severity at baseline, using the Leeds Revised Acne Grading System, iii) acne severity at each control visit, iv) daily dosage of oral isotretinoin for each month of therapy, v) occurrence of clinical side effects or laboratory anomalies, specifying the month of onset or diagnosis, vi) treatment discontinuation for any reason, vii) treatment duration in months. Regarding side effects, all adverse events which occurred during therapy were taken into account, except for lip xerosis, which was excluded as it is an expected effect.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5	The severity of acne is assessed using the Leeds Revised Acne Grading System, both at baseline and at subsequent control visits, which are scheduled at 12-week intervals.
Bias	9	Describe any efforts to address potential sources of bias	6	See: Sample size and Statistical analysis
Study size	10	Explain how the study size was arrived at	6	For the sample size calculation, historical data of our Acne Clinic were employed: a "seasonal" adverse events proportion (sunny period from June to September and not-sunny period from October to May) of 13.4% and 5.2%, respectively, was registered. A power estimation, based on the comparison of the two proportions, given a level $\alpha = 0.05$ and $1-\beta = 0.8$, allowed a sample size of 182 patients.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6, 7	See: Sample size and Statistical analysis

Table S1. Adherence to the STROBE checklist for observational studies. *(continued)*

	Item No	Recommendation	Page No.	Relevant text from manuscript
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6, 7	See: Sample size and Statistical analysis
		(*b*) Describe any methods used to examine subgroups and interactions	6, 7	See: Sample size and Statistical analysis
		(*c*) Explain how missing data were addressed	7, 8, 9	Discussed in "Results"
		(*d*) If applicable, explain how loss to follow-up was addressed	7, 8, 9	Discussed in "Results"
		(*e*) Describe any sensitivity analyses	NA	NA
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7	A total of 359 patients were included in the study. […] A total of 352 patients were evaluated for facial acne severity, 219 for back acne, and 118 for chest acne.
		(b) Give reasons for non-participation at each stage	NA	NA
		(c) Consider use of a flow diagram	NA	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7	See: Baseline study population features
		(b) Indicate number of participants with missing data for each variable of interest	7, 8	There is a minor discrepancy compared to the total number of enrolled patients, as the number of patients with facial acne and truncal cane was 353 and 119, respectively (Table S1). However, one subject did not have a baseline severity score recorded for the face. Similarly, one patient with chest acne lacked follow-up data for this site. They were therefore excluded from the analyses.
		(c) Summarise follow-up time (eg, average and total amount)	7	The effectiveness of oral isotretinoin treatment was assessed by comparing acne severity scores before treatment and at its completion, using the Leeds Revised Acne Grading System.

Table S1 continues

Table S1. Adherence to the STROBE checklist for observational studies. *(continued)*

	Item No	Recommendation	Page No.	Relevant text from manuscript
Outcome data	15*	Report numbers of outcome events or summary measures over time	7, 8	The effectiveness of oral isotretinoin treatment was assessed by comparing acne severity scores before treatment and at its completion, using the Leeds Revised Acne Grading System […] The seasonal safety profile of oral isotretinoin was assessed by comparing the daily dosage, occurrence of adverse events, and treatment discontinuation rates between the non-sunny months (October to May) and the sunny months (June to September).
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8	For facial acne, the median severity score significantly decreased from 3 (2–4) at baseline to 0 (0–1) after treatment (P<0.001). Similarly, for back acne, the median score dropped from 3 (2–4) to 0 (0–1) (P<0.001). Chest acne also showed substantial improvement, with the median score decreasing from 2 (1–3) to 0 (0–1) following treatment (P<0.001). […] The median isotretinoin dose was significantly lower during the sunny months (10.0 mg; (10.0– 15.0)) compared to the non-sunny months (15.0 mg; (10.0–20.0)) (P<0.001). Adverse events were reported by 39.2% of patients during the non-sunny months, while this figure decreased to 28.3% during the sunny months (P<0.001). […]Treatment discontinuation rates remained consistent across the two periods, with 1.1% of patients discontinuing oral isotretinoin during the non-sunny months and 1.2% during the sunny months (P=0.999).
		(*b*) Report category boundaries when continuous variables were categorized	NA	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9	A further study objective was to assess the therapeutic response based on the daily dosage of oral isotretinoin across the three different skin sites. The relationship between the differential daily dose and the differential Leeds scores, for each site, showed no significant association.
Discussion				
Key results	18	Summarise key results with reference to study objectives	9, 10	The most noteworthy aspect of this study, which was not specifically addressed in previous research, is its primary objective, i.e., assessing the safety of oral isotretinoin when administered during sunny seasons. The rates of adverse events observed during the sunny months were no higher than those recorded during the non-sunny periods. In fact, our experience indicates that the incidence of side effects was lower during the sunny months compared to the rest of the year.

Table S1. Adherence to the STROBE checklist for observational studies. *(continued)*

	Item No	Recommendation	Page No.	Relevant text from manuscript
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10, 11	The study results have several limitations. As a retrospective study, it did not allow for the collection of detailed information on patients' sun exposure habits, including the use of photoprotection. Given the young age of the participants, it is likely that their ultraviolet exposure was primarily recreational rather than occupational, but specific data on this were not available. Additionally, while comparing the four months with the highest UV radiation to the remaining eight months was a rational approach, it was somewhat arbitrary. The findings of this study are specific to the geographical area in which it was conducted and may not be generalizable to regions with different radiation levels. Furthermore, the subjects included were all Caucasian, while other ethnic groups were not represented.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11	Despite these limitations, this is the first study to specifically address the use of oral isotretinoin during sunny seasons, with a focus on its safety profile. The study suggests that reducing the daily dose of oral isotretinoin during the sunny months may be a reasonable strategy to minimize the occurrence of adverse events. Based on our findings, there is no evidence to support postponing the start of treatment until the fall or suspending it during the summer months. On the contrary, oral isotretinoin can be safely administered during sunny seasons to reduce acne severity, alleviate its emotional burden, and prevent scarring, which can be worsened by delaying appropriate treatment. While reducing the daily dose may help mitigate side effects during sunny months, it does not appear to compromise the drug's therapeutic effectiveness.
Generalizability	21	Discuss the generalizability (external validity) of the study results	10, 11	The findings of this study are specific to the geographical area in which it was conducted and may not be generalizable to regions with different radiation levels. Furthermore, the subjects included were all Caucasian, while other ethnic groups were not represented.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1	This was an observational study conducted without external funding.

Dermatology Practical & Conceptual

Autoantibodies against Components of Sensory Nerve Formations in the Intervertebral Disks and Adjacent Structures are Antigens Recognized by the Sera from Patients Affected by a New Variant of Endemic Pemphigus in El Bagre, Colombia

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Key words: Endemic pemphigus foliaceus, Autoantibodies, Adjacent structures, Neural receptors

Citation: Abreu Velez AM, Vélez Arango JM, Upegui-Zapata YA, Olarte Aponte AM, Autoantibodies against Components of Sensory Nerve Formations in the Intervertebral Disks and Adjacent Structures are Antigens Recognized by the Sera from Patients Affected by a New Variant of Endemic Pemphigus in El Bagre, Colombia. *Dermatol Pract Concept*. 2025;15(4):5649. DOI: https://doi.org/10.5826/dpc.1504a5649

Accepted: June 12, 2025; **Published:** October 2025

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Funding: Georgia Dermatopathology Associates, Atlanta, Georgia, USA, Mineros Colombia, Office of the major of El Bagre, Antioquia, Colombia South America, Japan International Cooperation, Colombia South America.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT: **Background:** Patients affected by a new variant of endemic pemphigus foliaceus in El Bagre, Colombia have autoantibodies directed against different proteins in the skin and internal organs. In this study we investigated autoantibodies in the intervertebral disk (IVD) and surrounding spinal structures since most patients suffer from back pain.

Methods: We tested autoreactivity using indirect immunofluorescence, reflectance, and confocal microscopy using patient autoantibodies, with both human and bovine tissue as antigen sources. We tested 45 sera from patients and 45 control sera from the endemic area matched by age, sex, demographics, and work activity. Additional mass bone density and trabecular bone score (TBS) were determined in selected cases.

Results: Most of the patient sera revealed polyclonal autoreactivity against previously known and new neural receptors present in the IVD (translamellar cross-bridges of the annulus fibrosus and the nucleus pulposus), neurovascular bundles, and paraspinal neurovascular packages as well as in the anterior and posterior longitudinal ligaments ($P<0.001$). Patient autoantibodies co-localized with commercial antibodies to MYZAP, desmoplakins I–II, plakophilin-4, and ARVCF ($P<0.001$). Controls were negative. Triton X-100 and paraformaldehyde allowed us to see the complex morphological 3-dimensional shape of the nerves and receptors. We also found that the patients showed altered microarchitecture of the lumbar spine and low trabecular density, thus suggesting osteoporosis and/or osteopenia.

Conclusions: The autoantibodies to neural receptors in the IVD and surrounding structures and the osteopenia may contribute to patient back pain. Also, El Bagre-EPF autoantibodies provide a new tool to study the complexity of these neural receptors.

Introduction

An orphan autoimmune disease (a new variant of endemic pemphigus foliaceus, EPF; denominated pemphigus Abreu-Manu, or El Bagre-EPF) is present endemically in El Bagre, Colombia and surrounding municipalities and has been documented and partially characterized earlier [1-4]. In contrast to typical EPF, which primarily affects children and young adults, El Bagre-EPF affects older males and a few post-menopausal females [5]. Clinically, El Bagre-EPF is characterized by skin lesions; consistently, the primary autoantigens are cell junction proteins like plakins, i.e., desmoplakins, envoplakin, periplakin, and plakoglobin [6]. Other studies have demonstrated that El Bagre-EPF autoantigens were not restricted to cutaneous proteins but also proteins in internal organs [2-4]. In fact, using sera from those patients, Dr. Ana Maria Abreu Velez and co-workers discovered it contains autoantibodies against proteins that form parts of cell junctions and other membrane proteins as well as intracellular and nuclear proteins.

Patients affected by El Bagre-EPF frequently report back pain in the spinal area as well as low bone mass by densitometry, suggesting the involvement of spinal joints and ligaments, intervertebral disks (IVD), and, presumably, paraspinal muscles and fascia. Supporting this view, we detected autoantibodies against cells junction proteins in the IVD as well as in their surrounding structures (manuscript submitted). Whether additional nerves supplying all these structures are altered has never been investigated. Nonetheless, a reduction in cutaneous nerve fibers and fragmentation of the subepidermal neural plexus areas in El Bagre-EPF patients have previously been reported [7].

Therefore, our present research was designed to analyze in detail whether patients with El Bagre-EPF present changes in multiple anatomic structures of the lumbar region, including the peripheral nervous system.

Materials and Methods

As an antigen source, we bought fresh bovine vertebra including the intervertebral area from two- to three-year-old cows via a local United States Department of Agriculture (USDA)-certified slaughterhouse. Additionally, we used two lower IVDs from a human adult cadaveric tissue bank. Tissues were incubated for four minutes (min) with 1X PBS and 3.5% paraformaldehyde (to allow partial fixation, including lipids). We used this method to preserve some lipid components as well as Triton X-100 to expose membranes and intracellular antigens. Slides with tissue sections were then washed twice thoroughly with PBS for 10 minutes per wash and partly permeabilized using 1X PBS combined with 0.1% Triton X-100 (for partial solubilization of cell membranes and protein complexes) and 1% normal goat serum (for blocking). For our complete methods, please see File S1, and Table 1.

Further, in El Bagre-EPF patients and the correlated controls, spine densitometry was evaluated via an osteodensitometry analysis using Prodigy DXA systems© 2024 GE HealthCare™. GE Healthcare (Chicago, Illinois, USA)

Table 1. Antibodies Used for the IIF and Confocal Microscopy Studies, their Dilutions, Catalog Numbers, and Sources. We also present the commercial antibodies that colocalize with the commercial autoantibodies.

Catalogue No.	Antibody description, dilution, and producer. Dilute all in PBS IX. Dil=Dilution		
SKU:114202	Anti-human albumin FITC, High F/P - 5-9.0, Dil 1:50, From Kent Laboratories (with sodium azide 0.1%).		
SKU 104202	Anti-human IgE FITC 1:25 Dil, Low F/P - 2-4.9, from Kent Laboratories.		
SKU:117202	Anti-human Kappa FITC, Low F/P - 2-4.9, Dil 1:50 from Kent laboratories.		
SKU:110202	Anti-human complement C-5 (B1F) FITC, Low F/P - 2-4.9, Dil 1:25, from Kent laboratories		
SKU 103202	Anti-human IgM FITC (mu chain specific), Low F/P - 2-4.9, Dil: 1:25, from Kent laboratories.		
SKU:105202	Anti-human complement C-3 (B1C/B1A) FITC, Low F/P - 2-4.9, Dil 1:25, from Kent laboratories.		
SKU:116202	Anti-human immunoglobulins (IgA, IgA, IgM) "Polyvalent" FITC, Low F/P - 2-4.9, Dil 1:25, from Kent laboratories.		
SKU:111202	Anti-human C1q FITC, Low F/P - 2-4.9, Dil 1:20, from Kent laboratories.		
SKU:101202	Anti-human IgG FITC, Low F/P - 2-4.9, Dil:1:25, from Kent laboratories.		
SKU: CON-102202	Anti-human IgA FITC, Low F/P - 2-4.9, Dil:120, from Kent laboratories.		
SKU:127202	Anti-human IgD FITC, Low F/P - 2-4.9, Dil: 120, from Kent laboratories.		
SKU: 109202	Anti-human complement C-4 (B1E) FITC, High F/P - 5-9.0, Dil: 120, from Kent laboratories.		
SKU: 107202	Anti-human fibrinogen FITC, Low F/P - 2-4.9, Dil 1:50, from Kent laboratories.		
SKU: 118242	Anti-human lambda FITC, Dil 1:25, from Kent laboratories		
GP155, Progen, Germany	Polyclonal antibody to ARCVF source guinea tested in human and bovine (100ul).	A31570, Invitrogen	Alexa fluor® 555 goat anti-guinea pig (H+L) highly cross-adsorbed from Molecular Probes Life technologies, Invitrogen, ThermoFisher.
65146 Progen	Mouse monoclonal multi-epitope cocktail to anti-desmoplakin 1 & 2, (reacts with human, bovine, dog, rat, mouse chicken) (5ml vial). Clones DP-2.15, DP2.17, DP-2.20.	Goat anti-mouse Texas red conjugated IgG (H & L).	Catalog # T-6390 from Molecular Probes Life technologies, Invitrogen, ThermoFisher Scientific.
641166 Progen	Mouse monoclonal multi-epitope cocktail to -anti-P0071 (reacts with human, bovine, murine) (5ml vial). Clones 406.3.1, 433.10.3, 7.7.9.	Goat anti-mouse Texas red conjugated IgG (H & L).	Catalog # T-6390 from Molecular Probes Life technologies, Invitrogen, ThermoFisher Scientific.
651169 Progen	Mouse Mab to Myozap. Clone 517.67	Goat anti-mouse Texas red conjugated IgG (H & L).	Catalog # T-6390 from Molecular Probes Life technologies, Invitrogen, ThermoFisher Scientific

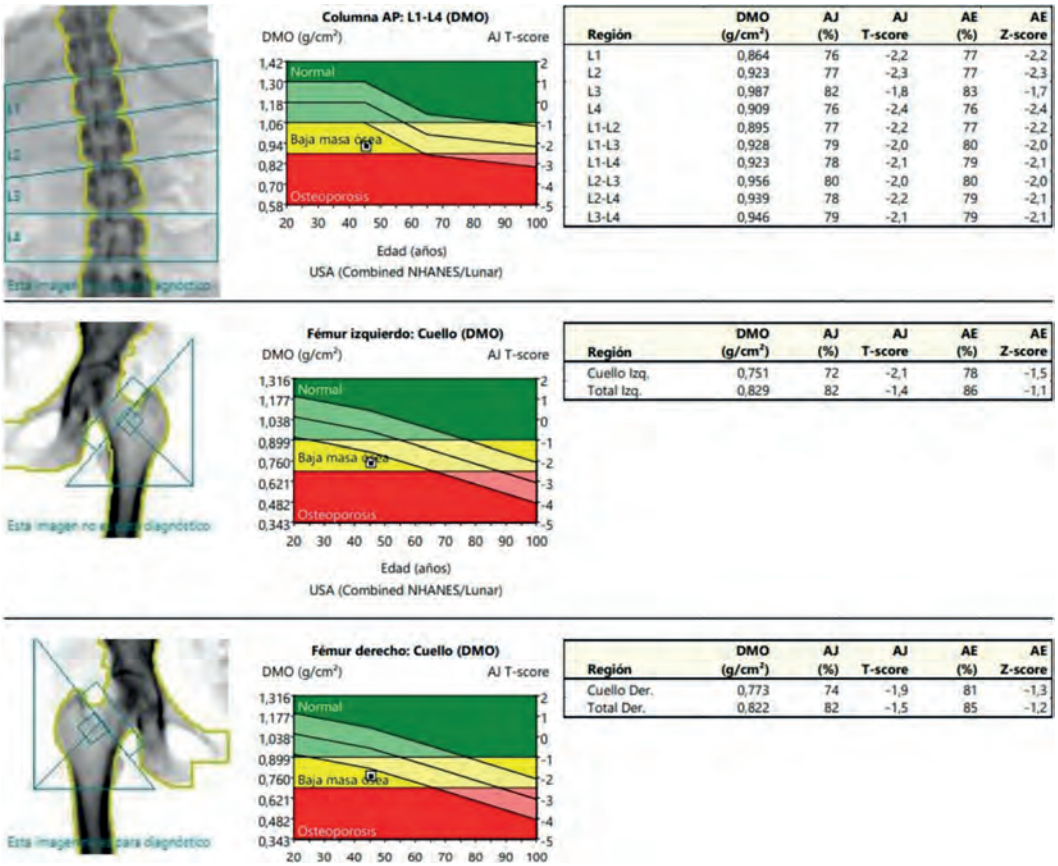
Osteodensitometry includes testing bone mineral density (BMD) to search for osteoporosis as well as an Optional Integrated Trabecular Bone Score (TBS). An Advanced Hip Assessment (FRAX)® was used to assess borderline cases. The dual absorption of X-rays were performed via General Electric Prodigy advance. We also reviewed axial slices of the spines using a Philips Brilliance *CT 16-slice* computerized tomography (CT) (CT16) scanner© Koninklijke Philips N.V.USA), with multiplanar coronal and sagittal reconstructions.

Results

The CT16 scans available in five patients and in five controls indicated no observable fracture trace in the bone window cuts. However, the presence of osteophytes (also called bone spurs) in lumbar vertebral bodies were seen in El Bagre-EPF patients and not in the controls. Furthermore, specific alterations in bone densitometry were detected at the lumbar spine scan. In L1–L4, a bone mass density (BMD) of 0.923 g/cm2, equivalent to a T-SCORE -2.1, was demonstrated. In the dual hip scan femoral neck, a BMD of 0.751 g/cm2 was equivalent to a T-SCORE. -2.1, and a Z-SCORE of -1.5. In the hip total scan, a BMD of 0.822 g/cm2 was equivalent to a T-SCORE -1.5 and a Z-SCORE of -1.2. These results indicated low bone mass by densitometry. It was suggested to rule out secondary causes via TBS: 1,228 partially deteriorated microarchitecture points (Figure 1). As far as we know, no bone change has ever been reported in Bagre-EPF patients.

In Figure 2 we summarize the results for the positivity found against multiple proteins located in the IVDs and their surrounding structures. All 45 patients affected by the El Bagre-EPF (combining the Senear-Usher-like and systemic disease forms) displayed autoantibodies against multiple proteins detected in the anterior and posterior longitudinal ligaments, in the annulus fibrosus (AF), and in the nucleus pulposus (NP). The same proteins, in variable amounts, were also detected in sensory nerve formations (SNFs) of different shapes and sizes present in the paraspinal structures and the neurovascular branches feeding and innervating these structures. The autoimmune response against all SNFs was polyclonal in nature. None of the controls from the endemic area showed positivity against these structures. Most of the SNFs identified do not correspond with typical morphotypes of SNFs reported in the IVD and paraspinal structures.

In figure 3, we show examples of multiple positive sensory nerve formations (SNFs) and the neural receptors at the fibrosus (AF) and in the nucleus pulposus (NP) as part



Región	DMO (g/cm²)	AJ (%)	AJ T-score	AE (%)	AE Z-score
L1	0,864	76	-2,2	77	-2,2
L2	0,923	77	-2,3	77	-2,3
L3	0,987	82	-1,8	83	-1,7
L4	0,909	76	-2,4	76	-2,4
L1-L2	0,895	77	-2,2	77	-2,2
L1-L3	0,928	79	-2,0	80	-2,0
L1-L4	0,923	78	-2,1	79	-2,1
L2-L3	0,956	80	-2,0	80	-2,0
L2-L4	0,939	78	-2,2	79	-2,1
L3-L4	0,946	79	-2,1	79	-2,1

Región	DMO (g/cm²)	AJ (%)	AJ T-score	AE (%)	AE Z-score
Cuello Izq.	0,751	72	-2,1	78	-1,5
Total Izq.	0,829	82	-1,4	86	-1,1

Región	DMO (g/cm²)	AJ (%)	AJ T-score	AE (%)	AE Z-score
Cuello Der.	0,773	74	-1,9	81	-1,3
Total Der.	0,822	82	-1,5	85	-1,2

Figure 1. Shown are the body mass density (BMD), the Trabecular Bone Score (TBS), and the computerized tomo graphy studies on one of the El Bagre-EPF patients.

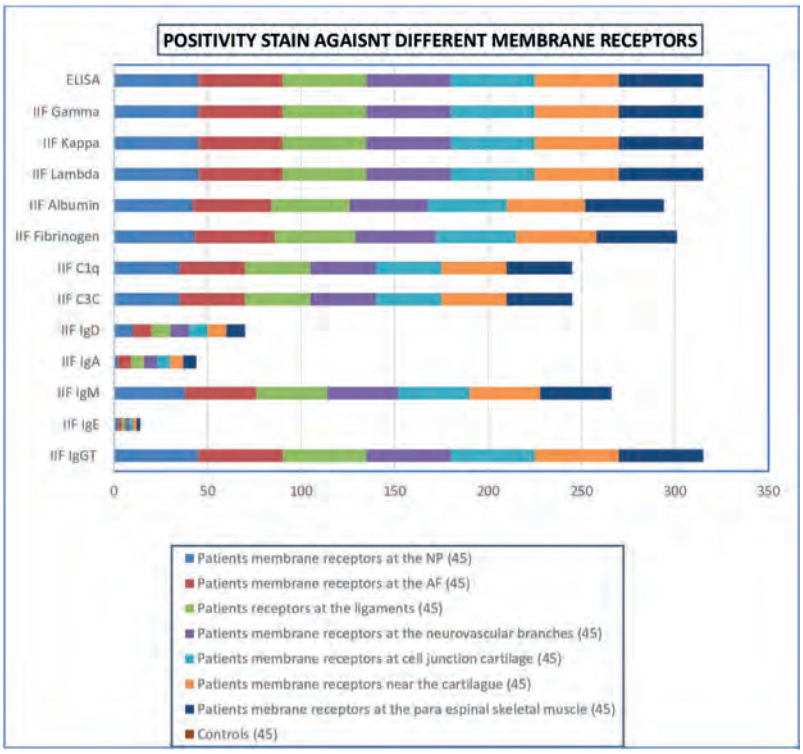


Figure 2. Summary of the results for the positivity found against multiple proteins located in the IVDs and their surrounding structures comparing patients and controls.

of the intervertebral structures. Most (43/45) of the patient sera exposed polyclonal autoreactivity with the antibodies against human (IgG, IgM, IgD, Kappa, Gamma, C3C, C1Q, and C4), (P<0.001) as well as positive with antibodies against fibrinogen and albumin against previously known and new neural receptors present in the IVD (translamellar cross-bridges of the annulus fibrosus, and the nucleus pulposus), neurovascular bundles, paraspinal neurovascular packages, and the anterior and posterior longitudinal ligaments. Controls were negative (P<0.001). In figure 4, we confirm by confocal microscopy the positivity and 100% colocalization of the patients autoantibodies with the commercial antibodies to plakophilin 4 (p0071), armadillo repeat gene deleted in the velo-cardio-facial syndrome (ARVCF), desmoplakins I and II (DP I-II), and myocardium-enriched zonula occludens-1-associated protein (MYZAP) (P<0.001). Several of the SNFs did not show the morphology of the currently documented sensory corpuscles in connective tissues, including IVD and paraspinal structures. Of interest, the neural receptors were of different forms and shapes, with some large globular structures and some smaller, and some along the myelinated fibers presenting as thinly encapsulated clusters.

Discussion

We recently demonstrated that El Bagre-EPF displays autoreactivity against proteins in tissues of the intervertebral disk (IVD) and adjacent structures with anomalies in the spine and using radiographs and magnetic resonance imaging (MRI) and the Back Pain Functional Scale (BPFS). Here we extended the focus to the cartilage of the IVD, the bodies of the lumbar vertebrae, and the paraspinal ligaments and muscles, since patients who suffer from El Bagre-EPF disease frequently report lower back pain. In the current study, lumbar osteophytes with decreased bone density were observed in some El Bagre-EPF patients relative to the controls. Whether these bone and joint alterations are a result of the El Bagre-EPF disease remains to be established, because pertinent diagnostic equipment is not available in the endemic area and thus not all the patients and controls have access to this.

In the present study, the most interesting finding was that in El Bagre-EPF patients there was great involvement of presumably afferent nerve fibers and SNFs, present both in intervertebral discs and in tissues surrounding them. We also confirmed that both the neurovascular bundles in the IVDs and surrounding structures had multiple SNFs recognized as antigenic in patients affected by El Bagre-EPF. Interestingly, these membrane receptors also perfectly colocalized with multiple commercial antibodies including DPI-I, MYZAP, p0071, and ARVCF. The MYZAP ARVCF, DP-I II, and p0071 are autoantigens detected by El Bagre-EPF patient sera, especially of those who have clinical forms resembling Senear-Usher syndrome and the systemic form that affects cell junctions throughout the body. We previously described that the patient sera contained autoantibodies against classic

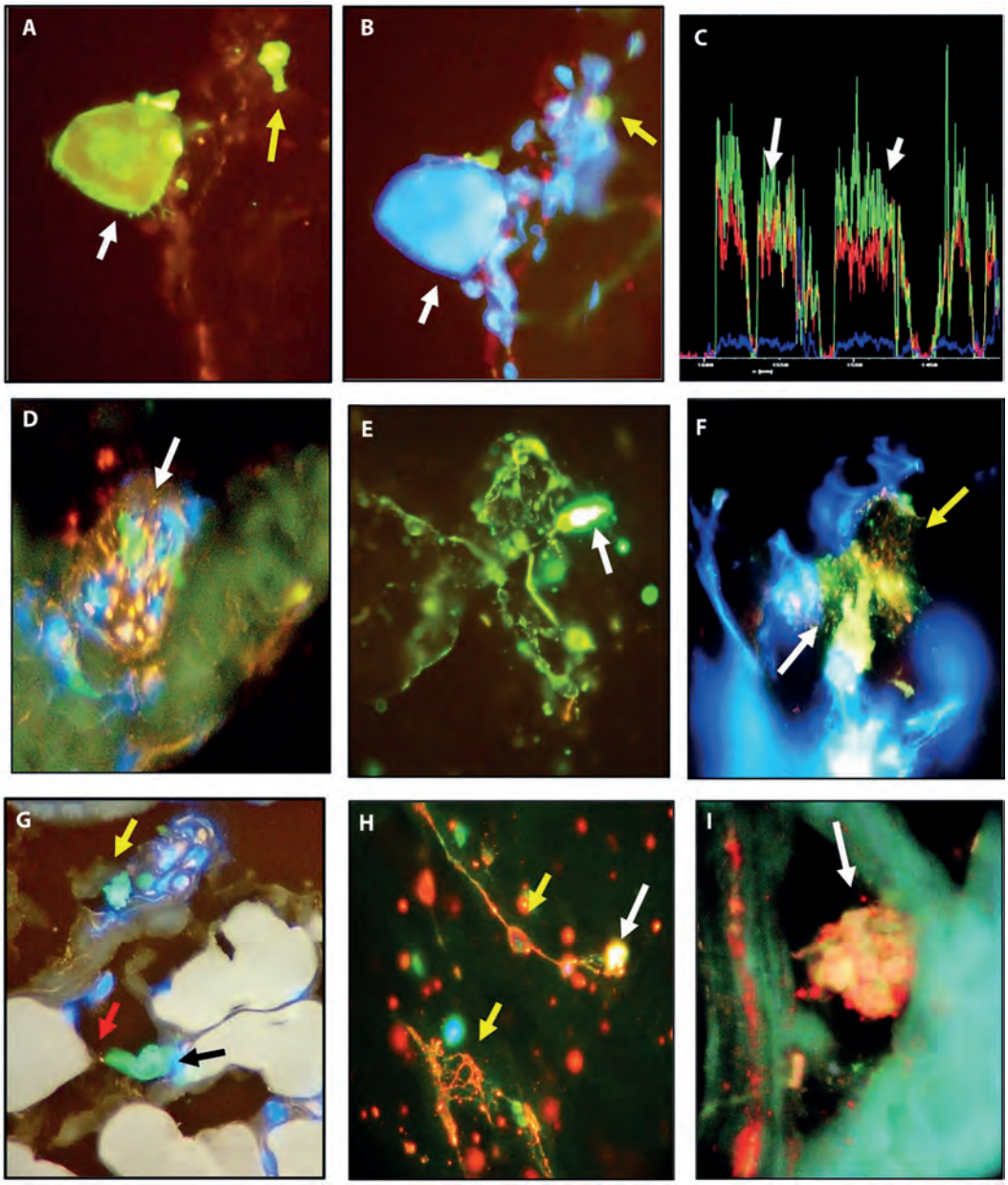


Figure 3. A through i, IIF and at 1000X. In Figures A and B, we show positive staining in SNFs. The white arrows point to large globular structures in the myelinated fibers. In A and B, we used the antibodies against FITC conjugated human complement C4 (green staining) and the antibody against desmoplakins I-II Texas red conjugated (red staining). The smaller SNFs are of unknown nature and are highlighted by yellow arrows. The nuclei of the receptors were counterstained with DAPI (blue staining). Figure 3C) Confocal microscopy (CFM) shows the perfect colocalization of the peaks detecting the antibodies (the patient antibodies in green, and desmoplakins in red; white arrows). Figures 3D to I, (also IIF). We detected reactivity against components of SNFs (white arrows). In Figure 3D, a complex SNF resembled a cauliflower with an intricate network of fine neural components; it was separated from the neighboring connective tissue by a structure lacking lamellae. In this SNF, we observed colocalization with antibodies against FITC conjugated human IgG (green staining) and the commercial antibody to MYZAP (yellowish and orange staining). These SNF was of about 350 microns in length, located at the junction of the AF connective tissue and at the paraspinous musculature. In Figures 3E and F, we also observed several SNF in which the patients autoantibodies directed to IgM FITC conjugated, perfectly colocalize with monoclonal *antibodies* against glial fibrillary acidic protein (*GFAP*) commercial antibody. In figure E, yellow arrow, and Figure F, the yellow arrow shows positive GFAP as component of this complex receptor. Figure 3 G) we show an example of two different shape SNF adjacent to a cell junction (red arrow). The receptors are shown in green, one is pointed at the black arrow, and the other with the black arrow. Figure 3F) we show examples of double SNFs that have no nuclei and were positive for anti-human FITC conjugated fibrinogen, colocalizing with the antibody against MYZAP (yellow-orange color). Figure 3H) we found net-like receptor structures (yellow arrows) using the antibodies of the patients using IgG FITC conjugated, and the commercial antibodies to GFAP. The white arrow shows a lighter receptor only reactive by GFAP. These were often seen in several areas around the IVDs; some of these SNFs resembled Meissner corpuscles. Figure 3 I, the white arrow points to a few of the SNFs that did not show the morphology of the SNFs typical of the skin.

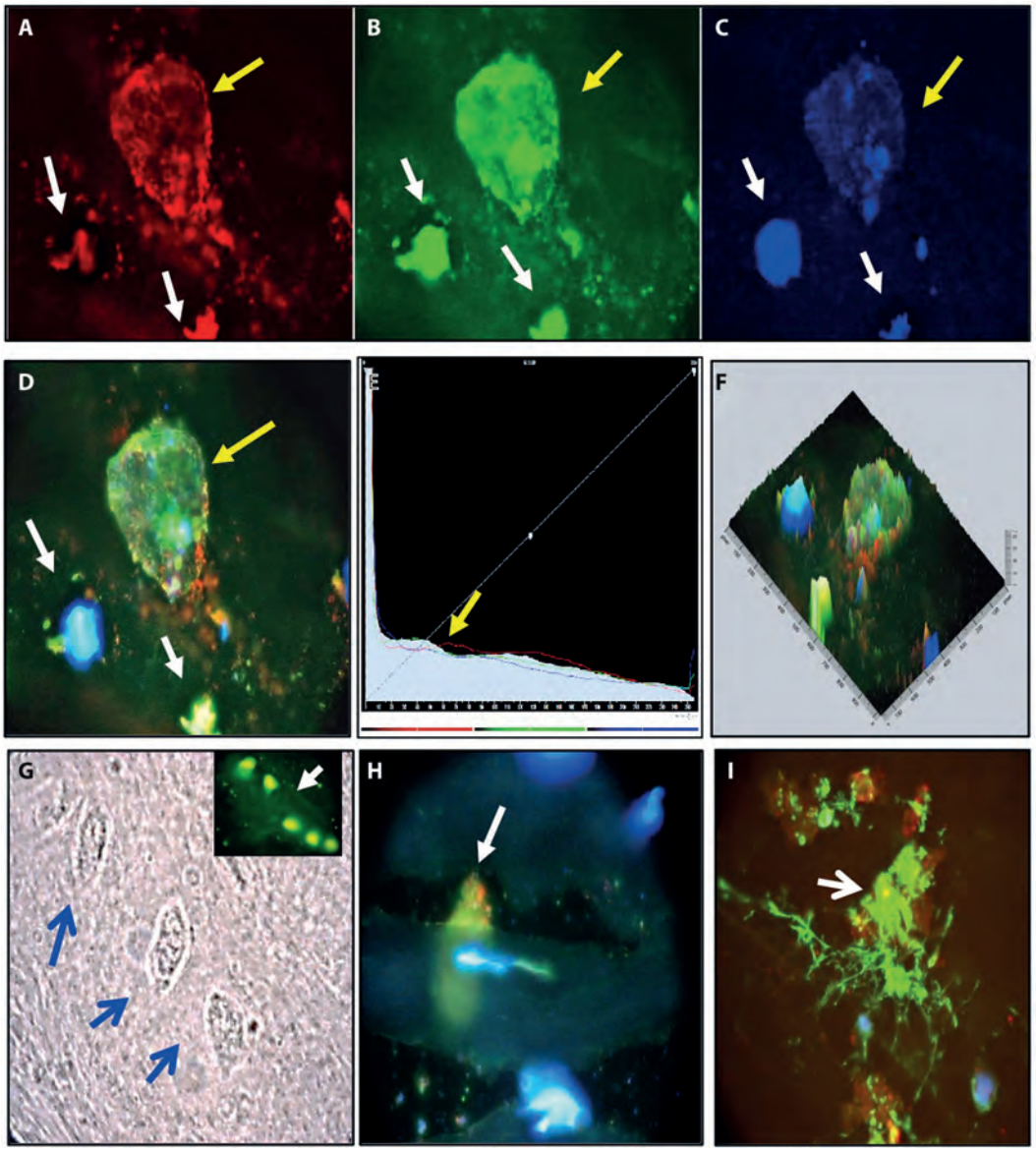


Figure 4. A-I. (All in 1000X). We observed other morphotypes of SNFs, varying considerably in size and shape. They displayed various positive areas of intricate stain inside their globular structures, differing from those documented in Figure 3. Figures 4 A, B and C show the large capsule of the larger receptors (yellow arrows), near small receptors (white arrows). The larger receptors displayed a prominent thick capsule. For Figures 4A through F, we used human FITC conjugated anti-human lambda antibodies (green staining) and a Texas red conjugated antibody against MYZAP (red staining). Both antibodies show perfect colocalization using the confocal microscopy. In Figure 4C, we demonstrate that these two types of receptors have nuclei for their positivity to DAPI (blue color). Figure 4E shows the peaks of reactivity of these antibodies perfectly colocalize (yellow arrow). Figure 4F the blue arrows shows 3D imagen demonstrating how three types of receptors being close to each other and seem to be not in the same plane suggesting a subspecialized cell signaling. Figure 4G shows a reflectance microscopy image using polarized light of three receptors of same kind of linear repetitive pattern. The IIF in Figure 4G, top right corner shows four receptors in linear pattern. Figure 4H are receptors with similar shape of Meissner receptor positive to anti human IgM antibody FITC conjugated colocalizing with the commercial antibody to p0071 Texas red conjugated. Figure 4I, using the same antibodies as in Figure 4H, we detected some clusters of SNFs with a larger receptor (white arrow) attached to a neurovascular branch of blood vessels, with at least six other SNFs of different shapes.

desmosomes, hemidesmosomes, adherent and gap junctions as well as other more complex junctions [2,7,8]. Several members of the armadillo (arm)-family of catenin proteins are part of the cell junctions in most organs of the body. These include β-catenin, plakoglobin as well as members of the p120-catenin subfamily including p120-catenin, p0071-catenin (also known as PKP4), ARVCF, δ-catenin (also known as neurojungin or neural plakophilin-related protein), and plakophilins 1-3 (frequently associated with desmosomes) [9].

Most published studies about the innervation of the IVD and adjacent ligaments in vertebrates have demonstrated that nerve fibers are found only at the periphery of the AF [10,11]. The afferent innervation of the IVD is represented

by free nerve endings and different morphotypes of SNFs, including Ruffini-like, simple lamellar corpuscles, and Pacini-like and Golgi-like corpuscles [12]. On the other hand, the paradiscal ligaments also have rich innervation.[10-13] However, most of the SNF morphotypes we identified did not correspond to the classic ones described in the skin and joints. This may be attributable, at least in part, to changes in SNFs caused by the disease itself.

An important question remains: which of the main components of SNFs are targeted by the autoantibodies of El Bagre-EPF patients? SNFs or sensory corpuscles, [14] also known collectively as end-organ structures, [14] and cutaneous end-organ complexes in the skin [16] are placed at the peripheral tip of nociceptors (as free nerve endings) or low-threshold mechanoreceptors (LTMRs) [17]. Structurally, SNFs consist of a nociceptor or LTMRs-axon close to terminal glial cells and variably arranged [15,18], with a more or less developed capsule of endoneurial-perineurial cells, all embedded in a biochemically complex extracellular matrix.[19] The proteins identified in the different components of SNFs have included structural and axoplasmic proteins, proteins for synaptic vesicles, membrane receptors for different growth factors, ion channels, intercellular adhesion proteins, and others [19, 20]. Therefore, given the complexity and variety of proteins present in SNF cells, it is very difficult to know which ones are autoantigens in El Bagre-EPF patients.

Of great interest is the concept that has been overlooked regarding communications and signals, including the neural receptors, postsynaptic communications, and other living processes that are not simply linear and, or in two planes but in multiple dimensions. This perception was indeed demonstrated that an electrostatic motif exists on the outward part of biological macromolecules as a certain structural pattern of electrostatic potentials [21]. Indeed, we have observed over and over that the antigens in El Bagre-EPF are often located in cells junctions in at least three or multidimensional planes. Therefore, as suggested by Botti SA et al. (1988), [21] we believe studying as a whole the receptors in both interfaces that are possibly linked with lipids and water. Additionally, the α/β-hydrolase fold superfamily of proteins (neural cell adhesion members) utilize their extracellular or soluble cholinesterase-like domain to attach associated partners across cell membranes, however the neuroligins can be present intracellularly [22].

Conclusion

The clinical significance of the presence of autoantigens in the sera of El Bagre-EPF patients and the possible correlation between these findings and lower back pain reported by most El Bagre-EPF patients with the systemic form remains to be clarified. We conclude that patients affected by a new variant of endemic pemphigus foliaceus in El Bagre have autoantibodies to lumbar IVDs and surrounding structures, especially SNFs. Using conformational antibodies, we were able to explore the intricate nature of these SNFs. Because these autoantibodies have multiple conformational epitopes, they thus represent an outstanding tool to be used in biotechnological and clinical applications.

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Dermatology Practical & Conceptual

Supplementary file

File S1:

Laboratory tests: We assessed 45 sera from patients with El Bagre EPF and 45 normal sera from the endemic area. The patients and controls were paired by demographics, including age, sex, nutritional status, and occupation. A human quality assurance review board approved the studies at the ESE Nuestra Senora del Carmen in Antioquia state, Colombia. The study participants signed informed consent forms, and sera was taken to be evaluated by indirect immunofluorescence (IIF). Additionally confocal microscopy (CFM) examinations were performed as previously described [2,8]. Only patients who fulfilled full diagnostic standards for El Bagre-EPF were included, as follows: i) patients displaying clinical and epidemiological features designated for this disease; ii) patients living in the endemic area; iii) patient autoantibodies presenting intercellular staining (ICS) between epidermal keratinocytes using antihuman IgG, IgM, Kappa, lambda, IgG4, Complement/C3, fibrinogen, and albumin using direct immunofluorescence studies (DIF) as well as IIF. Additional staining could be seen, including epidermal pericytoplasmic and/or dotted patterns between epidermal keratinocytes utilizing anti-human IgD, fibrinogen, and albumin antibodies. Positive staining with the antibodies was also defined as a dotted pattern along the dermal/epidermal basement membrane zone (BMZ) by either DIF or IIF as previously reported [2,8]. Likewise, positive staining could be seen in the lower part of the BMZ with the antibodies. An added polyclonal immune response could be seen in the epidermal corneal layer as well as in dermal appendageal structures as dotted ICS. Positive staining could be seen at dermal mesenchymal-endothelial cell junctions. Additional diagnostic criteria of El Bagre-EPF disease included the patient serum being positive by immunoblotting (IB) reactivity against desmoglein (Dsg) 1 as well as for envoplakin, periplakin, and BP230 plakin molecules as previously described [2,8]; v) the patient serum immunoprecipitated a Concanavalin A affinity-purified antigen, the bovine tryptic 45-kDa ectodomain portion of Dsg1; vi) the patient serum generated a positive result using an ELISA when screening for autoantibodies to El Bagre-EPF antigens and colocalization of patient autoantibodies with desmoplakins I-II, p0071, ARVCF, and MIZAP.

Indirect immunofluorescence (IIF): Our studies were performed as previously described [4–6]. Bovine tissue including intervertebral and vertebral tissue from 2– 4-year-old cattle were acquired from the abattoir within two hours of slaughter. Tangential sections were cut successively, in the plane tangential to the lamellae, from the outermost annular layer to the beginning of the nucleus pulposus pulpous (NP). Serial slices were taken at intervals of two slices (4 µm thick) as antigen sources for the IIF. These were incubated for four minutes (min) with 1X PBS and 3.5% paraformaldehyde (partial fixation). The slides were then washed twice with PBS for 10 minutes per wash, then moderately permeabilized, using 1X PBS with 0.1% Triton X-100 and 1% normal goat serum (for blocking and permeabilization) for 10 minutes under rotation, and rewashed again twice with PBS. Slides were then counterstained with 4′,6-diamidino-2 -phenylindole (DAPI) (Pierce, Rockford, Illinois, USA). For colocalization, we used commercial antibodies produced against DP-I–II (mouse monoclonal multi-epitope cocktail, Progen Cat. no. 65146) dilution 1:50, ARVCF polyclonal antibody (source guinea pig, tested in human and bovine) Cat no. GP155 (dilution 1:50); for its secondary, we used Alexa Fluor®555 goat-anti-guinea pig from Molecular Probes/Life Technologies/Thermo Fisher Scientific (Waltham, Massachusetts, USA). We also used plakophilin-4 (dil 1:50), Cat. no.651166, and a mouse monoclonal antibody for Myozap, MIZAP Cat no.651169. As a secondary antibody against DP-I–II, p0071, and Myozap, we used Texas red-conjugated goat anti-mouse IgG from Thermo Fisher. The antibodies against DP-I-II, ARVCF, p0071, and MIZAP were obtained from Progen Biotechnik in Germany. The samples were consistently run with positive and negative controls. We also used monoclonal *antibodies* specific for glial fibrillary acidic protein (*GFA*) conjugated with Alexa Fluor 594® from Thermo Fishers (Waltham, Massachusetts, United States). Two independent researchers with inter-rater reliability assessed the value of the experiments.

Confocal microscopy studies (CFM): These were performed as previously described [2,8]. Standard 20x, 40x and 100x objective lenses were used. Each frame included an area of 440 to 330 mm. Images were taken using an EZ-1 image analysis software (Nikon, Tokyo, Japan). For

colocalization experiments with the serum autoantibodies, we used the antibodies against DPI-II, ARVCF, p0071, and MIZAP.

Reflectance confocal microscopy (RCM): RCM images were acquired by means of near-infrared reflectance confocal laser scanning microscopes (Vivascope 1000s and Vivascope 1500s, Lucid Inc., Henrietta, New York), which use an 830 nm laser beam with a power of 35 mW. Each image corresponded to a horizontal section at a selected depth with an approximately 0.5 to 0.5 mm field of view, a lateral resolution of 1.0 mm and an axial resolution of 3–5 mm. A sequence of montage images ('block' images) was acquired for each lesion at the level of the IVD.

Statistical analysis: We used Fisher's exact test to assess two nominal variables (e.g., positive, and negative) of the antibody response. We recorded these data points: i) positivity of the El Bagre-EPF autoantibodies between patient cases and controls; ii) patient antibody results versus the commercial antibodies against Myozap, p0071, DP-I–II, and ARVCF. $P<0.05$ with a 95% confidence interval or more reflected statistical significance. We used the GraphPad QuickCalcs software from GraphPad Software (La Jolla, California, USA).

Dermatology Practical & Conceptual

Differential Expression of Claudin-3 and Claudin-1 in Mycosis Fungoides: Implications for Disease Monitoring

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Key words: Mycosis Fungoides, Claudin-1, Claudin-3, Disease Monitoring, Biomarker

Citation: Aktaş A, Erduran F, Tuğrul B, Eren F, Fırat Oğuz E. Differential Expression of Claudin-3 and Claudin-1 in Mycosis Fungoides: Implications for Disease Monitoring. *Dermatol Pract Concept*. 2025;15(4):5679. DOI: https://doi.org/10.5826/dpc.1504a5679

Accepted: June 28, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

ABSTRACT

Introduction: Claudins are integral transmembrane proteins that play a pivotal role in regulating tight junctions within epithelial and endothelial cells. In addition to their fundamental function in preserving cell-cell adhesion and barrier integrity, claudins are implicated in various biological processes, including those critical to cancer development and dermatological disorders. However, the role of claudin-1 and claudin-3 in mycosis fungoides (MF) pathogenesis remains unexplored and has yet to be comprehensively studied.

Objectives: This study aimed to investigate the serum levels of claudin-1 and claudin-3 in MF patients and assess their potential clinical significance as biomarkers for disease progression.

Methods: A total of 88 MF patients and 88 healthy controls were included in this case-control study. Serum claudin-1 and claudin-3 levels were measured using enzyme-linked immunosorbent assay (ELISA). Statistical analyses were performed to compare claudin levels between groups and examine correlations with disease stage and duration.

Results: Serum claudin-3 levels were significantly higher in MF patients compared to controls ($P<0.001$), while no significant difference was observed in claudin-1 levels ($P=0.448$). Additionally, a weak but statistically significant positive correlation was found between claudin-3 levels and MF stage ($r=0.219$, $P=0.041$), suggesting its potential role in disease progression. No significant correlation was observed between claudin-1 levels and MF stage.

Conclusion: Our findings indicate that elevated serum claudin-3 levels are associated with MF and correlate with disease severity, suggesting that claudin-3 may serve as a valuable biomarker for monitoring disease progression. Further research is required to elucidate its underlying mechanisms and assess its potential as a therapeutic target in MF.

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Introduction

Claudins are integral membrane proteins that play a crucial role in the formation and function of tight junctions, which are essential to maintaining the integrity of epithelial and endothelial cell layers. They regulate paracellular permeability and are involved in various cellular processes, including growth and adhesion [1-3]. In recent years, these proteins have garnered significant attention and have been implicated in a variety of diseases [1,4]. Alterations in claudin expression have been implicated also in various malignancies, influencing tumor behavior, including proliferation, invasion, and metastasis [5].

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma, characterized by the proliferation of malignant T lymphocytes in the skin. The pathogenesis of MF involves complex interactions between malignant cells and the skin microenvironment, leading to the disruption of normal skin architecture and function [6].

Among the claudin family, claudin-1 and claudin-3 have been identified as significant contributors to the structural and functional properties of the skin [1]. However, the specific roles of claudin-1 and claudin-3 in the pathogenesis of MF remain underexplored. Claudin-1 is a critical component of the skin's barrier function. Studies have shown that claudin-1-deficient mice experience significant water loss due to impaired tight junctions in the epidermis, highlighting its importance in maintaining skin integrity [7]. In the context of MF, although disruptions in skin barrier function are not directly studied, alterations in claudin expression could contribute to such barrier defects. Research on various skin cancers has demonstrated changes in claudin expression [8,9]. A previous study showed that claudins 1, 2, 3, 4, 5, and 7 exhibit distinct expression patterns in solar keratosis and cutaneous squamous cell carcinoma, supporting their involvement in the progression from premalignant to malignant lesions [10] Although MF is a distinct entity, these findings can imply that claudins may influence the behavior of skin malignancies.

Understanding the expression patterns of these proteins in MF could provide valuable insights into the mechanisms underlying the disease and may offer potential biomarkers for diagnosis and prognosis. Furthermore, monitoring serum claudin levels during treatment may provide insights into treatment efficacy and potential resistance mechanisms [4].

Objectives

Our study aimed to investigate the serum levels of claudin-1 and claudin-3 in patients with MF and to assess their potential clinical significance in the context of MF.

Methods

Ethical Approval and Study Design

Prior to the study, ethical approval was obtained from the Ankara Bilkent City Hospital Ethics Committee on 4 September 2024, under protocol number TABED 2-24-453. The study included 88 patients diagnosed with MF, and 88 age- and sex-matched healthy controls. All participants provided informed consent before the study. Data collected from patients included age, sex, disease duration, and disease stage.

Inclusion and Exclusion Criteria for the Participants

Participants aged 18 and over were included in the study. Exclusion criteria for the participants included individuals with inflammatory bowel disease, those who had experienced acute or chronic gastrointestinal infections within the three months preceding the study, individuals who had undergone any gastrointestinal surgery within the six months prior, unexplained weight loss, nonsteroidal anti-inflammatory drug use within the week before the study, individuals on a diet regimen, use of antibiotics, probiotics, or synbiotics within the three months prior, a history of malignancy, alcohol dependence, and/or chronic liver and pancreatic diseases; pregnant and breastfeeding females were also excluded.

Peripheral venous blood samples were collected after a 12-hour fasting period. After a 2-hour clotting period in serum separation tubes, samples were centrifuged at 1000×g for 20 minutes. The resulting serum aliquots were stored at –80° C until further analysis.

The concentrations of target proteins in the test samples were estimated based on previous studies [11], and an

appropriate dilution factor was selected to ensure that the diluted target protein concentrations fell within the optimal detection range of the kit. Concentrations read from the standard curve were multiplied by the dilution factor. All measurements were performed in accordance with the manufacturer's instructions.

To measure serum claudin-1 and claudin-3 levels (ng/ml), commercially available enzyme-linked immunosorbent assay (ELISA) kits from Elabscience, Texas, USA, were utilized. The kits used were:

- **Claudin-1** (Catalog No: E-EL-H0745; Lot No: WP-24FHJ89507; Detection Range: 0.16–10 ng/ml; Sensitivity: 0.09 ng/ml)
- **Claudin-3** (Catalog No: E-EL-H0754; Lot No: WP2346048679; Detection Range: 0.31–20 ng/ml; Sensitivity: 0.19 ng/ml)

Each measurement was performed in duplicate, and the average values were used for further analysis. For the aforementioned ELISA analyses, intra-assay and inter-assay coefficient of variation (CV) values were found to be below 10%.

Statistical Analysis

Data analysis was conducted using SPSS 11.5 software. Descriptive statistics for quantitative variables are reported as mean ± standard deviation and median (minimum-maximum), while qualitative variables are described by frequency (percentage). To assess the differences between two categories of a qualitative variable concerning quantitative variables, the Student's t-test was used if the normality assumption was met, and the Mann-Whitney U test was employed if normality was not assumed. To examine the relationship between two quantitative variables, the Spearman correlation test was used, as the normality assumption was not satisfied. The chi-square test was applied to assess the relationship between two qualitative variables. The statistical significance level was set at 0.05.

Results

Among the participants, 88 (50.0%) were diagnosed with MF, and 88 (50.0%) were in the control group. The average age of the patients with MF was 50.95 ± 13.98 years, whereas the average age of the control group was 52.39 ± 12.73 years. The mean age at disease onset and disease duration in MF patients were 41.97 ± 13.43 years and 8.85 ± 10.43 years, respectively. Regarding the disease stage, 38 (43.2%) patients were in stage 1A, 30 (34.1%) in stage 1B, 13 (14.8%) in stage 2A, five (5.7%) in stage 2B, one (1.1%) in stage 3A, and one (1.1%) in stage 4A. The mean claudin-1 and claudin-3 values for the participants were 13.45 ± 3.65 ng/mL and 1064.56 ± 261.71 ng/mL, respectively (Table 1).

There was no significant difference between the two groups in terms of sex and age (P=0.227 and P=0.079,

Table 1. Descriptors of Demographic Data.

Variables		Descriptive Statistics
Group, N (%)	MF	88 (50.0)
	Control	88 (50.0)
Sex, N (%)	Female	84 (47.7)
	Male	92 (52.3)
Age at disease onset (year)	Mean±SD	41.97±13.43
	Median (Min-Max)	43.00 (10.00-75.00)
Disease duration (year)	Mean±SD	8.85±10.43
	Median (Min-Max)	5.00 (0.50-78.00)
MF stage, N (%)	1A	38 (43.2)
	1B	30 (34.1)
	2A	13 (14.8)
	2B	5 (5.7)
	3A	1 (1.1)
	4A	1 (1.1)
Claudin-1 (ng/mL)	Mean±SD	13.45±3.65
	Median (Min-Max)	13.78 (4.85-23.80)
Claudin-3 (ng/mL)	Mean±SD	1064.56±261.71
	Median (Min-Max)	1037.26 (524.78-1724.92)

Abbreviations: SD: standard deviation, Min: minimum, Max: maximum, MF: Mycosis fungoide

Table 2. Comparisons of Variables between MF and Control groups.

Variables		MF	Control	p-value
Age (year)	Mean±SD	50.95±13.98	52.39±12.73	0.079[a]
	(Min-Max)	(18.00-82.00)	(30.00-83.00)	
Sex, N (%)	Female	38 (43.2)	46 (52.3)	0.227[c]
	Male	50 (56.8)	42 (47.7)	
Claudin-1 (ng/mL)	Mean±SD	13.66±3.73	13.24±3.58	0.448[a]
	Median (Min-Max)	13.77 (4.85-21,40)	13.78 (6,33.23,80)	
Claudin-3 (ng/mL)	Mean±SD	1223.45±226.09	905.67±188.65	**<0.001[b]**
	Median (Min-Max)	1202.35 (687.09-1724.92)	877.50 (524.78-1613.26)	

Abbreviations: SD: standard deviation Min: minimum, Max: maximum, a: Student's t-test b: Mann-Whitney U test c: chi-square test, MF: Mycosis fungoides.

respectively). However, a significant difference was found between the two groups regarding claudin-3 levels (P=0.079 and P<0.001, respectively). The mean claudin-3 (ng/mL) level was significantly higher in the MF group compared to the control group. Table 2 **presents the comparisons of variables between the MF and control groups.**

No significant correlation was found between MF stage and claudin-1 levels, whereas a weak but statistically significant positive correlation was observed between claudin-3 levels and MF stage (r=0.219, P=0.041). As the stage of MF increased, claudin-3 levels also increased. Table 3 **examines the relationship between claudin levels and the stage of MF.**

No significant correlation was found between claudin levels and either disease duration or disease onset age (P>0.05). Table 4 **examines the relationship between claudin levels and disease duration and disease onset age.**

Table 3. The Relationship between Claudin Levels and MF Stages.

Claudin Level		MF stage
Claudin-1 (ng/mL)	Correlation Coefficient	–0.002
	p value	0.982[a]
Claudin-3 (ng/mL)	Correlation Coefficient	0.219
	p value	**0.041[a]**

a: Spearman correlation test, MF: Mycosis fungoides

Discussion

The current study focused on evaluating serum claudin-1 and claudin-3 levels in patients with MF and their potential role as biomarkers for disease progression. Our findings demonstrate that serum claudin-3 levels were significantly elevated in the MF group compared to controls. Moreover, serum claudin-3 levels showed a positive correlation with disease stage, suggesting its involvement in the pathophysiology and progression of MF. In contrast, serum claudin-1 levels did not differ significantly between MF patients and controls, nor did it correlate with disease stage. These results suggest that claudin-3 may serve as a valuable biomarker for disease monitoring in MF, while claudin-1 appears to have limited utility in this context.

Alterations in claudin expression have been extensively documented in various malignancies. For instance, claudin-1 is one of the most widely studied claudins in cancer research, but its role as either a tumor promoter or suppressor remains controversial. In some cancers, reduced claudin-1 expression has been associated with enhanced tumor invasion and progression, whereas in others, its loss has been linked to improved patient outcomes [1,3,4,12]. In breast cancer, the expression of claudin-1 varies across pathological subtypes, with downregulation frequently associated with increased invasiveness and poor prognosis. Conversely, elevated claudin-1 expression has been observed in certain basal-like breast cancer subtypes [13]. Similarly, in esophageal squamous cell carcinoma, reduced claudin-7 expression is associated with enhanced invasiveness and metastatic potential , highlighting the complex role of claudins in cancer biology [14].

Claudin-3, primarily expressed in the epidermis and other epithelial tissues, plays a key role in regulating the permeability of tight junctions. Interestingly, both downregulation and upregulation of claudin-3 can contribute to tumor progression in a tumor-type-dependent manner [15]. In urothelial carcinomas, a strong correlation has been observed between claudin-3 upregulation and tumor grade and stage progression, aligning with findings from Nakanishi et al., who reported a link between high claudin-3 expression and advanced stage, high grade, and poor overall survival in a cohort of 129 upper urinary tract urothelial cancers [16]. In colorectal adenocarcinoma, nuclear localization of claudin-3 has been linked to tumor progression [17].

Table 4. The Relationship between Claudin Levels, Disease Duration, and Age at Disease Onset.

Claudin Level		Disease duration (year)	Disease onset - age (year)
Claudin-1 (ng/mL)	Correlation Coefficient	0.032	0.187
	p-value	0.768[a]	0.081[a]
Claudin-3 (ng/mL)	Correlation Coefficient	0.113	–0.095
	p-value	0.293[a]	0.381[a]

a: Spearman correlation test

In the context of MF, its overexpression may suggest either a compensatory response or a pathogenic factor contributing to disease progression. Elevated claudin-3 levels could enhance tumor development by strengthening cell-cell adhesion, facilitating the accumulation of malignant cells, or promoting the epithelial-to-mesenchymal transition, a crucial process in cancer metastasis [15]. We think the elevated claudin-3 expression observed in the current study may contribute to disease progression by enhancing tumor cell proliferation and invasiveness. The positive correlation between claudin-3 levels and disease stage further supports its potential role in MF advancement.

The role of claudin-3 as a biomarker extends to dermatology beyond oncology. Increased serum claudin-3 levels have been reported in psoriasis patients, indicating impaired intestinal permeability. This dysfunction suggests a potential avenue for therapeutic intervention by targeting the intestinal barrier [18]. Furthermore, claudin-1 has been evaluated as a potential biomarker in psoriasis, with reduced levels observed in specific subtypes and correlated with disease onset [19]. In another study, alterations in claudin expression were observed in chronic plaque psoriasis, with claudin-1 being absent in the epidermis of psoriatic plaques, while typical staining patterns are present in clinically normal skin [20]. These studies emphasize the diverse roles of claudins in various diseases and their potential as therapeutic targets.

To the best of our knowledge, there is a lack of studies in the current literature specifically assessing serum claudin-1 and claudin-3 levels in patients with MF or other cutaneous lymphomas. Our study contributes to this growing body of evidence by establishing a significant association between elevated serum claudin-3 levels and disease severity in MF. The findings align with prior research highlighting the involvement of tight junction proteins in cancer progression. While no significant association was identified between claudin levels and disease duration or age at onset, these findings may be influenced by the limited sample size of the study. Larger cohorts and longitudinal studies are needed to validate these results and explore the potential mechanistic pathways linking claudin-3 to MF pathogenesis.

Conclusions

In conclusion, this study provides compelling evidence that serum claudin-3 levels are significantly elevated in MF patients and correlate positively with disease stage. These findings suggest that claudin-3 may serve as a useful biomarker for assessing disease progression in MF. Further research is warranted to elucidate the precise role of claudin-3 in the pathogenesis of MF and to investigate its potential as a therapeutic target in this and other malignancies.

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Supplementary file

Table S1. Claudin-1 and Claudin-3 concentrations (ng/mL) according to Mycosis Fungoides stages.

MF STAGES	CLAUDIN-1 ng/mL	CLAUDIN-3 ng/mL	MF STAGES	CLAUDIN-1 ng/mL	CLAUDIN-3 ng/mL
1A	13.844	1133.73	1A	19.355	1334.73
1A	13.881	1126.71	1B	12.076	1206.58
2B	14.393	1724.92	1B	12.971	1208.38
3A	13.682	1547.66	2A	18.719	1347.81
1A	12.348	1571.39	1B	19.937	1131.97
1B	13.7	1040.25	1A	14.467	1081.45
1B	13.52	1410,09	1B	9.134	793.84
1A	16.534	1585.3	4A	16.416	1651.25
1A	16.2	1336.6	1B	7.79	1688.63
1A	11.524	793.84	1B	13.331	1224.6
1A	16.298	845.81	1A	11.236	1428.1
1B	12.194	1091.83	1B	10.477	1377.04
2B	18.383	1621.56	1A	5.931	1688.63
1A	14.337	1220.99	2A	9.531	1257.83
1A	18.362	1383.54	1A	11.278	1243.15
1A	15.695	1220.99	1A	11.765	1119.91
1A	21.396	863.36	1B	11.08	1313.61
1B	9.915	1161.97	2A	5.231	1543.64
1A	13.129	687.09	2A	15.321	1477.37
1B	12.059	134.,81	1B	13.928	1177.53
2A	18.93	1324.95	1A	14.898	1697.78
1B	12.692	1366.57	1A	14.826	1447.73
1A	13.917	1251.81	1B	15.566	918.5
1A	17.254	1427.26	1A	9.949	1452.66
1B	14.708	989.54	1B	6.053	1330.26
1B	12.831	1059.06	1A	7.833	1295.86
2A	8.258	1077.82	2A	11.743	1404.91
1B	20.971	1181.52	1B	17.398	1196.97
1B	13.112	1331	1B	9.705	1230.39
1A	19.291	1102.25	1B	9.178	1198.11
1A	11.474	1242.71	1B	9.627	1057.83
2B	10.069	1417.38	1A	15.236	1180.95
1A	21.396	1024.95	2B	9.685	1190.93
1A	9.885	1271.9	1A	14.374	1140.13
2A	16.812	964.51	1B	17.333	1213.06
1A	12.127	967.83	1A	15.924	885.23

Table S1 continues

Table S1. Claudin-1 and Claudin-3 concentrations (ng/mL) according to Mycosis Fungoides stages. (*continued*)

MF STAGES	CLAUDIN-1 ng/mL	CLAUDIN-3 ng/mL
1A	17.191	986.26
1B	16.615	956.41
2A	16.124	999.14
1A	10.077	1031.6
1A	4.845	949
2A	16.857	1171.84
2A	17.256	1088.4
2A	14.694	1394.55

MF STAGES	CLAUDIN-1 ng/mL	CLAUDIN-3 ng/mL
2A	17.672	1599.83
1A	12.066	1014.25
1B	15.529	1084.28
1B	13.433	1096.48
2B	12.294	1104.27
1A	8.465	1055.63
1B	15.48	1187.81
1A	19.305	1089.82

Dermatology Practical & Conceptual

Retrospective Analysis of Second Primary Malignancies in Patients with Mycosis Fungoides and Sézary Syndrome in Croatia

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Key words: Mycosis fungoides, Sézary syndrome, Primary cutaneous T-cell lymphoma, Primary malignancy, Breast cancer

Citation: Petkovic M, Ilic I, Ceovic R. Retrospective Analysis of Second Primary Malignancies in Patients with Mycosis Fungoides and Sézary Syndrome in Croatia. *Dermatol Pract Concept.* 2025;15(4):5683. DOI: https://doi.org/10.5826/dpc.1504a5683

Accepted: August 24, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Patients with mycosis fungoides (MF) have a higher risk of developing second primary malignancy. The type of second malignancy varies across the studies, and no established guidelines currently exist for screening MF patients.

Objective: To identify MF and Sézary syndrome (SS) patients at a potentially higher risk of developing a secondary primary malignancy, assess the prevalence of other secondary malignancies, and evaluate whether MF with other primary malignancies leads to a worse prognosis based on MF variants.

Methods: This observational single-center retrospective study followed 84 patients for a minimum of five years.

Results: We identified 16 patients (19%) with second malignancy, of whom eight (50%) had hematological neoplasms. Among other malignancies, breast cancer was the most common (N=5), followed by other malignancies, including lung cancer, prostate cancer, kidney cancer, and so on. The median age at disease onset was 53.0 years, while median age at second malignancy diagnosis was 60.5 years. No sex predominance was observed. Although not statistically significant, seven of sixteen patients (43.75%) who developed second malignancy had MF variant (such as folliculotropic MF) or Sezary syndrome. Disease progression was more common in patients with MF variant.

Conclusion: A higher risk for developing a second primary neoplasm was observed. However, additional cancer screening beyond routine age- and sex-appropriate examinations is not yet included in the current guidelines. Based on our findings, we recommend that MF patients undergo regular preventive screenings for the early detection of other primary malignancies.

Introduction

Primary cutaneous T-cell lymphomas (CTCL) belong to a heterogeneous group of non-Hodgkin lymphomas (NHL), primarily affecting the skin and not having extracutaneous manifestations at the time of diagnosis. NHL primarily appear in the lymph nodes, and in the case of extranodal occurrence, they most often affect the gastrointestinal system, and then the skin elsewhere. MF presents with clinical variants such as folliculotropic (FMF), pagetoid reticulosis, and granulomatous slack skin, and rare variants such as hypopigmented, hyperpigmented, ichthyosiform, palmar and plantar, poikilodermatic form, et cetera [1].

A second primary malignancy (SPM) is a new, unrelated cancer that arises in an individual with a history of cancer, separate from a recurrence or metastasis of the original disease.

Patients with MF and Sézary syndrome (SS) have a higher risk of developing other second primary malignancies, most commonly hematological cancers (non-Hodgkin lymphoma, Hodgkin lymphoma, lymphomatoid papulosis, leukemia, multiple myeloma) and solid tumors such as skin cancer, lung cancer, breast cancer, prostate cancer, kidney cancer, colorectal cancer, and bladder cancer, likely due to chronic immune dysregulation, prolonged inflammation, and prior treatments [2-8].

The objectives of our study were to identify MF and Sézary syndrome (SS) patients at a potentially higher risk of developing a secondary primary malignancy, to assess the prevalence of other secondary malignancies, and to evaluate whether MF with other primary malignancies leads to a worse prognosis based on MF variants.

Patients and Methods

This observational single-center retrospective study included patients diagnosed with CTCL at the Department of Pathology and Cytology and the Department of Dermatology and Venereology at the Clinical Hospital Centre Zagreb and University of Zagreb, a tertiary center with referral center for dermatological oncology. The diagnosis of CTCL was confirmed based on immunohistopathology analysis in conjunction with the clinical findings. All patients diagnosed with CTCL between 1 February 2003 and 31 December 2017 and followed for at least five years, were included in the study. A total of 84 patients (N=84) met the inclusion criteria and were followed up until 31 December 2022.

The following data were analyzed for MF patients: age at onset of lesions, age at diagnosis, staging at diagnosis, sex, disease progression, high-grade transformation, type of MF and MF variants, development of secondary primary malignancy, age at diagnosis of secondary primary malignancies, and development of non-melanoma skin cancer (NMSC) and melanoma. Staging of the disease was determined according to TNMB classification [9].

Statistical Analysis

The data are presented in tables and graphs. The normality of the distribution of numerical data was assessed using Smirnov-Kolmogorov test, and corresponding non-parametric statistical tests were applied based on the results. Quantitative data are presented as medians with interquartile ranges, while categorical data are reported as absolute frequencies with corresponding proportions or 95% confidence intervals (CIs). Differences in quantitative values were analyzed using the Mann-Whitney U test. Differences in categorical variables were analyzed by Fisher's exact test, or Fisher-Freeman-Halton's exact test in the case of contingency tables that were larger than the 2 x 2 format. The Kaplan-Meier curve with the associated log-rank test was used to analyze survival until disease progression. All p-values less than 0.05 were considered statistically significant. In the analysis and graphic displays, the licensed program support IBM SPSS Statistics for Windows, version 29.0.1, was used.

Results

The study included total of 84 patients: 50 males and 34 females. The majority of patients (N=48, 57.1%) had early-stage disease (IA + IB). Disease progression was observed in 19 patients (22.6%), and 14.3% of the patients had fatal outcome. Among our cohort, 33.3% (28 patients) had some of the variants of MF or SS. The MF variants of MF included nine patients with large cell transformation (eight patients had CD30+ large cell transformation, while one patient had CD30- large cell transformation), two with hypopigmented MF, three with erythroderma, six with folliculotropic MF (FMF), two with syringotropic MF, 1 with

poikilodermatous form, and one with CD4+CD8+ MF. Additionally, five patients had SS. All patient with SS had stage 4A according to TNMB classification. Disease progression was significantly more common in this subgroup (P<0.001). A significant association was found between advanced disease stages and the presence of MF or SS variants, with higher stages more prevalent in these patients (P<0.001). These patients also had a significantly shorter survival time to disease progression (P<0.001) (Table 1).

Within our cohort, 16 patients (19.0%) developed a second primary malignancy, with eight (50.0%) of these with hematological neoplasms. No case of melanoma was diagnosed; however, five patients developed NMSC during follow-up. All patients who developed NMSC had been previously treated with PUVA therapy. The most common solid organ malignancy was breast cancer (five patients). Other primary malignancies included papillary thyroid cancer, endometrial cancer, prostate cancer (two patients), sublingual squamous cell carcinoma, lung cancer, and kidney cancer, together accounting for 8% (9.52%) of study population (Table 2). Among these 16 patients, four (25%) had two or more other primary malignancies in addition to CTCL. Of these four patients, three were female, and all three had breast cancer as one of the other primary malignancies. One patient had MF, breast cancer, and endometrial cancer. The second patient had SS, breast cancer, and squamous cell sublingual cancer. The third patient had MF, breast cancer, papillary thyroid cancer, and monoclonal gammopathy of

Table 1. Average Survival to Progression according to the Specific Form of MF or SS. Patients with specific form of MF or SS had a significantly shorter survival to progression (P<0.001).

	Median survival to progression			
			95% CI	
Variant of MF or SS	Time (months)	Standard error	Lower	Upper
No	47.81	2.25	43.40	52.23
Yes	7.46	1.39	4.74	10.18
Total	34.09	3.89	26.47	41.71

Table 2. Type of Second Primary Malignancy.

Second primary malignancy		N=16 (19%)
Hematologic neoplasms		N=8 (50%)
Chronic lymphatic leukemia (N=2) Hodgkin lymphoma B-cell large cell NHL Tonsillar NHL Monoclonal gammopathy MGUS (Monoclonal gammopathy of undetermined significance) SMM (Smoldering, multiple myeloma)		
Non-hematologic neoplasms		N=8 (50%)
Breast cancer (N=5) Prostate cancer (N=2) Kidney cancer (N=2) Thyroid papillary cancer Endometrial cancer Sublingual squamous-cell cancer Lung cancer		
Non-melanoma skin cancer		N=5 (5.95%)
BCC (N=4) SCC		
Melanoma		None

undetermined significance (MGUS). The only male subject in this subgroup, in addition to MF, had chronic lymphocytic leukemia (CLL) and kidney cancer. Of these 16 patients who developed a second primary malignancy, seven (43.75%) had an MF variant. Among these seven patients, five (31.25%) experienced disease progression, although these findings were not statistically significant (Table 3).

In the group of patients who developed second primary malignancy, the distribution by sex was the same: 50% were female (N=8) and 50% were male (N=8). The median age at onset of CTCL was 53.0 years (interquartile range, 40.5–62.8 years), and the median time to diagnosis was 3.0 years (interquartile range ,1.0-10.0 years). The median age at diagnosis of the second malignancy was 60.5 years. In this cohort, CTCL preceded the appearance of the second primary cancer, with an average time of 7.5 years between the two diagnoses (Table 4).

Discussion

Our study supports the evidence of an increased risk of second primary malignancies in patients with MF. We examined the percentage of patients who developed a second primary malignancy, considering that previous literature has reported an increased incidence of a second primary malignancy in patients with CTCL [2-8,10-13]. In our cohort of 84 patients 19% (N=16) developed another primary malignant disease.

Among these second primary malignancies, hematological neoplasm were the most frequent, occurring in 50% (N=8) of patients, which is in concordance to previous

Table 3. Differences in Categorical Clinical Indicators in relation to the Specificity of the Disease.

		MF variant or SS				
		No		Yes		
		N=55		N=28		
		N	%	N	%	p-value
Sex	Male	34	61.80%	16	55.20%	0.642
	Female	22	38.20%	12	44.80%	
Stage*	IA	18	21.40%	0	0.00%	<0.001
	IB	25	29.8%	5	5.96%	
	IIA	2	2.40%	1	1.19%	
	IIB	6	7.14%	12	14.29%	
	IIIA	0	0.00%	4	14.80%	
	IIIB	0	0.00%	1	1.19%	
	IVA	1	1.19%	5	18.50%	
	IVB	0	0.00%	0	0.00%	
Second primary malignancy	No	47	83.93%	21	75.0%	0.158
	Yes	9	16.07%	7	25.0%	
Hematological neoplasms	No	52	92.86%	24	85.7%	0.118
	Yes	4	7.14%	4	14.3%	
Breast cancer	No	52	94.5%	27	93.1%	1.000
	Yes	3	5.5%	2	6.9%	
Other non-hematological malignancies	No	48	87.3%	28	96.6%	0.253
	Yes	7	12.7%	1	3.4%	
Folliculotropic MF	No	55	100.0%	23	79.3%	0.001
	Yes	0	0.0%	6	20.7%	

Table 4. Descriptive Statistics of Sociodemographic Values.

	N	Min	Max	Centile		
				25.	Median	75.
The median age at the onset of disease	80	8.00	83.00	40.50	53.00	62.75
Median time to diagnosis CTCL	71	1.00	51.00	1.00	3.00	10.00
The median age at the second primary malignancy	16	34.00	82.00	52.25	60.50	70.50

studies [2-4,8,10,12-14]. The most common solid organ cancer was female breast cancer, observed in 31.25% (N=5) of the cases. The types of second primary malignancies varied across studies. According to the meta-analysis and systematic review by Goyal et al. [7] in 2021, which included 12 studies and 11,214 patients with MF and CTCL, 8.5% developed a second primary malignant disease. In that cohort, the most common second primary malignancies were non-Hodgkin lymphoma (NHL) 20%, Hodgkin lymphoma (HL) 17.8%, lung cancer 15.1%, bladder cancer 8.3%, breast cancer 6.5%, melanoma 3.2%, and kidney cancer 2.9% [7]. Contrary to these findings, Brownel et al. did not find an increased incidence of lung, colon, urinary tract, melanoma, or biliary system cancer development [4]. The type of second primary malignant disease differed in the studied groups of patients, and some study groups (like ours) report no melanoma case [2,6,8]. In contrast, there are studies that identified melanoma as a frequent secondary malignancy (Goyal et al. excluded melanoma in situ in their study) [3,11,15].

Our study did not find any sex predominance, in contrast to previous studies, which reported a higher incidence in males, with a male-to-female ratio ranging from 1.2:1 to 2.9:1, according to the systematic review and meta-analysis by Goyal et al. [7]. The average age at CTCL diagnosis was between 44.6 and 68.0 years, and the median age at diagnosis of second primary malignancy was 3.29 years after CTCL diagnosis (ranging from 2.1 to 5.4 years). In our study, the interval between CTCL diagnosis and second malignancy was longer. However, unlike some studies, we did not exclude patients whose second malignancy preceded their CTCL diagnosis. The age at onset of CTCL and other primary malignant diseases has differed in the studies published so far. The median age at diagnosis of second primary malignant disease in our cohort was 60.5 years, and the average time from CTCL diagnosis to the development of another primary malignancy was 6 years (median: 54.5 years). Our study found a higher percentage other primary malignancies compared to previously published reports [2-6,8,11-15]. We believe that this may be due to the study design. Some studies excluded patients who developed a second malignancy before or within the first year of CTCL diagnosis, likely to assess potential treatment-related factors (3,4,8). However, we believe that studies designed in that way may not provide the prevalence of other primary malignant diseases in CTCL patients. Our result of 19.5% of patients with a second primary malignancy is comparable to the 20.2% reported by Macagno et al. [11], a study that similarly did not exclude cases in which the second malignancy preceded CTCL. According to that study, 39.5% of patients had NMSC, and 28.9% had MM. In contrast, in our study, there was no case of melanoma, and five cases of NMSC (5.95%). The patients who developed NMSC in our study were treated with PUVA therapy. We also considered an MF variant as a potential risk factor for developing second primary malignancies. Although statistical significance was not reached, 43.75% (7/16) patients who developed another malignancy had MF variant or SS. In our study group, patients with FMF more often had disease progression, consistent with the findings of Agar et al. [16]. Their study demonstrated that FMF is associated with an increased risk of disease progression, and multivariate analysis identified advanced skin stage (T), the presence of tumor clone without Sézary cells in peripheral blood (B0), elevated LDH levels, and FMF as independent predictors of poor survival and increased risk of disease progression. Furthermore, large cell transformation and tumor distribution were independent predictors of disease progression [16].

Conclusion

We believe that further research is needed to explore the relationship between primary cutaneous lymphomas and other primary malignancies. Even though the association between CTCL and other primary malignancies was proven more than 40 years ago, possible risk factors for their development have still not been discovered. The hypothesis of a single causative factor for the development of both neoplasms is less likely due to the heterogeneity of the second primary malignancies in relation to CTCL. Several previous studies excluded patients with a second primary malignancy preceding CTCL to determine whether the type of treatment affected the development of a second primary malignancy, but the heterogeneity of other primary cancers makes this unlikely. It is more likely that the cause is a tumorigenic microenvironment and an altered immune response that led to the development of the first neoplasm. In our study, as in most previous studies, a higher risk of developing a second primary neoplasm was demonstrated, but additional tests for early detection of cancer beyond routine age- and sex-appropriate examinations are still not part of the guidelines. Regular check-ups and a multidisciplinary approach are necessary. Based on this study, we conclude that patients with CTCL should regularly undergo preventive examinations for the purpose of early detection of other primary malignant diseases.

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Dermatology Practical & Conceptual

Pigment Network Analysis in Melanoma and Nevi: Retrospective Study from Snippets to Full Dermoscopic Images

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Key words: Pigment network (typical/atypical), Snippet, Melanoma, Visual context

Citation: Kremer N, Dana IN, Chousakos E, et al. Pigment Network Analysis in Melanoma and Nevi: Retrospective Study from Snippets to Full Dermoscopic Images. *Dermatol Pract Concept*. 2025;15(4):5700. DOI: https://doi.org/10.5826/dpc.1504a5700

Accepted: April 28, 2025; **Published:** October 2025

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Funding: Supported in part by the National Institutes of Health/National Cancer Institute Cancer Center Support Grant P30 CA008748. The funder played no role in any aspect of the study.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Atypical network is a dermoscopic criterion that helps in the diagnosis of melanoma. Despite its importance, the interpretation of atypical networks varies widely among experts.

Objective: This study examined the impact of viewing the whole lesion versus viewing foci of pigment network (i.e., snippets) in isolation from within the lesion on expert classification of pigment network in dermoscopic images.

Method: Six dermoscopy experts, blinded to the diagnosis, each evaluated a total of 92 images (80 nevi and 12 melanomas) for the presence of typical versus atypical pigment network. While 57% of images had consistent classification of the network between whole lesion and snippets, 43% shifted the network classification between the snippet to the whole lesion view. Melanomas were more prone than nevi to intra-rater discrepancy between whole lesion and snippets (54.2% vs. 41.7%; odds ratio (OR): 1.65; 95% confidence interval (CI): 1.11–2.47). The inter-observer agreement was higher for the snippet view (65.22%) than for the whole lesion view (55%).

Results: These findings suggest that both the objective morphology of the pigment network and the subjective interpretation of the network in context with other features within the lesion influence expert classification of pigment network.

Conclusion: Factors such as the variability in the distribution, thickness, and color of network lines, overall pattern, and other dermoscopic structures likely contributed to the classification changes.

Introduction

Atypical network is a dermoscopic criterion that helps in the diagnosis of melanoma[1]. The definition of an atypical network, according to the 2003 Internet Consensus Meeting [2] and the 2007 International Dermoscopy Society (IDS) consensus meeting [3], is "a black, brown, or gray pigment network with irregular holes and thick lines." Over time, this definition evolved from focusing primarily on the variability in color and line thickness to include the degree of symmetry in its distribution, leading to the 2016 IDS consensus meeting [4] definition of an atypical pigment network as "one with increased variability in the color, thickness, and spacing of the lines; asymmetrically distributed; gray color". However, since 2016, there remains a low-to-moderate agreement regarding the classification of atypical networks. Lallas et al. [5] reported that the inter-observer agreement for atypical network was low, with a kappa value of 0.39. In a more recent study conducted by Liopyris et al. [6], including dermoscopy experts, almost perfect agreement was achieved for the presence/absence of network in lesions, but there was variable agreement on the type and localization of the network within the lesion.

Observations regarding dermoscopic criteria for melanoma diagnosis emphasize the importance of evaluating the number of colors, structures, and their distribution rather than focusing solely on specific structures such as network in isolation [1,7-9]. Consequently, interpreting pigmented network as typical or atypical is likely influenced not only by its objective morphology but also influenced by the subjective visual context based on the presence or absence of other structures and colors within the lesion [10].

Objectives

The primary objective of this study was to examine the impact of viewing the whole lesion versus viewing foci of pigment network (i.e., snippets) in isolation from within the lesion on expert classification of pigment network in dermoscopic images. The secondary objectives included examining inter-observer agreement regarding the classification of the pigment network and assessing whether expert reviewers' definitions of an atypical pigment network align with the current definition outlined in the literature [4].

Methods

This retrospective observational study was performed between November 2022 and August 2024. The study was approved by the Institutional Review Board (IRB) under approval number 16-458.

Image Selection, Network Annotation, and Generation of Circular Pigment Network Foci

Dermoscopic images of melanomas and nevi captured between 2002 and 2019 displaying a discernible pigment network were selected from a clinical database at Memorial Sloan Kettering Cancer Center (MSKCC) and from the ISIC Archive (https://www.isic-archive.com/). An expert dermoscopist (A.A.M) annotated the boundaries of network regions within each image, which were stored as binary mask images[11]. Pixels belonging to contiguous areas of the network were marked in white, while all other pixels were marked in black (Figure 1). Circular snippets were then extracted from these annotated regions using a Euclidean distance transform [12], ensuring that the snippets were centered within the network areas. The largest possible circular snippets were then automatically extracted from the network-patterned areas (Figure 2). To ensure that the snippets were informative enough for readers to determine the type of network, snippets with fewer than 10 holes were excluded from the dataset. The total number of snippets generated in this manner was 141, ranging from one to seven per lesion image. Most images

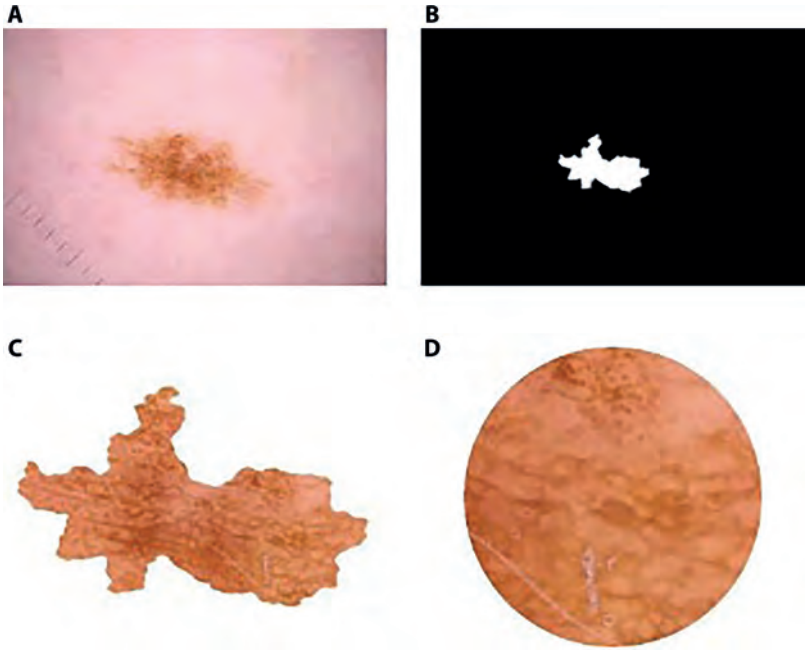


Figure 1. Creating Snippet. a. An expert dermoscopist (A.A.M) annotated the images to identify the regions of predominant pigment network. b. From these annotations, binary masks were created. c. The area of pigmented network extracted from the original whole dimension dermoscopy image. Euclidean-distance transform was applied to the binary masks. d. From the transformed images, circular areas were extracted.

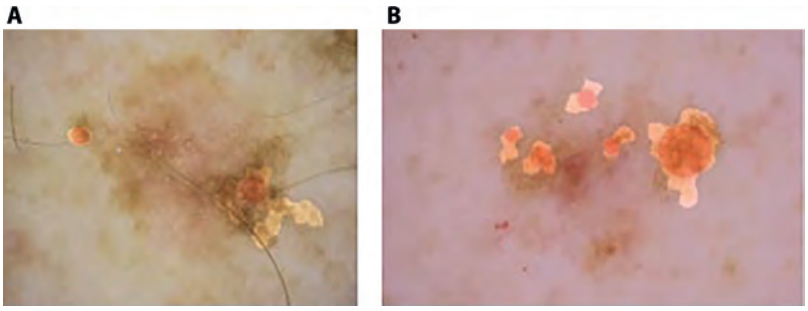


Figure 2. The largest possible circular cutouts were extracted from the network-patterned areas. (a) Melanoma with two circular areas. (b) Nevus with five circular areas. Two circles with fewer than 10 holes were excluded, and only 3 circles were shown to the six experts.

(60 out of 92) yielded a single circular snippet. The average number of snippets did not differ significantly between nevi and melanomas (approximately 1.5 per lesion).

Web-Based Data Collection Instrument

Six dermoscopy experts participated in the study, completing a web-based intake form with three modules. In the Preliminary Module, each participant provided his/her definition of an atypical network. In the Network Foci Module (Snippet), circular snippets from the same lesion were presented to each reader simultaneously, and readers classified the network as typical, atypical, or both (typical and atypical). In the Whole Image Module, whole dermoscopic images were shown, and readers classified the network in the image as either typical, atypical or both.

In each module, the cases were presented in a random order without diagnostic or demographic information. This random order was consistent for all readers to ensure uniformity in response (Figure S1). The same set of lesions was presented as cases in both the Network Foci Module and Whole Image Module.

Eligibility Criteria

Inclusion Criteria: melanocytic lesions with a discernible and in-focus pigment network visible on the dermoscopic images.

Exclusion Criteria: low-quality dermoscopic images and non-melanocytic lesions with a pigment network.

Statistical Analysis

The snippet and whole-image modules were independently assessed for network classification frequencies and inter-rater agreement, which was measured as percent agreement, Scott's/Fleiss' kappa, and Gwet's AC. Ninety-five percent confidence intervals (95% CI) were estimated.

Responses from snippet and whole-image modules were pooled to analyze intra-rater network classification consistency. Network classifications of a given lesion between the two modules by the same rater were viewed as a paired response and analyzed using confusion matrices and sankey diagrams. A binary variable indicated whether the rater's classification of a given lesion differed between the two modules. The relationship between network classification consistency and lesion type (nevus or melanoma) was analyzed using logistic regression and chi-square statistics.

Data management and analysis were performed using StataMP v16.1, StataCorp, and RStudio Build 524.

Results

Six dermoscopy experts, blinded to the diagnosis, each assessed 92 melanocytic neoplasms displaying network within the lesion, including 12 melanomas and 80 nevi. Across both snippet and whole-image modules, 1,104 observations were collected, resulting in 552 paired responses (72 of melanoma and 480 of nevi). All melanomas were confirmed as in situ by histopathology and 65% of the nevi were diagnosed as dysplastic nevi through histopathology, while the remaining 35% presented with benign and stable morphology during consecutive dermoscopic follow-up.

Classifications of Pigment Network by Image Type

The proportions of typical and atypical pigment network classifications were similar between snippets and whole lesion images (Table S1). Fifty-seven percent (N=315) of paired responses maintained consistent network classification across snippet and whole dermoscopic image evaluation (Figure 3). Of these, a slightly higher proportion of snippets were classified as typical networks (28%, N=153) compared to those classified as atypical networks (25%, N=139).

Forty-three percent (N=237) of paired responses shifted in network classification from the snippet to a whole image (Figure 3). A slightly higher proportion of snippets changed from typical network to atypical network in the whole lesion images, observed in 14% (N=77), compared to 10% (N=57) of snippets classified as atypical shifting to typical in the whole lesion images (Figures 3 and 4, sankey diagram).

Classifications of Pigment Network by Lesion Diagnosis

Of nevi, 58.3% (N=280) of paired responses maintained the same network classification from snippet to whole dermoscopic images (Table 1), with the majority (31.5%, N=151) classified as having a typical network, 22.9% (N=110) as atypical network, and 4% (N=19) as both types of networks (Figure 5A). Of the 41.7% (N=200) that underwent

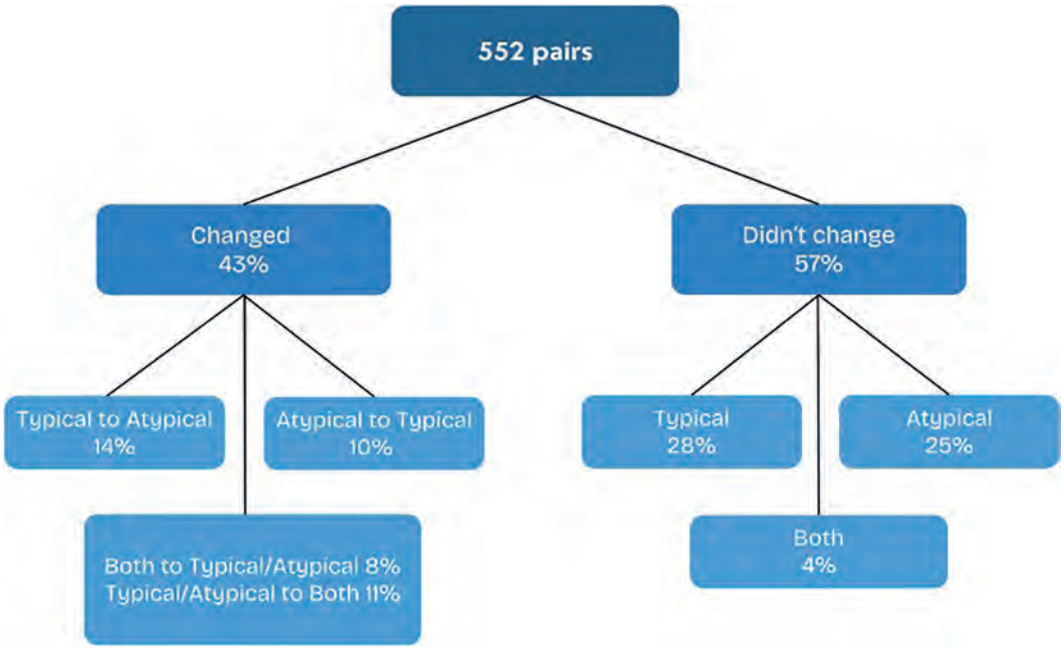


Figure 3. Chart of the relative frequency (%) of evaluations for the snippet and the whole dermoscopic image.



Figure 4. Sankey diagram depicting flow of pairs of lesion observations from snippet to whole dermoscopic image evaluation of the lesions.

Table 1. Distribution of Classification Flux Between Snippet and Whole Dermoscopic Image Observations Stratified by Lesion Diagnosis.

		Overall (n=552)		Lesion Diagnosis			
				Nevi (n=480)		Melanoma (n=72)	
		n	proportion	n	proportion	n	proportion
Classification from snippet to whole image	Same	313	56.7%	280	58.3%	33	45.8%
	Changed	239	43.3%	200	41.7%	39	54.2%

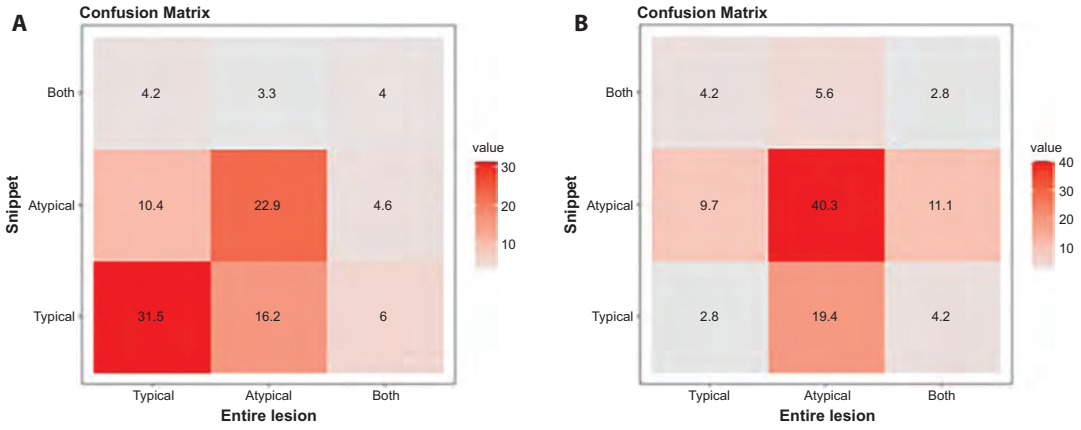


Figure 5. Confusion matrix of the relative frequency (%) of evaluations for the snippet and the whole dermoscopic image for nevi (a) and melanoma (b).

a change, there was a slightly higher shift from a typical network to an atypical network, observed in 16.2% (N=63) of paired responses, compared to a 10.4% (N=50) shift from atypical to typical.

In melanoma, 45.8% (N=33) of paired responses maintained the same network classification (Table 1). Among these, 40.3% (N=29) were identified as having an atypical network (Figure 5B), while only 5.6% (N=4) were classified as either typical network or both types of networks. Of the 54.2% (N=39) that had a change in network classification, the most notable shift was from a typical network to an atypical network, occurring in 19.4% (N=14) of cases, compared to 9.7% (N=7) that shifted from an atypical to a typical network. Paired responses involving melanomas were more likely than those of nevi to have inconsistent network classification, with an odds ratio (OR) of 1.65 (95% CI: 1.11–2.47). Additionally, the classification in melanomas shifted to having both network types slightly more frequently

Table 2. Breakdown of Atypical Network Features According to 6 Experts' Definitions.

	Expert 1	Expert 2	Expert 3	Expert 4	Expert 5	Expert 6
Network / line thickness	+	+	+	+	+	
Network / line color		+	+	+	+	+
Network / line distribution		+		+		+
Network / lines shape	+	+				
Holes diameter / lines spacing			+	+		
Gray color						
Other			Deviation from the expected appearance.		More than 1 different networks in the same lesion.	Negative network, pseudopods, heavily pigmented dots and globules, veiling.

than that of nevi, with 15.3% (N=11) changing to having both network types compared to 10.6% (N=51) of paired responses involving nevi (Figure 5A-B).

Classifications of Pigmented Network by the Experts

The definitions of an atypical network provided by the six experts were different from the definition established at the 2016 IDS consensus meeting[4]. All six experts' definitions for atypical networks are detailed in Table S2. Five out of six experts include thickness, 5/6 color, 3/6 distribution, 2/6 shape, and 2/6 spacing of the lines (Table 2). None of the experts mentioned gray color, which was included in the 2016 IDS consensus meeting[4]. However, one expert included in his definition also negative network, dots, globules, and pseudopod, and another expert defined it as any network that deviates from the benign expected nevus pattern.

There were clear differences in the experts' classification of the pigment network, with some experts showing more discrepancies than others between the snippet and the whole dermoscopic image (Figure S2). The snippets showed better inter-observer agreement compared to whole lesion images across all three measures, with moderate agreement (65.2%) for the snippets and low-moderate agreement for the whole lesion images (55%); Gwet's AC was 0.51 for snippets versus 0.35 for whole lesion images; Scott/Fleiss' kappa was 0.41 for snippets versus 0.27 for whole lesion images (Table S3).

Discussion

This study investigated the classification of pigment network across snippets and whole lesion dermoscopic images of 80 nevi and 12 melanomas. Our findings reveal that a significant portion of paired responses (43.3%) had inconsistent classification between snippets and whole lesion images across the six experts, with variations observed associated with the lesion type, nevus, or melanoma.

Network classification inconsistencies were more common in melanomas, with an OR of 1.65. Conditioned on paired responses with network classified "typical" in snippet-view, 73% involving melanomas were classified "atypical" in whole-image view as compared to 30% involving nevi. This suggests that visual context plays an important role in interpreting the network as atypical in melanoma compared to nevi. Several factors in the visual context may influence the expert's classification of the network as atypical:

1. Network's distribution – Observing the distribution of the entire network can alter the classification especially if it is asymmetrically located at the periphery or the line thickness and color are unevenly distributed across the lesion[13], as demonstrated in Figure 6a.
2. Additional Dermoscopic Structures: Other dermoscopic structures[14], beyond atypical networks, which are correlated with atypia/melanoma can serve as diagnostic anchors that influence experts' interpretation of the network as atypical. Examples of such structures are illustrated in Figure 6b.
3. Overall Architectural Organization or Heuristic Method ('Blink' Approach): In melanoma, dermoscopic structures and colors are often distributed in a disorganized manner, resulting in a chaotic appearance within the lesion[7]. Experts frequently employ the heuristic method,

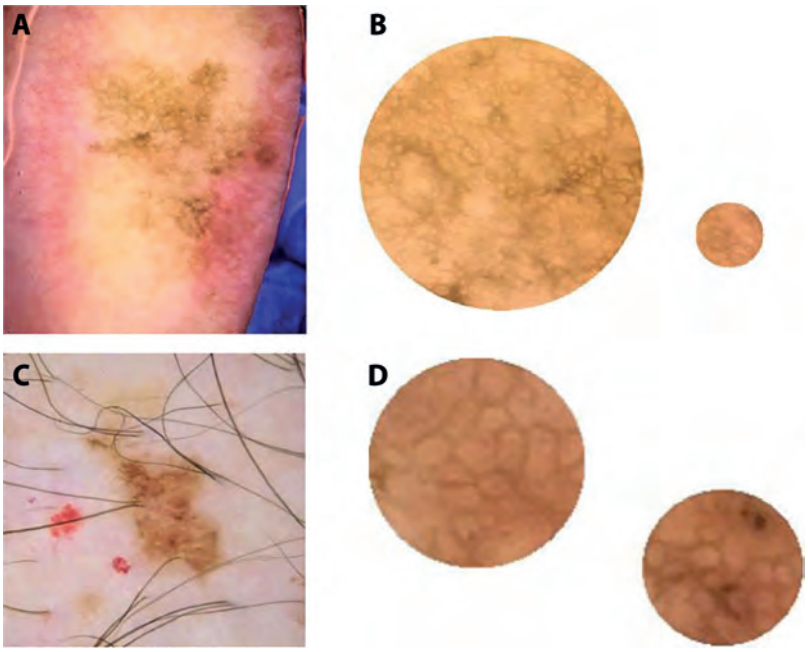


Figure 6. Melanoma in (A) and (C): lower snippet, upper whole image. (A) Classification changed from typical to atypical for 4 readers with asymmetric distribution of the network line thickness and color in the whole lesion image. (C) The streaks (peripheral radial lines) in the upper left quarter could explain why 3 out of 6 experts changed their classification from typical to atypical.

which involves recognizing the overall dermoscopic pattern of a lesion and relying on intuition or a "gut feeling"[15]. Evaluation of the whole dermoscopic image can change the expert's classification from typical to atypical network due to the disorganized context or "gestalt", rather than simply relying on the morphology of the network itself.

Because many melanomas exhibited a combination of asymmetric network distribution, other melanoma specific dermoscopic features, and overall architectural disorganization as illustrated in Figure 7a-b, it is not possible to pinpoint which specific factor in the visual context influenced the experts' change in network classification. Additionally, individual expert interpretations, which rely on different contextual elements based on their definitions of an atypical network, likely contributed to the change in network classification[16]. However, this shift in classification of networks emphasizes the importance of the entire dermoscopic lesion assessment, as the context provided by the whole image impacts the classification of network beyond just the morphology of the network as viewed in the snippets.

Unlike melanoma, which exhibits greater architectural complexity, nevi tend to be more symmetric and organized[13] (Figure S2). Since all nevi included in the study were required to have a reticular network, and because the primary morphological feature in our nevi likely had a

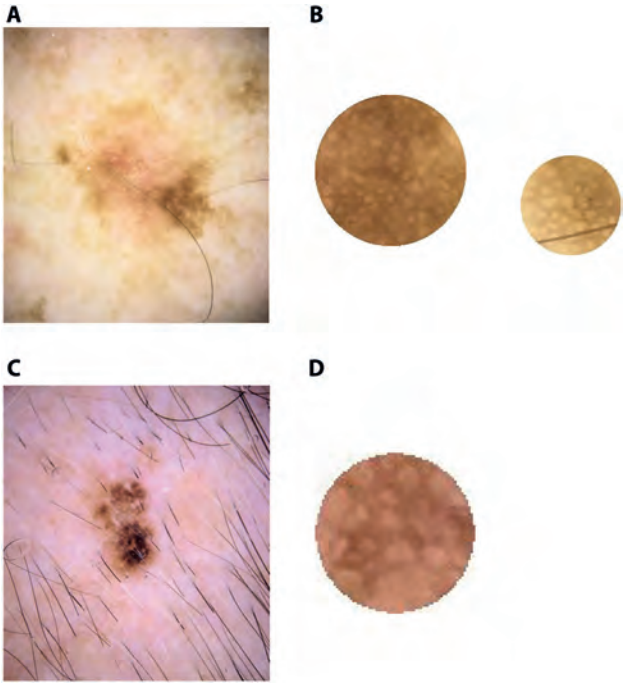


Figure 7. Melanoma in (A) and (C): lower snippet, upper whole image. (A) Melanoma with disorganization in colors and structures, shiny white lines (chrysalis), pink structureless areas and red dots in addition to atypical network unevenly distributed. Classification changed from typical to atypical for 3 readers (C) Melanoma with disorganization in colors and structures, linear angulated lines (polygons) and black blotch in addition to atypical network unevenly distributed. Classification changed from typical to atypical for 4 readers.

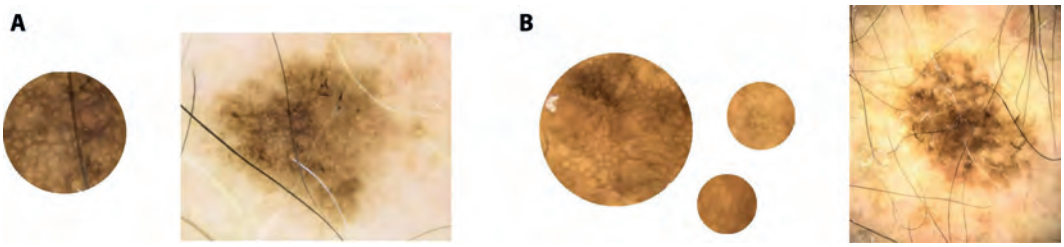


Figure 8. Melanoma in (A) and (B): left snippet, right whole image. Both with dominant morphologic structure of atypical pigment networks with thickened lines. (A) Classification remained the same (atypical) for 6 readers. (B) Classification remained the same (atypical) for 4 readers.

typical network appearance, the context of the lesion was less critical in classifying the network. These findings are consistent with the literature, which indicates that melanoma is usually diagnosed based on a combination of morphologic structures rather than a single feature[1]. Additionally, melanomas that did not change in network classification for most experts had atypical pigment networks as their main feature (Figure 8a-b). For these melanomas it is most likely that the thickened lines were noticed as atypical in the snippet and in the whole image (Figure 8a-b). However, in the nevus cases where there was a shift in the network classification, there was likely an influence on the network distribution and overall pattern in the whole image (Figure S4a). In contrast to melanoma, where additional dermoscopic structures could contribute to the change in classification this was true for only one nevus case (Figure S4b).

The definitions of an atypical network provided by the six dermoscopy experts were not consistent with the definition established during the IDS 2016 consensus meeting[4]. There were notable variations in how they interpreted the typicality of the network with low inter-observer agreement for the whole image view and low-moderate inter-observer agreement for the snippet view. Some experts showed more significant discrepancies between the snippet and the whole lesion image. This variability in the interpretation aligns with existing literature; for example, a study by Lallas et al.,[5] (2018) reported interobserver agreement of approximately 0.393 (kappa) for atypical network and a study by Carrera et al.,[16] indicated that interobserver agreement ranged from poor to fair. These findings highlight the lack of a unified agreed-upon definition of what constitutes a typical versus an atypical network[16]. The higher inter-observer agreement for the snippet supports our assumption that context provided by the whole dermoscopic image influences the classification of the network. When focusing only on the snippet, the interobserver agreement was higher, likely due to the removal of confounding visual context information and forcing the readers to focus only on the objective morphology of the network in its classification. However, when examining the whole image, the additional context led experts to interpret the network both objectively and subjectively, resulting in more disagreements among experts regarding the classification of the network as typical, atypical or both.

Limitations

Limitations of the study include the reliance on a single dermatologist's annotations for the pigment network, rather than employing more objective methods such as automated pigment network detection techniques[17]. Additionally, we were unable to precisely determine which factor in the context affected the change in classification of the network.

Conclusions

Factors such as variability in the network distribution, thickness or color of the network lines, overall pattern, and other dermoscopic structures likely contributed to changes in classification. This study highlights that the classification of a pigment network depends not only on its objective morphology, as seen in the snippets, but also on its subjective interpretation within the visual context of the whole lesion. Future studies should focus on identifying and defining the objective features that distinguish typical from atypical network. Additionally, further research is needed to determine the exact contextual factors that influence the classification of a network as typical or atypical. Identifying both the objective and subjective features involved in pigment network classification will be valuable for clinicians and could help improve AI algorithms.

Acknowledgments: The authors would like to acknowledge the colleagues and collaborators who provided valuable insights and assistance throughout the project. Special thanks to the ISIC Archive for granting access to the image dataset used in this research. We would also like to thank Dr. Michael Marchetti and Dr. Miguel Cordova for contributing cases from their archives.

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Dermatology Practical & Conceptual

Supplementary file

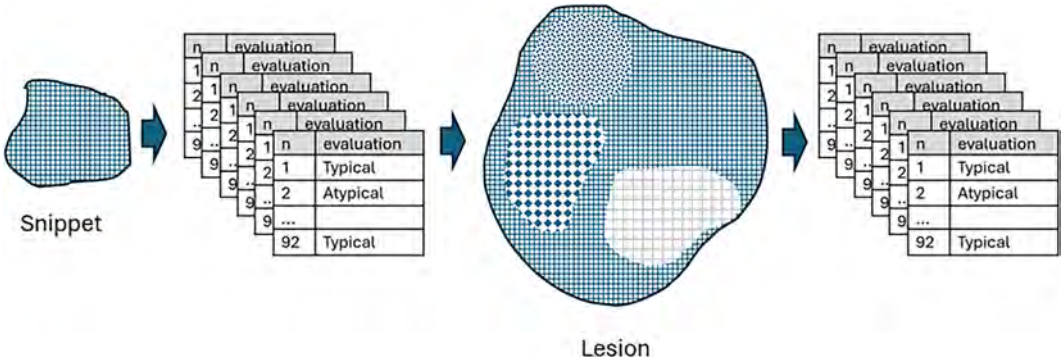


Figure S1. Study design. For each case, experts were required to classify the network as either typical, atypical, or both for the snippet and the whole dermoscopic image. In each module, the cases were presented in a randomized order.

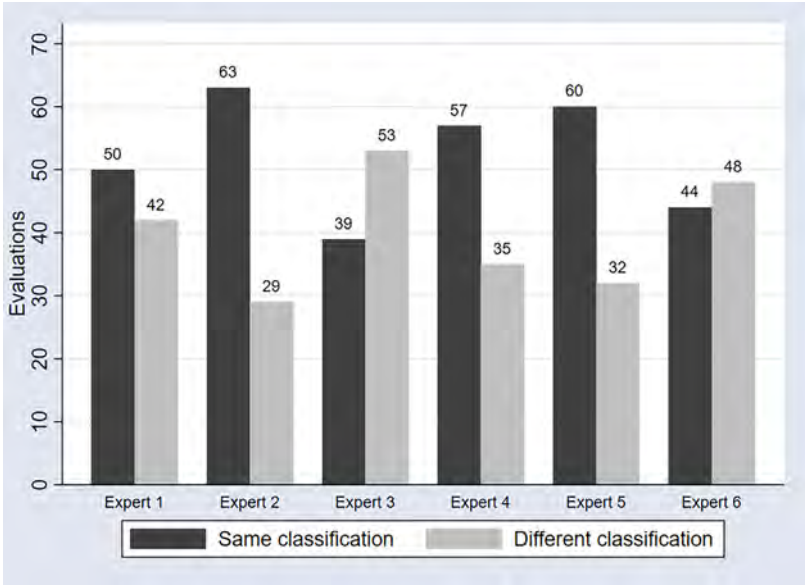


Figure S2. Bar chart of the six experts, showing for each the percentage of change and consistency in pigment network classification from the snippet presentation to the whole dermoscopic image presentation. Reader 7 showed the greatest change, whereas Reader 6 showed the least.

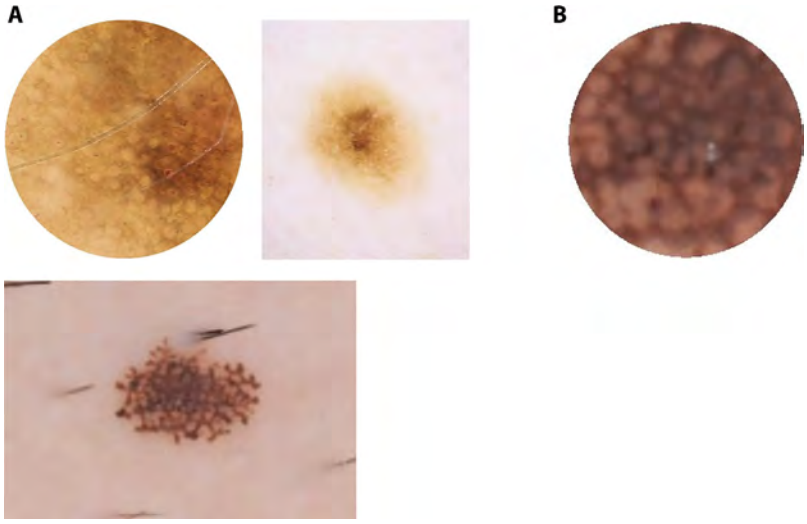


Figure S3. Left snippet, right whole dermoscopic image. Nevus with typical network symmetrically distributed over the entire lesion as the only morphologic structure. Classification remained the same (typical) for all experts.

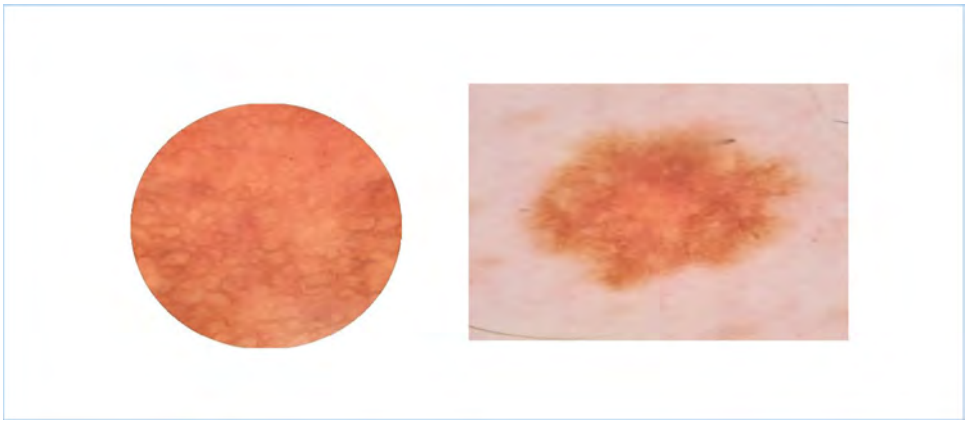


Figure S4. Nevus in (A) and (B): left snippet, right whole image. In both nevi, four experts changed their classification. (A) changed from atypical to typical network. In the snippet, there is a combination of thin and thick pigment networks, but in the whole image, the thick network is centrally distributed, while the thin network appears in the periphery, forming an overall symmetric pattern. (B) In one nevus case, symmetric peripheral pseudopods observed in the whole image may explain the shift in classification from a typical to an atypical network.

Table S1. Distribution of Experts' Classifications by Image Type (N=552) for the Snippet and Whole Dermoscopic Image.

		Snippet	Full image
		N (%)	N (%)
Reader Classification	Typical	262 (47.5)	233 (42.2)
	Atypical	226 (40.9)	236 (42.8)
	Both	65 (11.6)	83 (15.0)

Table S2. Six Experts' Definitions of Atypical Network.

Expert Number	Expert definition of atypical network
5	The presence of irregularity in the network, which may appear with increased thickness or variation in the shape of the lines.
6	Different in color, size/width, and/or shape of the thickness and distribution of the predominant pattern of network/lines.
7	Network consists of a combination of lines and holes. When these structures deviate from the expected appearance (either in the same lesion or other lesions in similar anatomic sites), I call this atypical network. Examples of this deviation from the expected can be the thickness or color of lines and/or the diameter of the holes, etc.
8	Variability in the color, thickness, and spacing of the lines of the network; asymmetric distribution.
10	A network with significant heterogeneity in terms of color and/or thickness of the lines (more than one different network in the same lesion).
11	Atypical/irregular - for melanocytic lesions, I define atypical/irregular as: i) lacking symmetry in pigmentation and network pattern; ii) uneven network; iii) negative network; iv) presence of pseudopods; v) heavily pigmented dots and globules; vi) veiling.

Table S3. Multi-Reader Agreement for Whole Dermoscopic Image and Snippet Evaluations on Three Levels (Typical, Atypical, and Both).

	Whole image			Snippet		
		95% CI			95% CI	
	Coefficient	Lower	Upper	Coefficient	Lower	Upper
Percent Agreement	0.55	0.49	0.61	0.65	0.6	0.71
Scott/Fleiss' Kappa	0.27	0.19	0.35	0.41	0.33	0.50
Gwet's AC	0.35	0.26	0.44	0.51	0.42	0.59

Dermatology Practical & Conceptual

Therapeutic Modulation Of Peripheral Blood Cells And Inflammatory Indices During 52 Weeks Of Risankizumab In Responder Patients With Moderate-to-Severe Psoriasis: Results From A Multicenter Prospective Study

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Key message: Biologic therapies act on specific immune-pathogenic pathways and potentially on systemic inflammation as well. Risankizumab modulates relevant peripheral inflammatory indices such as neutrophils-to-lymphocyte-ratio, pan-immune-inflammation-value, systemic-immune-inflammation-index, and systemic-immune-response-index, especially in super-responder patients, with potential impact on long-term psoriatic patients' prognosis.

Key words: Psoriasis, Risankizumab, SII, SIRI, NLR

Citation: Di Cesare A, Rosi E, Trovato E, et al. Therapeutic Modulation Of Peripheral Blood Cells And Inflammatory Indices During 52 Weeks Of Risankizumab In Responder Patients With Moderate-to-Severe Psoriasis: Results From A Multicenter Prospective Study. *Dermatol Pract Concept*. 2025;15(4):5733. DOI: https://doi.org/10.5826/dpc.1504a5733

Accepted: August 31, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT **Introduction:** Whole blood cells and derived indices can be used as a read-out of the inflammatory pathogenic processes in many human diseases, including psoriasis. Indeed, systemic treatments with special regard to anti-IL-23 agents could exert anti-inflammatory and disease modifying effects; however, there is still a lack of conclusive data.

Objectives: We aimed to assess the therapeutic effect of risankizumab on whole blood cells and inflammatory indices in psoriatic patients.

Methods: We performed a prospective multicenter observational study on adult patients with moderate-to-severe psoriasis who underwent risankizumab therapy for at least 52 weeks. Blood cell count, CRP, and ESR were prospectively recorded for each patient included in the study, at routine visits up to week 52. The ratio between peripheral cells, namely NLR, PLR, MLR, SII, and PIV, were calculated and compared at time 0 and at weeks 12, 24, and 52 of treatment. At different timepoints, modulation of laboratory values and derived indices and their correlation with disease severity and response to treatment were analyzed. Subanalysis of very early responders and late responders was performed as well.

Results: We observed a progressive reduction in inflammatory indices such as CRP, ESR, NLR, and SII during treatment, with prominent modification involving SIRI as well, in patients who had a very early and almost complete response to risankizumab. Reduction in neutrophils and MPV, a transient increase in eosinophils at week 12, and a progressive increase in peripheral basophils were associated with therapeutic response.

Conclusion: Risankizumab promotes a progressive anti-inflammatory effect, more prominent in patients with a faster response in the early phases of treatment.

Introduction

Despite consistent data on disease pathogenesis and on the efficacy of different biologic therapies, there is still a need for manageable and accessible tools to optimize psoriasis treatment. Innate and acquired immune cells such as lymphocytes and neutrophils are key drivers in psoriasis onset and maintenance, and their ratio (NLR) is a recognized marker of systemic inflammation [1–4].

Other blood-derived indices, such as pan-immune-inflammation value (PIV) and systemic immune inflammation index (SII), have been evaluated as risk factors for disease development, prognostic markers of evolution, or of treatment response in human diseases and inflammation [5–10]. Recently, two metanalyses summarized the potential application of systemic inflammatory indices in psoriasis compared to the general population, with special regard to NLR (neutrophil-to-lymphocyte ratio) and PLR (platelet-to-lymphocyte ratio) and their possible correlation to disease severity. Some studies retrospectively investigated the effect of systemic treatment on peripheral blood cells and their derived parameters, including SII and SIRI (systemic immune response index) [11–14].

For these reasons, we performed a prospective observational study on patients with moderate-to-severe cutaneous psoriasis treated with risankizumab in order to assess therapeutic effect overtime on whole blood cell count and derived indices with regard to clinical efficacy of the drug.

Materials and Methods

Patients with moderate-to-severe psoriasis, defined as PASI ≥10 or PASI <10 but BSA >10 and involvement of special sites/difficult-to-treat areas (i.e., scalp, genitals, face, and palmoplantar regions), eligible to therapy with risankizumab were prospectively enrolled in the study. Patients were prescribed risankizumab SC 150 mg at T0, week 4, and every 12 weeks thereafter.

Baseline demographic and clinical features as well as complete hematologic data, including whole blood cell count, c-reactive protein (CRP), and erythrocyte-sedimentation rate (ESR), were recorded at baseline and during risankizumab treatment at weeks 12, 24, and 52. Patients were considered responders to risankizumab if they reached at least PASI 75 within three risankizumab injections, with clinical evaluation at week 24. Patients with incomplete data or who did not reach week 52 and discontinued risankizumab, either due to primary failure (one patient) or to adverse events or for personal reasons (i.e., moved to another town, three patients) were excluded from the analysis (Figure 1). At each time point, calculation of NLR, PLR, MLR (monocyte-to-lymphocyte ratio), PIV, SII, and SIRI was performed.

The formula for SII, PIV, and SIRI were, respectively: i) [neutrophil (103/mmc) × platelet (103/mmc)]/lymphocyte (103/mmc); ii) [neutrophil (103/mmc) × platelet (103/mmc) × monocyte (103/mmc)]/lymphocyte (103/mmc) count; iii) neutrophil (103/mmc) × monocytes (103/mmc)]/lymphocyte (103/mmc) count.

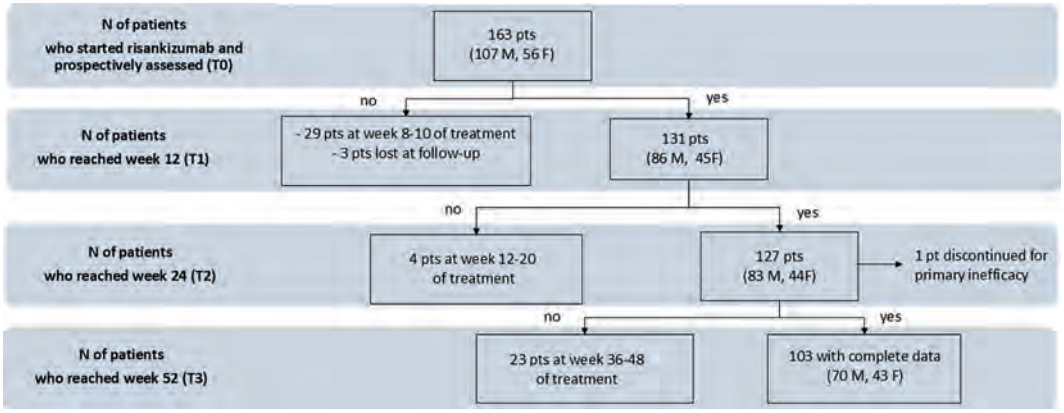


Figure 1. Flow diagram depicting the number of patients (pts) who were screened and started on risankizumab and therefore enrolled in the prospective study at baseline (T0), and the number of patients who completed each follow-up time point (T12, T24, and T52). Only patients who reached week 52 (N=103) of continuous risankizumab therapy with complete hematologic data were included in the analysis.

The primary aims of the study were to analyze the modulation of laboratory values and derived indices at different time points, and their correlation with disease severity.

The co-primary endpoint was the assessment of differences between patients who reached PASI ≥90 as early as week 12 (super-responders, SR) versus patients who reached PASI ≥75 from week 24 (late responders, LR).

Statistical Analysis

Descriptive statistics were used to summarize the characteristics of the study population. Normal distribution was tested for all samples and not parametric tests were used where appropriate. For continuous variables, the significance of the difference between medians of the groups was investigated by using Mann-Whitney test. One-way ANOVA test for independent measures (Kruskal Wallis test, plus Dunn's correction) was used to compare the means of ≥3 independent samples simultaneously. Treatment effect was studied by comparing medians of values at different time points either with Wilcoxon matched-pairs signed-rank test or with matched Friedman ANOVA test with Dunn's post-test for ≥3 samples simultaneously. Categorical variables were analyzed with Pearson's chi-square test. Fisher exact test was also used when appropriate. Correlation between variables was assessed with non-parametric Spearman rank coefficient test. All p-values cited are two-sided, and values of *P* less than .05 were considered statistically significant.

Results

Total Population and Baseline Clinical Features

In total, 103 patients (70 M, 43 F; median age: 54, IQR: 45–67) were included in the study (Figure 1). Patients were all affected with cutaneous plaque psoriasis (median PASI 13.7, IQR 9.7–16.8), and 18.4% (19/103) had concomitant arthritis (PsA). Special areas including scalp, nail, palmoplantar, genital, and face regions were involved in 55.3% (57/103), 35.9% (37/103), 33.98% (35/103), 25.2% (26/103), and 6.8% (7/103) of patients, respectively. Patients had all been previously treated with conventional systemic agents: (69/103; 66.9%) cyclosporin A, 41/103 (39.8%) methotrexate, 27/103 (26.21%) acitretin, and 1/103 (0.97%) dimethyl-fumarate or phototherapy (44/103; 42.7%), nbUVB and/or PUVA; 16/103 (15.5%) were naïve to biologics. Among bio-experienced patients, 37/103 (35.9%) had failed one, 34/103 (33%) two, 7/103 (6.8%) three, 6/103 four (5.85), 2/103 five (1.9%), and 1/103 (0.97%) six biologic agents, with a median number of one biologic agent (IQR 1–2/patient).

Patients had a median body mass index (BMI) of 26.54 (IQR: 24.14–29.41), and 21/103 (20.4%) patients were obese (BMI ≥30). Comorbidities were reported for 65/103 (63%) patients, the most common being systemic hypertension (35/103; 33.98%), dyslipidemia (24/103; 23.3%), and type 2 diabetes (9/103; 8.74%). Latent TB, previous HCV infection, and inactive HBV infection were recorded in 13/103 (12.6%), 3/103 (2.9%) and 8/103 (7.7%) patients, respectively. Baseline laboratory values of the overall population and derived indices are reported in Table 1.

A significant correlation between age and BMI was found (*P*=0.015; r= 0.2391), mainly linked to lower BMI in females (M: *P*=0.24 r=0.142; F: *P*= 0.014, r=0.424). Actually, male patients (BMI: 27.28; IQR: 25.36–29.76) were significantly overweight compared to females (BMI: 24.14, IQR: 21.14–28.19) (*P*=0.0015), while no gender difference in disease severity (PASI M= 13.75; IQR: 9.7–16.23; PASI F= 13.9; IQR 10.8–17.4; *P*=0.9089) or age at observation (age M=53; IQR: 45.75–64.25); Age F=57; IQR 41–71; *P*=0.9089) was found.

Table 1. Whole Blood Cells and Derived Indices at Baseline and their Therapeutic Modulation during Risankizumab Treatment.

	T0	Week 12	Week 24	Week 52	p
WBC mmc/10^3	6.95 (3.58-8.91)	7.18 (5.86-8.41)	7.18 (5.67-8.690)	6.91 (5.72-8.17)	0.3746° 0.0869@
RBC mmc/10^6	5.120 (4.82-5.4)	5.11 (4.76-5.38)	5.13 (4.77-5.37)	5.11 (4.66-5.39)	0.6545 0.9586@
PLT mmc/10^3	261 (228-306)	253 (219-316)	269 (215-319)	265 (217-318)	0.3588° 0.2444@
MPV Fl	10** (8.45-10.75)	10.03** (8.5-10.7)	10.13 (9.02-11.1)	10.13** (9.11-11.07)	**0.0016°** **0.0004@**** T0-W52, W12-W52
Neutrophils mmc/10^3	5.2 (3.98-6.15)	5.01 (3.98-6.05)	5.07 (3.73-6.11)	4.61 (3.59-6)	**0.0364°** 0.0562@
Lymphocytes mmc/10^3	2.1 (1.53-2.41)	2.15 (1.7-2.39)	2.14 (1.73-2.36)	2.15 (1.76-2.34)	0.9821° 0.6090@
Monocytes mmc/10^3	0.58 (0.39-0.86)	0.58 (0.41-0.85)	0.56 (0.39-0.8)	0.57 (0.4-0.77)	0.4397° 0.1156@
Eosinophils mmc/10^3	0.23** (0.16-0.41)	0.27** (0.18-0.45)	0.24* (0.15-0.35)	0.24* (0.15-0.34)	0.3751° **0.0007@*** T0-W12,**W12-W24nd 52
Basophils mmc/10^3	0.07 (0.03-0.11)	0.08* (0.04-0.14)	0.08* (0.04-0.13)	0.08* (0.04-0.14)	**0.0439°** **0.0008@***W12-24; *W24-52
ESR mm/h	27.0**** (15.25-38)	22 (13.25-29.75)	25* (13.25-29)	19****,* (13-23)	**<0.0001°** **<0.0001@****** T0-W52; *W24-W52
CRP mg/dL	0.47***,**** (0.34-0.53)	0.36***,** (0.27-0.45)	0.31****,** (0.21-0.39)	0.26****,*** (0.2-0.33)	**<0.0001°** **<0.0001@***** T0- W12, W12-W52, **W12-W24, ****T0-W24 and 52
NLR	2.44 (1.81-3.18)	2.42 (1.79-2.82)	2.35 (1.74-2.89)	2.31 (1.79-2.67)	**0.0063°** 0.2394@
PLR	123.2 (100.9-61.6)	129.5 (101.-162.3)	127.8 (102.6-61.4)	126.3 (100-159.6)	0.3840° 0.4252@
MLR	0.29 (0.196-0.43)	0.29 (0.21-0.41)	0.28 (0.19-0.38)	0.27 (0.2-0.38)	0.4093° 0.6665@
PIV	340.9 (175-710.5)	325.6 (175-568.1)	329.7 (179.4-497.5)	274.9 (178.2-439.5)	0.0971° 0.0719@
SII	626.2 (447.3-69.4)	592.7 (390.0-804.2)	603.1 (444.3-823.7)	578.2 (392.3-822.4)	**0.038°** 0.0889@
SIRI	1.35 (0.75-2.28)	1.26 (0.84-2.3)	1.15 (0.74-2)	1.13 (0.80-1.74)	0.0698° 0.3421@

Results are shown as median with IQR; °Wilcoxon matched-pairs signed rank test; @ ANOVA matched Friedman test with Dunn's post-test.

However, neither disease severity measured as PASI score nor BMI, age, presence of PsA, special sites involvement, previous exposure to biologics, or concomitant comorbidities affected results in terms of median values or correlation to disease severity (correlation matrix, Spearman rank test for each marker and subgroup with $P>0.05$, data not shown).

ESR positively correlated with CRP ($P=0.006$; r=0.29), and both values were positively correlated to neutrophils (ESR $P=0.004$, r=0.29; CRP $P=0.001$, r=0.33), NLR (ESR $P=0.001$, r=0.29; CRP $P=0.001$, r=0.32), PIV (ESR $P=0.002$, r=0.31; CRP $P=0.005$, r=0.29), SII (ESR $P<0.001$, r=0.40; CRP $P=0.001$, r=0.32), and SIRI (ESR $P=0.012$, r=0.252; CRP

P=0.008, r=0.27). ESR was also related to RBC (*P*=0.001, r=0.32), PLT (*P*=0.009, r=0.26), eosinophils (*P*=0.004, r=0.29), basophils (*P*=0.013, r=0.25), and PLR (*P*=0.01, r=0.26), with a negative correlation only with MPV (*P*=0.012, r=-0.28).

Therapeutic Modulation of Whole Blood Cells and Derived Indices

Total Population

From T0 to week 52, risankizumab modulated different parameters, with an increase in MPV (*P*=0.0016) and basophils (*P*=0.0439) and a decrease in neutrophils (*P*=0.0364), ESR (*P*<0.0001), CRP (*P*<0.0001), and SII (*P*=0.038) (Table 1).

A dynamic increase in MPV and basophils and a transient increase in eosinophils were detected (Table 1).

A positive correlation was found between changes in PASI and NLR (ΔPASI versus ΔNLR, from T0 to week 52; *P*=0.02, r=0.23).

Super responders (SR) versus late responders (LR)

Overall, 64 patients were defined as SR (45 M, 19 F), while 39 (25 M, 14 F) patients were LR (Table 2).

Baseline median differences were observed only for neutrophils levels (SR: 4.52; IQR: 3.96–5.69 versus LR: 5.65; IQR: 4.01–6.35; *P*=0.0482) and BMI (SR: 26.09; IQR: 23.68–28.97 versus LR: 27.77; IQR: 24.98–31.64; *P*=0.0497, which were higher in LR patients. Normal weight patients did not display any baseline or over-time difference in blood-derived indices compared to patients with BMI >25 (data not shown). Moreover, BMI did not impact baseline disease severity or the overall response to risankizumab since all the patients reached PASI 75 at week 24, and no difference in PASI score at week 52 was found between LR and SR (Figure 2).

In LR patients, PASI score inversely correlated to lymphocytes (*P*=0.02; r= -0.372) and directly correlated to

Table 2. Baseline Demographic, Clinical, and Hematologic Features in SR versus LR patients.

	SR N=64	LR N=39	p
Sex (Male, N)	45	25	0.5223§
Age (years) median (IQR)	52 (42.5-63.75)	57 (49-71)	0.1038*
BMI median (IQR)	26.09 (23.68-28.97)	27.77 (24.98-31.64)	**0.0497***
PASI median (IQR)	14 (10.8-15.95)	12.30 (7-17.4)	0.2925*
Special sites involvement, N			
Scalp	37	20	>0.9999§
Nail	25	12	0.5257§
PP	16	19	0.5457§
Genital	13	13	0.1645§
Face	3	2	0.7069§
PsA, N	11	8	0.7943§
Comorbidities, N	39	27	0.5257§
HPT	12	10	0.4686§
Diabetes	4	5	0.2937§
Dyslipidemia	11	9	0.6083§
Previous systemic therapies, N			
Cyclosporin A	43	26	>0.9999§
Methotrexate	25	16	>0.9999§
UV (nbUVB-PUVA)	29	15	0.5425§
Acitretin	11	16	**0.0109§**
Number of previous biologics			
Median number (IQR)	1 (1-2)	2 (1-2)	0.6390*
0 (N)	8	8	0.4006§
1 (N)	26	11	0.2898§
2 (N)	23	11	0.5184§
3 (N)	4	3	>0.9999§
4 (N)	2	4	0.1965§
5 (N)	0	2	--
6 (N)	1	0	--

§fisher exact test *Mann Whitney t-test, N=number of patients

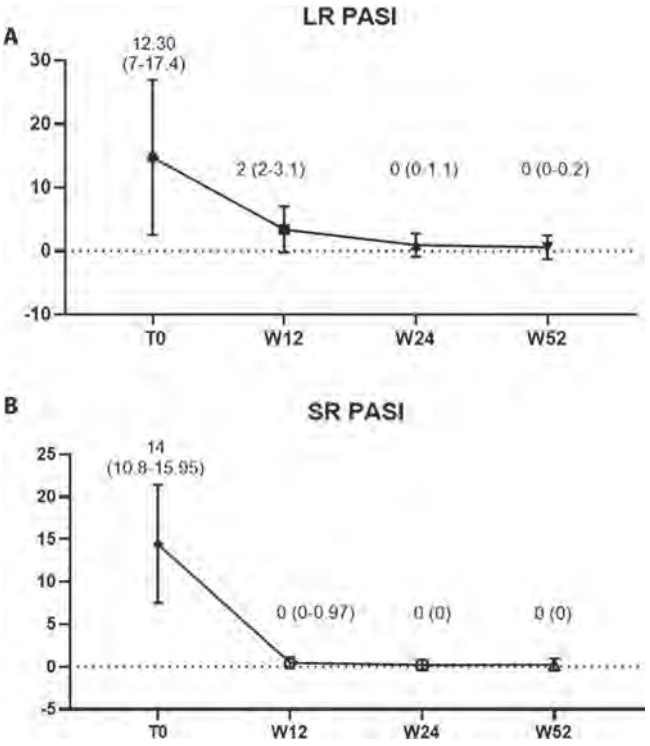


Figure 2. Efficacy of risankizumab on PASI score over time in LR (A) and SR (B) patients.

Changes in PASI score were significant as early as week 12 of treatment in both SR and LR subgroups; however, despite the fact that no difference at baseline was observed in SR versus LR patients (P >0.9999), at week 12 LR patients had significantly higher values of PASI (P<0.0001), which turned into similar scores at week 24 (SR versus LR, P>0.9999) and at week 52 (SR versus LR, P>0.9999) (multiple comparison, Kruskal Wallis test with Dunn's correction).

NLR (P=0.016, r=0.383), PLR (P=0.032, r=0.343), and SII (P=0.047; r=0.320) at baseline.

During treatment, the median number of neutrophils normalized as early as week 12 (SR: 4.625; IQR: 3.98–5.47 versus LR: 5.18; IQR: 3.98–6.32; P=0.1525).

In LR there was only a slight reduction in the inflammatory indices such as ESR (mm/h) (T0: 23; IQR: 15.5–36.5 versus Week 52: 18; IQR: 13.5–22.5; P= 0.0398), CRP (mg/dL) (T0: 0.45; IQR: 0.41–0.58 versus Week 52: 0.25; IQR: 0.22–0.35; P=0.0021), NLR (T0: 2.59; IQR: 1.81–3.61 versus Week 52: 2.48; IQR: 1.79–2.9; P=0.2491), SII (T0: 653.3; IQR: 348.4–822.1 versus Week 52: 611.5; IQR: 392.3–859.9; P=0.3872, PIV (T0: 359.3; IQR: 147.4–830.7 versus Week 52: 284.9; IQR: 178.2–575.3; p=0.6240) and SIRI (T0: 1.58; IQR: 0.67–2.24 versus Week 52: 1.28; IQR: 0.8–2.1; P=0.5759).

SR patient reached a significant reduction in ESR (T0: 28; IQR: 14–39 versus Week 52: 19; IQR: 12–23; P<0.0001), CRP (T0: 0.46; IQR: 0.31–0.52 versus Week 52: 0.27; IQR: 0.20–0.33; P<0.0001), NLR (T0: 2.23; IQR: 1.83–2.97 versus Week 52: 2.20; IQR: 1.78–2.54; P=0.0124), SII (T0: 596.3; IQR: 452.3–898.3 versus Week 52: 568.4; IQR: 388–815.5); P=0.0477), and SIRI (T0: 1.32; IQR: 0.76–2.36 versus Week 52: 0.99; IQR: 0.76–1.62; P=0.0462). PIV slightly reduced over time (T0: 327.1; IQR: 192.3–700.1 versus Week 52: 269.3; IQR: 178.6–408.8; P=0.0768).

Furthermore, at week 52, NLR was significantly lower in SR patients (SR: 2.2; IQR: 1.78–2.53 versus LR: 2.48; IQR: 1.79–2.91; P=0.0495), despite the fact that ΔNLR was positively correlated to ΔPASI only in LR patients (P=0.022, r=0.37).

The effect on transient increase in eosinophils was maintained in both LR and SR patients: for LR, T0: 0.26; IQR: 0.15–0.43; Week 12*: 0.32; IQR: 0.16–0.47; Week 24: 0.28; IQR: 0.16–0.40; Week 52: 0.26; IQR: 0.14–0.38; P= 0.0099. For SR, T0: 0.22; IQR: 0.16–0.4; Week 12*: 0.25; IQR: 0.18–0.42; Week 24: 0.22; IQR: 0.14–0.33; Week 52: 0.24; IQR: 0.16–0.32; P=0.0262), while in SR patients, only basophils (T0: 0.06; IQR: 0.03–0.10; Week 12: 0.10; IQR: 0.05–0.15; Week 24: 0.09; IQR: 0.04–0.14); Week 52: 0.09; IQR: 0.04–0.14; P=0.0001, increase) and MPV (T0: 9.8; IQR: 8.3–10.6; Week 12: 10; IQR: 8.3–10.6; Week 24: 10.11; IQR: 8.4–11.20; Week

52: 10.13; IQR: 8.9-11.04; *P*=0.0001, reduction) modified overtime.

Discussion

The role of cutaneous and systemic inflammation in psoriasis has been extensively studied and demonstrated [15–17]. However, understanding the potential effect of systemic treatment at the peripheral level is still under investigation.

Recently, many authors have focused on the application on simple indices such as the ratio between blood cells in order to identify disease severity and activity markers in many human diseases, from cancer to inflammatory disorders, including psoriasis [5,12,18–22].

Data in the literature suggest that patients with cutaneous psoriasis and PsA have significantly increased NLR, MLR, PLR, and SII compared to controls. Moreover, NLR and PLR positively correlate with the mean PASI scores being significant indicators of psoriasis severity [11,12,23,24]. Tiuca OM et al.[25] suggested that patients with mild psoriasis could be defined by WBC<6.25, neutrophils <3.64, NLR <2.35, d-NLR <1.49, and SII <408.8. In our opinion, these data need to be carefully validated and correlated to clinical cutaneous and general features of each patient.

In our patients, no correlation was found between inflammatory indices and disease severity, with the exception of patients that had a lower response to risankizumab. This fits with the concept that NLR might serve as marker of global disease severity. Indeed, LR patients had higher NLR levels at week 52 compared to SR group, and changes in NLR were correlated to changes in PASI score.

Modulation of inflammatory indices during systemic and biologic therapies has been reported, suggesting that treatment efficacy could impact the total inflammatory overload in patients who are at risk or are affected with several comorbidities such as diabetes, dyslipidemia, or hypertension. Indeed, all the above mentioned diseases have been linked to increases in such parameters [26–32].

Risankizumab is one of the latest molecules introduced for psoriasis and PsA, one of the anti-IL-23p19 agents, which have been proposed as having a disease-modifying effect [33–36]. Understanding the ability of risankizumab to obtain general anti-inflammatory effect could add relevant information for therapeutic decision making and timing. Indeed, it has been reported that MLR, NMLR (neutrophils+monocytes)/lymphocytes), and SIRI positively correlate with mortality in patients with psoriasis [37].

Albayrak H. [38] described NLR, MLR, PLR, SII, and neutrophil-to-monocyte ratio (NMR) variation during methotrexate, acitretin, and anti-TNF agents, suggesting that biologics are more effective in reducing inflammation.

In a retrospective study, anti-IL-17 agents (number of patients, 314) were more effective in reducing NLR, PLR, MLR, and SII compared to anti-TNF (N=49) and also to anti-IL-12/23+IL-23 agents (N=72), which exerted a significant effect on NLR and SII. However, no subanalysis of the single molecules was performed [39].

Morariu et al. [13] retrospectively looked at the effects of anti-TNF (adalimumab, N=22; etanercept, N=18; infliximab, N=6; certolizumab; N=6), anti-IL-17 (ixekizumab, N=61; secukinumab, N=41), anti-IL-23p19 (tildrakizumab, N=11; guselkumab, N=22; risankizumab, N=44), and anti-IL-23p40 (ustekinumab, N=17) biologics. A reduction in NLR, PLR, derived NLR/dNLR, SII, SIRI, AISI, MLR, and platelet-to-monocyte ratio/PMR was observed at week 52, with differences between molecules, but without class effect. Similar results were shown by Kulakli S et al. [14], while another retrospective study suggested that lower baseline levels of NLR could be predictive of response to anti-TNF agents [40]. A retrospective analysis [41] of the Voyage I and II and Eclipse studies showed that the ability to modulate NLR, MLR, and PLR of biologic agents such as guselkumab, secukinumab, and adalimumab was higher compared to placebo-treated patients during the first 16 weeks of treatment, while two other studies showed discording results on the superiority of anti-IL17 versus anti IL-23 agents in reducing systemic inflammation [42,43].

This study offers a prospective evaluation on hematologic indices in psoriasis, and it includes the largest population of patients treated with risankizumab analyzed for blood cells and inflammatory values.

The results of this study confirmed the potential ability of risankizumab to reduce systemic inflammation, lowering ESR, CRP, NLR, and SII overtime. It also demonstrated the effect of systemic treatment on PIV in psoriasis, which has been reported in other cutaneous diseases such as hidradenitis suppurativa [5,44–46].

Another new finding of our study is the transient increase in eosinophils during the first weeks, and their progressive restoration to baseline levels; this is potentially relevant, since the relative risk of psoriasis incidence increases with the increase in neutrophils, monocytes, and eosinophils. Eosinophils can have a potential impact on psoriasis severity [15].

We have also shown that risankizumab increases peripheral basophils, with special regard to SR patients. Recently, Zhang et al. showed that eosinophils and basophils positively correlate to PASI and that, although not significantly, they increase during treatment [39].

We understand that our results need to be implemented and compared with data on cutaneous samples; however, due to the very low levels of cutaneous and peripheral basophils, it may be difficult to dissect this pathogenetic aspect. Indeed, a next step could be to prospectively evaluate

class effect of hematologic markers, with a direct comparison between risankizumab and other anti-IL-23 agents and anti-TNF agents and IL-17 inhibitors.

An increase in MPV without a significant impact on platelet and PLR in our patients needs to be further assessed, as data on baseline MPV levels and their modulation in psoriasis and PsA are conflicting [47–50].

In our study, risankizumab lowered the number of neutrophils, but also restored them to the baseline difference in patients with initial slower response. Biologics are known to increase the risk of non-serious infections both in short- and long-term treatment. However, risankizumab profile is very safe [33,51], and in our patients the number of neutrophils was always within normal range at each time point, thus suggesting overall rebalancing of circulating and re-circulating cutaneous WBCs [52].

Activated neutrophils and NETosis have been associated with early phases of psoriasis development; thus, it is not surprising that higher levels of circulating cells could influence therapeutic response, as in the LR patients in our study [53–55].

It is well known that BMI represents a negative prognostic factor to therapeutic success [56–61]; of note, some authors have highlighted that weight reduction could reduce IL-23 levels [62]. Indeed, we and others have previously shown that risankizumab is effective regardless of baseline BMI. However, BMI could affect the time needed to reach the result within week 36, despite the fact that, in our patients, differences were resolved as soon as week 24, and no impact of BMI was observed in baseline disease severity [63–65].

Finally, the variation in PASI score significantly correlated to the variation of NLR, as reported by Zhang et al. [39].

Conclusions

Risankizumab treatment results in progressive modulation of hematologic parameters, with improvement in general systemic inflammation. Further research is needed to understand whether this modulation relates to cutaneous amelioration and whether the exerted anti-inflammatory effect lasts and contributes to disease modification, potentially offering the opportunity of treatment discontinuation or dose tapering in patients with stable response.

Ethics Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Azienda USL Toscana Centro, Firenze (CEAVC 19799).

Ethics Statement: Informed consent was obtained from all individual participants included in the study. The patients in this manuscript gave their written informed consent to the publication of their case details.

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Dermatology Practical & Conceptual

Predictors of Early Response and Relapse in Chronic Spontaneous Urticaria Treated with Omalizumab: The Role of Age, Sex, Disease Duration, and UAS7

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Key words: Omalizumab, Relapse, Chronic spontaneous urticaria, Sex, Age

Citation: Güner ME, Öztürk P, Yaray OC, Evran Kılıç EM, Kuş MM. Predictors of Early Response and Relapse in Chronic Spontaneous Urticaria Treated with Omalizumab: The Role of Age, Sex, Disease Duration, and UAS7. *Dermatol Pract Concept*. 2025;15(4):6169. DOI: https://doi.org/10.5826/dpc.1504a6169

Accepted: July 17, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Omalizumab is an established treatment for chronic spontaneous urticaria (CSU), yet variability in therapeutic response remains a clinical challenge. Identifying baseline predictors of early response may help optimize patient selection and management strategies.

Objectives: To evaluate the predictive value of age, sex, baseline disease severity, and disease duration for early response to omalizumab and to assess their relationship with relapse risk.

Methods: This retrospective study included 274 patients with CSU treated with omalizumab between 2011 and 2024. Early response was defined as achieving a UAS7 score <7 at one month. Baseline variables included age, sex, UAS7, and disease duration. Binary logistic regression and ROC curve analyses were conducted to identify independent predictors of early response.

Results: Among 274 patients (mean age 42.96±15.54 years; 66.4% female), early response was achieved in 37.6%. Early responders had significantly lower baseline UAS7 and shorter disease duration (both $P<0.001$). Logistic regression confirmed both variables as independent predictors. Age and sex were not independently associated with early response, although univariate analysis showed a higher early response rate in patients aged <45 years. ROC analysis demonstrated strong inverse

predictive value for UAS7 (AUC=0.917) and disease duration (AUC=0.940). Relapse risk was significantly lower in females and patients aged <45 years.

Conclusions: Lower baseline UAS7 and shorter disease duration independently predict early response to omalizumab. Younger age and female sex may be associated with lower relapse risk. These findings support earlier therapeutic intervention in patients with lower disease burden to improve outcomes.

Introduction

Urticaria is a condition characterized by the presence of wheals, angioedema, or both [1]. Its prevalence in females is 2– 4 times higher than in males [2]. Chronic urticaria is defined as urticaria persisting for more than six weeks. [1] Chronic spontaneous urticaria (CSU) is characterized by the spontaneous occurrence of symptoms lasting longer than six weeks. In CSU, lesions typically appear without a specific trigger. CSU is most commonly observed between the ages of 20 and 40 years, with the disease duration ranging between one and five years in most patients [3].

Second-generation antihistamines are the first-line treatment, but in patients who do not respond even after dose escalation up to four times the standard dose, omalizumab is added to the treatment regimen [1]. Omalizumab is a monoclonal anti-IgE antibody used in the treatment of asthma, allergic rhinitis, and chronic urticaria [4]. Omalizumab is now a well-established and highly effective therapeutic agent for patients with moderate-to-severe chronic spontaneous urticaria (CSU). Both pivotal randomized controlled trials and real-world observational studies have consistently demonstrated omalizumab's capacity to achieve disease control in a substantial proportion of patients. A meta-analysis encompassing 45 studies and 1,158 individuals with CSU reported that approximately 72% of patients achieved complete symptom resolution with omalizumab [5]. Nonetheless, response rates vary, and nearly one third of patients do not achieve adequate clinical benefit [6]. Furthermore, among responders, there is notable variability in the timing and extent of improvement. Some patients experience rapid relief of itching and hives within the first four weeks of therapy, whereas others require 2–3 months or longer to achieve well-controlled disease [7]. This heterogeneity in patient responses, both in terms of efficacy and speed of onset, underscores the need to better understand which patients are likely to benefit from omalizumab quickly, which may respond only later or partially, and which may fail to respond at all.

Given the variable outcomes with omalizumab, researchers have sought to identify baseline patient factors that predict treatment response. Demographic factors such as age and sex have been evaluated, but findings remain inconclusive. CSU occurs across all adult age groups, with a slight female predominance, yet sex has not emerged as a consistent predictor of omalizumab efficacy [5]. Similarly, the influence of age on treatment outcomes is unclear. Some real-world data suggest that older patients may achieve higher rates of disease control with omalizumab [8], whereas other studies report no significant age difference between responders and non-responders [5].

Disease severity at baseline has also been examined as a potential predictor of outcome. The urticaria activity score (UAS7), a 7-day composite itch and hive severity score, is often used to quantify baseline disease activity. There is evidence that patients with more severe baseline UAS7 scores tend to have poorer treatment responses to omalizumab. In a real-world cohort, non-responders had significantly higher median baseline UAS7 than did responders, and a baseline UAS7 above ~30 was found to predict non-response with moderate accuracy [5].

Another factor of interest is the duration of CSU prior to starting omalizumab. Long-standing disease might reflect a more entrenched or treatment-resistant urticaria endotype, potentially influencing outcomes. Some investigations have noted that longer disease duration is associated with an elevated risk of relapse after stopping omalizumab [9].

Determining predictors of early response and of relapse risk is of high clinical relevance in the management of CSU. Identifying patients likely to respond quickly to omalizumab could enable clinicians to optimize treatment plans, for instance, by continuing therapy in those showing early improvement or considering alternative strategies in those predicted to respond poorly. Early identification of likely non-responders may spare patients prolonged ineffective treatment and help guide the use of adjunctive therapies. In light of the above, the present study aimed to systematically evaluate the impact of four key patient factors (age, sex, baseline UAS7, and disease duration) on outcomes of omalizumab therapy in CSU. Specifically, we sought to determine whether any of these baseline characteristics predict an early treatment response to omalizumab, and whether they influence the risk of relapse after omalizumab discontinuation. By clarifying the role of age, sex, initial disease severity, and disease chronicity in early efficacy and post-treatment relapse, this study may help refine our ability to personalize CSU treatment and improve long-term management strategies.

Methods

Ethical approval for this study was obtained from the Clinical Research Ethics Committee (Date: 17.02.25, Session No: 2025/06, Decision No: 13).

This retrospective study included patients diagnosed with chronic spontaneous urticaria (CSU) who presented to the dermatology outpatient clinics of our hospital between June 2011 and January 2024 and who initiated omalizumab treatment. Patient records were reviewed to extract clinical data. The diagnosis of CSU and the assessment of disease activity were conducted in accordance with the EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for urticaria [1].

Patients were eligible for inclusion if they were over 18 years of age, had a confirmed diagnosis of CSU, were treated with omalizumab, and had completed at least 16 weeks of therapy without receiving additional systemic treatments. Patients with inducible urticaria were excluded. Disease activity was evaluated using the Urticaria Activity Score over 7 days (UAS7), which assesses the severity of wheals and pruritus.

Each patient received 300 mg of omalizumab every four weeks for 16 weeks. Disease activity and the therapeutic effect of omalizumab were evaluated using UAS7 measurements at baseline and at the 4th, 8th, 12th, and 16th week. Patients were then categorized based on their response to treatment over the 16-week period. Responders were defined as those with a UAS7 score <7, whereas non-responders were those with a UAS7 score of 7 or higher. "Early response" was defined as the resolution of CSU symptoms (UAS7 <7) within the first four weeks of omalizumab treatment [5].

After the initial treatment period, patients were followed for an additional eight weeks to monitor for relapse, defined as the need to reinitiate omalizumab due to recurrence of CSU symptoms after discontinuation.

The primary objective of the study was to evaluate early response and relapse rates according to age and sex. Secondary analyses explored the influence of baseline UAS7 and disease duration on treatment outcomes.

Statistical Analyses

Statistical analyses were conducted using IBM SPSS Statistics 26. Descriptive data are presented as N and % for categorical variables, and as mean ± standard deviation (Mean±SD) for continuous variables. The Kolmogorov–Smirnov and Shapiro–Wilk tests were used to assess the normality of continuous variables. Group comparisons were performed using the chi-square test for categorical variables and the Mann–Whitney U test for non-normally distributed continuous variables. A p-value of <0.05 was considered statistically significant.

Binary logistic regression analysis was performed to identify independent predictors of early treatment response, including baseline UAS7, disease duration, age group (<45 vs. ≥45 years), and sex. Results are reported as odds ratios (OR) with 95% confidence intervals (CI). Receiver operating characteristic (ROC) curve analyses were conducted to evaluate the discriminatory ability of baseline UAS7 and disease duration for predicting early response. The area under the curve (AUC) and optimal cutoff values were calculated based on sensitivity and specificity metrics.

Results

A total of 274 patients with chronic spontaneous urticaria (CSU) undergoing omalizumab treatment were included in the study, with a mean age of 42.96 ± 15.54 years (min=18, max=85). Among these, 92 (33.6%) were male, and 182 (66.4%) were female.

The mean duration of omalizumab treatment among the study participants was found to be 35.63 ± 27.78 months (min=3, max=120).

Among the patients, 143 (52.2%) were still continuing treatment, while 77 patients (28.1%) had discontinued treatment of their own will. The number of patients whose treatment was discontinued due to lack of efficacy was 15 (5.5%), while 36 patients (13.1%) initially responded to treatment but later discontinued due to loss of effectiveness. One patient discontinued treatment at the fourth month due to generalized numbness and fatigue. Another patient discontinued treatment at the fifth month due to a 7% reduction in body weight. Additionally, one patient developed a widespread maculopapular reaction within 24 hours after the fifth dose, leading to treatment discontinuation. Another patient experienced palpitations starting from the third dose, necessitating drug discontinuation. The total number of patients who discontinued treatment due to adverse effects was four (1.45%). Among these, two (0.74%) were male and two (0.74%) were female.

The mean age of male patients in the study was 43.15 ± 16.77 years, while that of female patients was 42.86 ± 14.93 years. No statistically significant difference was observed between the ages of male and female patients (P=0.885).

The mean follow-up duration for male patients was 35.52 ± 29.70 months, whereas for female patients, it was 35.68 ± 26.84 months. No significant difference was found between the sexes in terms of follow-up duration (P=0.964).

When evaluating early responders to omalizumab treatment based on sex, no statistically significant difference was observed between male and female patients in terms of initial response to the first dose (P=0.243) (Table 1).

Table 1. Treatment Response by Sex.

Sex	Number of Patients	Number of Early Responders	Number of Non-Responders	Relapse
Male	92	39	12	32
Female	184	64	25	42

Among patients who did not respond to omalizumab treatment, 12 were male, while 25 were female. No significant difference was found between the sexes regarding the lack of treatment response to omalizumab (P=0.874) (Table 1).

When evaluating relapse development in patients monitored after 16 weeks of omalizumab treatment, relapse was observed in 42 female patients (23.1%) and 32 male patients (34.8%). The relapse rate during omalizumab treatment was found to be significantly higher in male patients compared to female patients (p=0.02) (Table 1).

When patients who responded early to omalizumab treatment and those who did not were divided into two groups based on age—under 45 years and 45 years or older—a significant difference was observed in the response to the first dose in the younger age group compared to the older age group (P=0.01). Accordingly, the rate of benefiting from the first dose of omalizumab was significantly higher in patients under 45 years of age (Table 2).

When female patients who responded early to omalizumab treatment and those who did not were analyzed separately by age groups, no significant difference was found between the two age groups in terms of response to the first dose (P=0.446) (Table 2).

When relapse development after 16 weeks of omalizumab treatment was evaluated based on age groups, the recurrence rate was found to be significantly lower in the under 45 age group compared to the 45 years and older group (P=0.016) (Table 2).

Among the 274 patients, 103 (37.6%) achieved an early response to omalizumab as defined by a UAS7 <7 at the first month. Patients who achieved an early response had significantly lower baseline UAS7 scores compared to non-responders (P<0.001). Similarly, disease duration prior to omalizumab initiation was significantly shorter in early responders compared to non-responders (P<0.001).

Binary logistic regression was performed to determine whether baseline clinical characteristics were independently associated with early response to omalizumab (defined as UAS7 <7 at one month). The model was statistically significant (χ^2 = 277.765, P<0.001) and demonstrated good fit (Hosmer–Lemeshow test, P=0.788). Lower baseline UAS7 (odds ratio (OR): 0.657; 95% CI: 0.555–0.777; P<0.001) and shorter disease duration prior to omalizumab initiation (OR: 0.761; 95% CI: 0.697–0.831; P<0.001) were both independently associated with a higher likelihood of early treatment response. In contrast, sex (P=0.307) and age group (<45 vs. ≥45 years, P=0.872) were not independently associated with early response.

Notably, in univariate analysis, patients under 45 years of age showed a statistically significantly higher likelihood of achieving early response compared to those aged 45 years or older (P=0.01). However, this relationship did not persist after adjusting for disease duration and baseline UAS7 in multivariate analysis, suggesting the apparent age effect may be mediated through these clinical variables.

ROC curve analysis was performed to assess the ability of baseline UAS7 to predict early response to omalizumab. The area under the curve (AUC) was 0.083, indicating an inverse predictive relationship. Interpreted in clinical context, this corresponds to an AUC of 0.917 for lower baseline UAS7 predicting early response. Coordinate points suggested that patients with baseline UAS7 values below approximately 10–12 were most likely to achieve early response, whereas those with scores above 20 were highly unlikely to do so.

ROC curve analysis was conducted to assess the predictive value of disease duration for early response to omalizumab. The area under the curve (AUC) was 0.060, indicating an inverse association. Clinically, this corresponds to an AUC of 0.940 when interpreted for shorter disease duration predicting early response. Coordinate analysis suggested that a disease duration of less than six months was associated with the highest sensitivity for early treatment response, while durations exceeding 12–15 months were increasingly associated with non-response.

Discussion

In this study, we investigated the impact of age, sex, baseline UAS7, and disease duration on both early response and relapse risk in patients with chronic spontaneous urticaria treated with omalizumab. Our findings revealed that lower baseline UAS7 scores and shorter disease duration were both independently associated with a significantly higher likelihood of early response, while age and sex were not significant predictors in multivariate models. However, in univariate analysis, patients younger than 45 years were more likely to achieve early response. Additionally, relapse

Table 2. Treatment Response by Age Groups.

Age Groups	Number of Patients	Number of Early Responders	Non-Early Responders	Number of Female Early Responders	Number of Female Non-Early Responders	Relapse
UNDER 45 YEARS	151	67	84	39	65	32
46 YEARS AND ABOVE	123	36	87	25	53	42

rates were significantly higher in male patients and those aged 45 years or older, suggesting that these demographic factors may influence disease recurrence after treatment discontinuation. These findings support the clinical relevance of baseline disease burden and chronicity as predictors of early treatment benefit and also indicate that younger age and female sex may be associated with more sustained disease control following omalizumab therapy.

Chronic urticaria, defined as urticaria lasting more than six weeks, is reported to be 2–4 times more common in females than in males and is most frequently observed between the ages of 20 and 40 [1-3]. In our study, the mean age was 43 years, and the female-to-male ratio was found to be 1.97:1, consistent with previous epidemiologic data. This supports the representativeness of our study population in relation to the general CSU demographic.

Di Bona et al. reported a mean follow-up duration of 91 asthma patients treated with omalizumab as 45.6 months [10]. Similarly, in our study, the mean follow-up duration was found to be 35.5 months. In the same study by Di Bona et al. [10] six patients (6.6%) discontinued treatment due to adverse effects, whereas, in our study, the rate of treatment discontinuation due to adverse effects was lower, at 1.45%, suggesting a favorable tolerability profile of omalizumab across patient populations.

Sirufo et al. [11] conducted a study involving 26 female and 16 male patients and found that female patients had a better response to omalizumab. Additionally, at the end of the six-month initial treatment cycle, the recurrence rate was lower in female patients (15.4%) compared to male patients (50%). Conversely, a study by Bozat et al. [12] on pediatric patients with CSU suggested that sex did not influence treatment response. Similarly, Gouder et al. [13] investigated the effects, tolerability, and treatment responses of omalizumab in 17 male and 11 female asthma patients and found no significant differences between the sexes. In a study by Yu et al. [14], it was observed that the speed at which disease control was achieved with omalizumab was not associated with sex. In our study, no significant difference was found between the two sexes in terms of response to the first dose or lack of response to treatment, aligning with the general literature. However, when recurrence rates during omalizumab treatment were analyzed by sex, the recurrence rate was found to be significantly higher in male patients. In this regard, our study is consistent with the findings of Sirufo et al. [11], who suggested that this difference may be related to the effects of female hormones on histamine receptor profiles and mast cells [11].

In a study by Kitao et al. [15] involving 52 patients with chronic urticaria receiving omalizumab, patients were divided into two groups—those aged over 65 and those under 65—to examine the drug's effectiveness. They found that treatment response was significantly reduced in patients over 65 years of age. Similarly, Korn et al. [16] conducted a study on 174 asthma patients receiving omalizumab and found no significant difference in treatment response between patients aged over 50 and those under 50. Additionally, Ghazanfar et al. [17] analyzed 154 urticaria patients and found no association between older age and treatment response. In our study, when patients who benefited from the first dose of omalizumab were compared with those who did not, dividing them into two groups based on age (under 45 and 45 or older), the proportion of patients benefiting from the first dose was significantly higher in those under 45 years of age. In this aspect, our findings are consistent with the study by Kitao et al. [15]. Furthermore, in our study, when relapse development was analyzed based on age group, the recurrence rate was found to be significantly lower in the under 45 age group compared to the 45 years and older group. Overall, these results highlight that while age and sex may have some influence on relapse dynamics, they are unlikely to serve as stand-alone predictors of treatment response.

In addition to age and sex, we investigated baseline clinical factors that might predict early treatment response to omalizumab. Our findings revealed that lower baseline UAS7 scores and shorter disease duration were both significantly associated with achieving early response at four weeks. These observations suggest that patients with less severe disease activity and shorter-standing urticaria may experience faster clinical improvement following omalizumab initiation. Several previous studies support these observations. Chen et al. [5] demonstrated that CSU

patients with lower baseline UAS7 scores were significantly more likely to achieve early response to omalizumab (median UAS7 28 vs. 35, $P<0.01$), highlighting the relevance of initial disease severity in predicting treatment success. Similarly, Cubiro et al. [18] reported that patients with shorter disease duration exhibited better symptom control at 12 weeks, suggesting that early intervention may enhance therapeutic outcomes. In a Korean cohort, Kim et al. [19] further confirmed that shorter disease duration was independently associated with achieving disease control at three months. However, the literature also reflects some inconsistency. In contrast to our findings, Tonacci et al. [20] and Cubiro et al. [18] reported that baseline disease severity did not significantly influence response rates. Moreover, Marzano et al. [9] observed that while disease duration did not predict initial response to omalizumab, longer pre-treatment disease duration was associated with a higher risk of symptom relapse after therapy discontinuation.

Both baseline disease severity (UAS7) and chronicity (duration in months) showed strong discriminatory ability in predicting early response to omalizumab. ROC analysis revealed inverted AUC values of 0.917 and 0.940, respectively, for baseline UAS7 and disease duration. These findings suggest that initiating omalizumab in the earlier phases of CSU and in patients with lower symptom burden may substantially increase the probability of achieving early disease control.

Taken together, our findings suggest that early identification of patients with favorable baseline characteristics, such as lower disease activity and shorter duration of symptoms, may allow for a more tailored approach to omalizumab therapy in CSU. While sex and age did not independently predict initial response, their influence on relapse risk, particularly the higher recurrence observed in older and in male patients, highlights the importance of individualized follow-up and treatment continuation decisions. Integrating simple clinical parameters like baseline UAS7 and disease duration into treatment planning may help clinicians better predict treatment trajectory and optimize outcomes for CSU patients receiving omalizumab.

While our study provides clinically relevant insights, several limitations should be acknowledged. As a single-center retrospective study, generalizability may be limited, and certain laboratory biomarkers such as total IgE or autologous serum test results were not available for correlation. Relapse assessments were based on clinical follow-up without standardized timing, which may underestimate late recurrences. Despite these limitations, our findings reinforce the importance of baseline disease severity and duration as strong predictors of early omalizumab response. Additionally, the observed associations between younger age, female sex, and reduced relapse risk may guide treatment continuation and monitoring strategies. Integrating these accessible clinical parameters into treatment planning could support a more personalized approach in CSU management and improve patient outcomes.

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Dermatology Practical & Conceptual

Rethinking Melanocytic Tumors: A Critical Appraisal of the WHO Classification and the Myth of Nevus-to-Melanoma Progression

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Key words: Melanocytic tumors, Dysplastic nevus, WHO classification, Nevus-to-melanoma progression, Dermoscopy, Diagnostic gray zone

Citation: Argenziano G, Briatico G, Di Brizzi EV, et al. Rethinking Melanocytic Tumors: A Critical Appraisal of the WHO Classification and the Myth of Nevus-to-Melanoma Progression. *Dermatol Pract Concept*. 2025;15(4):6994. DOI: https://doi.org/10.5826/dpc.1504a6994

Accepted: October 7, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: The recent WHO classification of melanocytic tumors introduces a refined molecular and histopathological framework suggesting distinct pathways and precursor lesions for all melanoma subtypes. While conceptually appealing, its clinical applicability is increasingly questioned.

Objectives: This review critically examines the transformation theory from benign nevi to melanoma, highlighting inconsistencies between the proposed models and real-life practice.

Methods: Through illustrative cases and key epidemiological evidence, we evaluated the validity of current models proposing intermediate lesions in melanoma development.

Results: We argue that most melanomas arise de novo and that the so-called intermediate lesions, such as dysplastic nevi and atypical Spitz tumors, may mimic melanoma but are not true biological precursors.

Conclusions: We propose a simplified, clinically oriented reclassification of melanocytic lesions based on morphologic ambiguity and actual behavior, aiming to guide therapeutic decisions and reduce diagnostic overinterpretation.

Introduction

The classification and management of melanocytic tumors remain among the most debated areas in dermatology. Advances in molecular diagnostics and the recognition of a diagnostic gray zone [1] have blurred the boundaries between nevi, atypical lesions, and melanoma. This gray zone comprises lesions that resist clear categorization, resulting in considerable variability in diagnosis, terminology, and management.

The latest World Health Organization (WHO) classification [2] seeks to impose order by introducing molecularly defined pathways and attributing biological significance to many lesions traditionally regarded as intermediate. According to this model, virtually all melanomas arise from precursor lesions that evolve from benign to intermediate, then finally, to malignant, following specific molecular trajectories (Table 1).

While theoretically elegant, this concept has raised concerns among clinicians who rarely observe these progression models in everyday practice. This review critically examines the WHO model, particularly its concept of biologically intermediate melanocytic tumors. We argue that the transformation theory, in which nevi evolve into melanocytomas and ultimately into melanoma, is overemphasized and sometimes misleading. Instead, we advocate for a pragmatic, observation-based classification focused on morphologic ambiguity and risk of recurrence or invasion.

The Diagnostic Gray Zone: Clinical and Pathological Perspectives

Most melanocytic lesions encountered in dermatology can be safely diagnosed as clearly benign or clearly malignant. Yet a small but important subset falls into a diagnostic gray zone, displaying architectural disorder, cytologic atypia, or unusual dermoscopic patterns without fulfilling the criteria for melanoma [1].

For dermatologists, this gray zone consists of lesions that raise suspicion but lack definitive malignant features. For pathologists, the dilemma is greater; they are expected to provide definitive diagnoses, yet many such lesions can only be described with umbrella terms such as dysplastic nevus, atypical Spitz tumor, or melanocytoma that convey uncertainty more than precision.

These ambiguous lesions are often graded biologically (low or high grade) to imply malignant potential. However, such assessments rely on variably interpreted histopathological criteria and lack robust prospective validation.

The result may be over- or underdiagnosis, over- or undertreatment [3], and patient anxiety. A biopsy showing architectural disorder and cytologic atypia may be labeled high-grade dysplastic nevus, prompting re-excision despite no clinical evidence of aggressiveness. Conversely, a melanoma with blunt morphologic features might be under-classified and undertreated. These paradoxes highlight the limits of current diagnostic frameworks and the need for a case based clinical approach.

The WHO Classification: A New Paradigm or Theoretical Overreach?

The 2018 WHO Classification of Skin Tumours marked a conceptual shift. Moving beyond the traditional clinical and histopathological categories of superficial spreading, nodular, lentigo maligna, and acral lentiginous melanoma, it proposes nine molecularly-defined pathways, each linked to a specific melanoma subtype and its putative precursor.

Table 1. WHO Melanoma Pathways: The 9 Progression Routes.

Pathway No.	WHO Designation	Cumulative Sun Damage (CSD)	Proposed Precursor
1	Low-CSD melanoma including superficial spreading melanoma	Low	Common and dysplastic nevus
2	High-CSD Lentigo Maligna Melanoma	High (chronic)	Intraepidermal melanocytic proliferation
3	Desmoplastic Melanoma	High (chronic)	Intraepidermal melanocytic proliferation
4	Spitz Melanoma	None	Spitz nevus
5	Acral Melanoma	None	Acral nevus*
6	Mucosal Melanoma	None	Mucosal melanosis*
7	Melanoma in Congenital Nevus	Variable	Congenital nevus
8	Melanoma in Blue Nevus	None	Blue nevus
9	Uveal Melanoma	None	Uveal melanocytic proliferation

*Note: In some pathways (e.g., mucosal, acral), the precursor lesion is hypothetical or histologically undefined.

According to this model, most melanomas emerge through stepwise transformation from a benign nevus to an intermediate lesion and ultimately to melanoma. Each pathway is presented as a predictable, lineage-specific progression, similar to the multistep evolution of certain epithelial cancers.

While intellectually appealing and valuable for research, the clinical utility of this stratified model is doubtful. The assumption that every melanoma derives from a known precursor contradicts decades of clinical observation [4]. Several proposed sequences remain biologically speculative and lack corroboration in daily practice.

For example, the Spitz pathway posits a linear evolution from Spitz nevus to Spitz melanocytoma to melanoma, a sequence rarely, if ever, documented [5]. Likewise, the idea that all superficial spreading melanomas arise from a common acquired nevus progressing through dysplastic stages to melanoma in situ and then invasive disease is seldom reflected in clinical case series or histopathological slides [6].

The most striking logical flaw involves congenital nevi. The WHO classification suggests that transformation proceeds through proliferative nodules to an in situ melanoma. Yet by definition, an in situ melanoma confined to the epidermis cannot logically arise as the next step after an already invasive dermal proliferative nodule.

Thus, while the WHO framework enriches molecular taxonomy, applying it rigidly in clinical dermatology risks overinterpreting histopathological atypia as biological aggressiveness, leading to unnecessary surgeries and psychological burden.

Class I and II Melanocytic Tumors: What Do They Really Mean Clinically?

A central feature of the new WHO classification is the division of melanocytic tumors into four broad classes according to biological behavior and presumed risk of progression. While Classes III and IV refer to clearly malignant melanomas (thin and thick invasive lesions, respectively), Classes I and II encompass the so-called precursor melanocytic tumors.

Class I lesions are described as low-grade melanocytic tumors with an estimated risk of malignant transformation of about 1 in 10,000 [7]. The WHO advises no treatment beyond conservative excision. This group includes:

- Common acquired nevi (no atypia)
- Congenital nevi (no atypia)
- Dysplastic nevi (low grade)
- Common blue nevi

For clinicians this categorization seems acceptable. These lesions have indolent behavior and are rarely problematic. Yet calling them precursor lesions creates confusion, because they appear entirely banal clinically and dermoscopically.

Class II lesions, in contrast, are labeled as high-grade melanocytic tumors, with a low but not negligible risk of progression (approximately 1 in 100) [7]. The WHO recommends complete excision and often re-excision. This group includes:

- Dysplastic nevi (high grade)
- Spitz nevi
- Cellular blue nevi
- Deep penetrating nevi (plexiform)
- Lentigo maligna
- Melanoma in situ

This classification leads to striking therapeutic inconsistencies. Conventional Spitz nevi and melanoma in situ, which are biologically and clinically distinct, are placed in the same category. Likewise, the inclusion of cellular blue nevi, lesions that very rarely progress to melanoma, alongside lentigo maligna is not supported by clinical experience.

A particularly problematic example is the high-grade dysplastic nevus. Despite its ominous label and histopathological atypia, it is very common, especially in young individuals, and usually benign. Many dermatologists therefore find themselves re-excising lesions that are biologically indolent simply because of a category assignment rather than any real clinical risk. By contrast, dysplastic nevi are very rare in the elderly, a diagnosis in this age group likely representing an under-classification of a featureless melanoma. These contradictions expose the gap between histopathological theory and patient care. The WHO framework assigns a theoretical progression risk based on morphology, whereas clinical decision-making must also consider age, body site, dermoscopic pattern, patient history, and lesion dynamics. Without this context, strict application of the WHO classification system risks unnecessary treatment and loss of personalized care.

The Spitz Conundrum

Among the most debated elements of the WHO classification is the idea that Spitz tumors represent a biological continuum culminating in melanoma. The proposed Spitz pathway describes a linear evolution from Spitz nevus to Spitz melanocytoma (previously termed atypical Spitz tumor), then to melanocytic tumor of uncertain malignant potential or spitzoid tumor of uncertain malignant potential, and finally to Spitz melanoma.

This sequence finds little support in clinical reality. Dermatologists and dermatopathologists seldom observe a conventional Spitz nevus evolving into melanoma. In fact, Spitz nevi, especially in children and adolescents, usually regress or stabilize and often develop a more conventional appearance over time [8]. Even when they grow asymmetrically or exhibit worrisome features, excision typically confirms a benign Spitz nevus without evidence of progression.

Moreover, the diagnosis of Spitz melanoma is exceptionally rare and often based solely on histopathological features without documented clinical evolution from a precursor. This raises the possibility that some lesions classified as Spitz melanoma are actually melanomas with spitzoid morphology rather than descendants of a benign Spitz lineage.

Confusion is amplified by the bidirectional overlap of morphology: some melanomas can mimic Spitz nevi and vice versa. As a practical safeguard, any spitzoid-looking lesion that appears after puberty is usually excised [9].

The overall picture is not one of linear progression but of morphological overlap between two distinct entities. Conflating overlap with true progression risks diagnostic inflation and unnecessary re-excisions, increasing both patient anxiety and healthcare costs. The Spitz example illustrates the danger of applying rigid theoretical models to lesions whose behavior is better understood through clinical observation and dermoscopic follow-up.

Three Clinical Cases that Challenge the Progression Theory

While the transformation model from benign nevus to melanoma is conceptually appealing, clinical evidence often tells a different story. The following cases highlight how real-world dermatology practice contradicts the notion of stepwise nevus to melanoma transformation.

Case 1: The Supposed Precursor that Became a 7.5 mm Melanoma

A 45-year-old male presented with a pigmented lesion on the face that was excised and diagnosed as a junctional melanocytic proliferation consistent with a dysplastic nevus, a WHO Class I low-grade lesion (Figure 1). Two and a half years later, a nodular lesion appeared in the same location and proved to be a 7.5 mm thick melanoma with 12 mitoses per square millimeter (Figure 2).

Either the first lesion transformed in record time, or it was already a melanoma misdiagnosed as a nevus. Given the short interval and aggressive behavior, misclassification is the more likely explanation.

Case 2: A High-Grade Dysplastic Nevus that was Clearly Benign

A 27-year-old female had two pigmented lesions excised. One was called a low-grade dysplastic nevus, and the other one was diagnosed as a high-grade dysplastic nevus. This latter lesion, located on the leg, showed no clinical or dermoscopic sign of malignancy (Figure 3). The WHO guidelines called for re-excision, yet clinical judgment favored simple observation.



Figure 1. A pigmented lesion on the cheek of a middle-aged male. Dermoscopically, no prevalent benign criterion is seen. Furthermore, a black blotch could be suggestive of an invasive melanoma, a diagnosis that was not supported by the histopathologists, who concluded it was a dysplastic nevus.

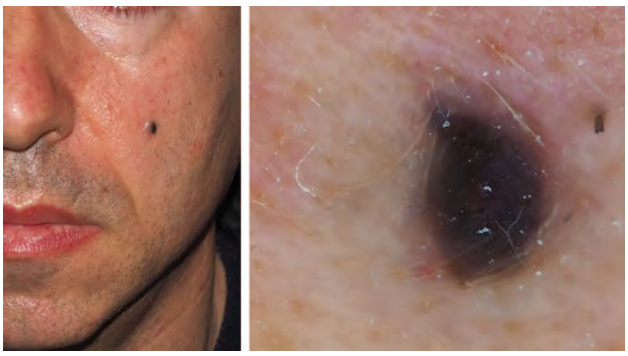


Figure 2. Same patient as Figure 1. A relapse of the previous lesion was observed and diagnosed histopathologically as a melanoma, 7.5 mm Breslow thickness.

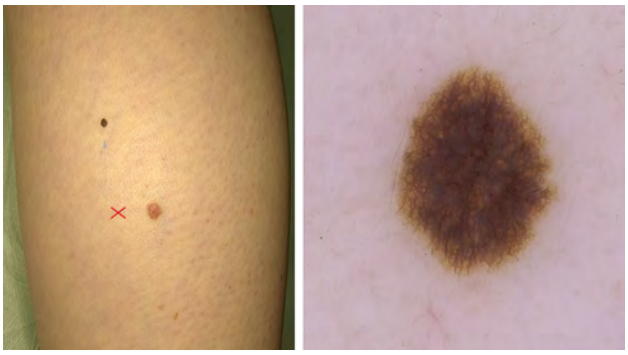


Figure 3. The patient's young age and the regular pigment network suggest the diagnosis of a benign nevus. However, histopathologically, this lesion was diagnosed as high-grade dysplastic nevus.

Case 3: A High-Grade Dysplastic Nevus that was a Melanoma

A 58-year-old female presented with a solitary pigmented lesion on the leg (Figure 4). Histopathology labeled it a compound nevus with severe dysplasia. However, the asymmetry and dermoscopic pattern strongly suggested melanoma in situ.

Together, these cases show that so-called intermediate diagnoses can obscure the true nature of a lesion, either by exaggerating or underestimating risk, and they demonstrate

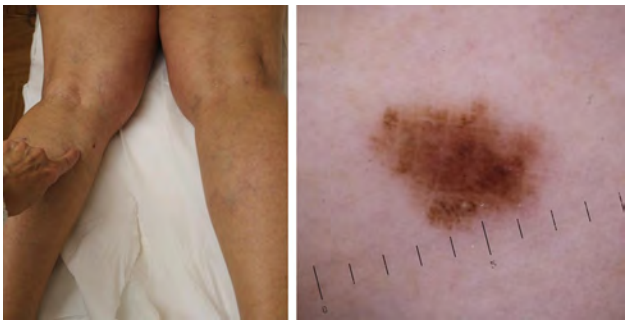


Figure 4. Solitary lesion on the leg of a middle-aged female. Dermoscopically, atypical network, atypical globules, and prominent skin markings are visible, suggesting the diagnosis of melanoma in situ. Again, the histopathological diagnosis was high-grade dysplastic nevus.

the need to integrate clinical and dermoscopic information with histopathology.

Three Facts That Undermine the Precursor Theory

Fact 1: Over 70% of Melanomas Arise De Novo

Multiple studies have shown that more than 70% of melanomas are not associated histopathologically with a pre-existing nevus [10]. In other words, in the majority of cases, no nevus remnant is found within or adjacent to the melanoma. Proponents of the progression theory argue that the original nevus may have been obliterated early in the malignant process, thus becoming undetectable. However, this explanation is neither parsimonious nor consistent with clinical experience. It implies that nevus remnants should vanish while the lesion is still very small, given that even in a series of very small melanoma, excised when they were less than 5 mm, nevus remnants are usually not found (Figures 5 and 6). The absence of nevus remnants in the vast majority of melanomas weakens the concept of obligatory precursor lesions and instead supports the idea that most melanomas arise de novo, from a single melanocyte of the normal skin acquiring tumorigenic mutations.

Fact 2: The Progression Sequence Is Never Seen in Full

If the stepwise model were valid, we would expect to see histopathological specimens showing coexisting zones of common nevus, dysplastic nevus, and melanoma within the same lesion. In practice, such histopathological continuity is extremely rare-to-nonexistent. Moreover, among the minority (about 30%) of melanomas that do appear associated with a nevus, more than half arise from banal dermal nevi, not dysplastic ones [11] (Figure 7). This observation challenges the logic of the progression model, which would require dysplastic nevi as obligatory intermediates. Rather than true

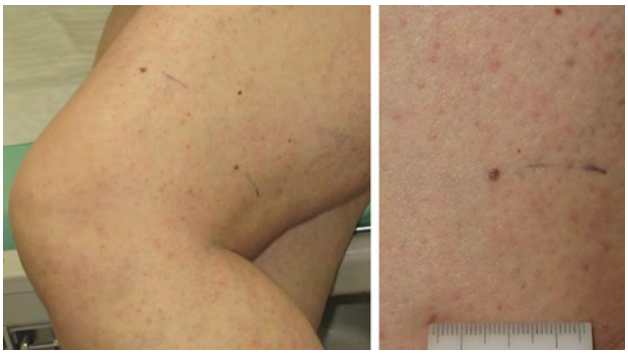


Figure 5. This is a melanoma in situ with a diameter of about 2 mm.

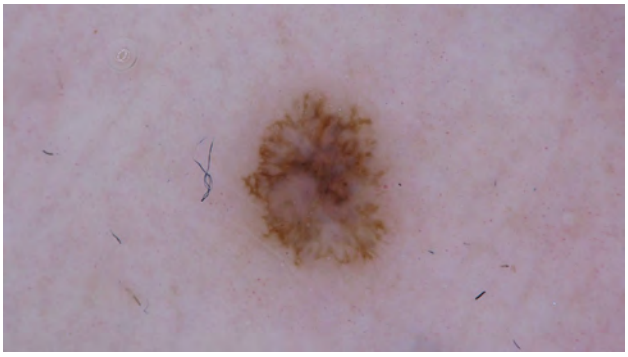


Figure 6. Dermoscopic image of the lesion shown in Figure 5 showing clear-cut melanoma-specific features such as irregular streaks at the periphery and regression structures in the center. This is a melanoma in situ with no clinical, dermoscopic, or histopathological sign of an associated nevus.

progression, these may represent collision tumors, i.e., the coexistence of an evolving melanoma adjacent to or superimposed on a pre-existing nevus, without biological lineage continuity.

Fact 3: The Statistical Probability Is Exceedingly Low

Large-scale epidemiological studies have estimated that the risk of malignant transformation of a single nevus is approximately 1 in 200,000 [7]. This extremely low figure is incompatible with the idea that nevi are common steppingstones toward melanoma.

Even in high-risk patients with hundreds of nevi, most melanomas still arise de novo (Figures 8 and 9). This further invalidates the rationale for treating dysplastic or atypical nevi as biologically dangerous entities requiring special attention. Certainly, individuals with many nevi need long-term monitoring with total body photography and sequential digital dermoscopy imaging [12], but the main aim of sequential surveillance is to facilitate the detection of a melanoma developing among the numerous clinically similar nevi rather than monitoring nevi that may progress to melanoma, which is much less likely to happen.

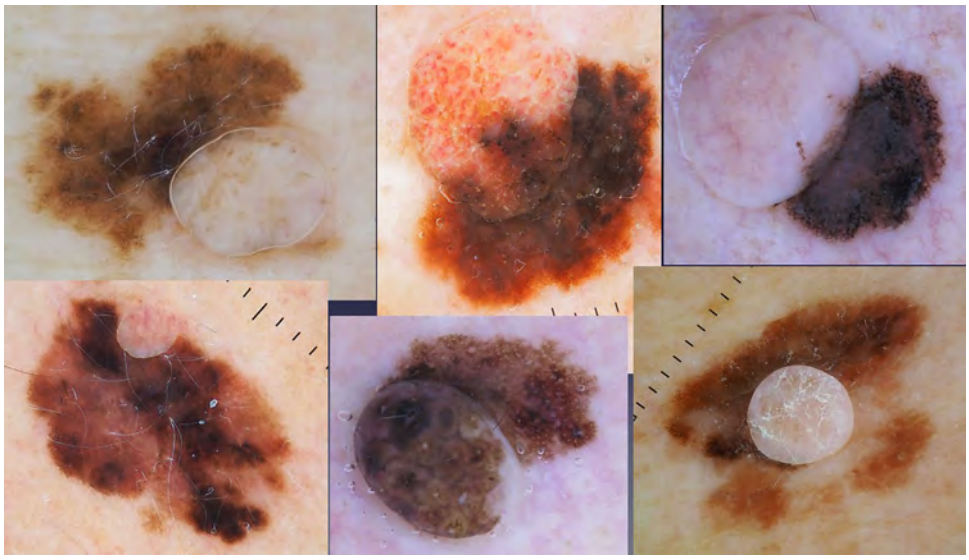


Figure 7. Six dermoscopic images of nevus-associated melanomas. The nevus component is represented by a classical dermal nevus.



Figure 8. Clinical image of a patient with multiple nevi.

Taken together, these three facts provide compelling evidence that the nevus-to-melanoma transformation model is an exception, not the rule. As such, it should not drive routine clinical decision-making, particularly in the absence of a good clinical-histopathological correlation.

A Proposal for a More Useful Classification

The current WHO classification, while theoretically sophisticated and grounded in molecular pathology, attempts to impose a linear logic on the process of melanoma genesis. However, clinical observations suggest that, like most complex biological phenomena, melanoma genesis is nonlinear, chaotic, and unpredictable. As discussed, the insistence on assigning to every melanoma a defined precursor lesion is not supported by clinical experience or epidemiological data.

In light of these discrepancies, we propose a simplified and pragmatic classification of melanocytic tumors that better reflects the reality of clinical dermatology. Rather than relying on assumed biological progression or histopathological terminology with variable interpretation, we suggest categorizing lesions based on the degree of morphological ambiguity and actual clinical behavior.

This framework would consist of three primary categories:

1. Clearly Benign Melanocytic Nevi
   - Diagnostically straightforward in most cases
   - Rarely if ever recur or evolve
2. Clearly Malignant Melanomas
   - In situ or invasive melanomas with well-established clinical, dermoscopic, and histopathological criteria
   - Require prompt excision and staging
3. Ambiguous Melanocytic Tumors (The "Gray Zone")
   - Lesions that defy easy classification, either clinically, dermoscopically, or histopathologically
   - Management should be individualized based on clinical scenario, dermoscopic features, histopathological criteria, and multidisciplinary discussion
   - Re-excision should be decided case-by-case, not mandated by label alone

Such a framework would better align with daily practice, minimize over- and underdiagnosis and over- and undertreatment, and still integrate pathology and molecular insights where they add genuine value.

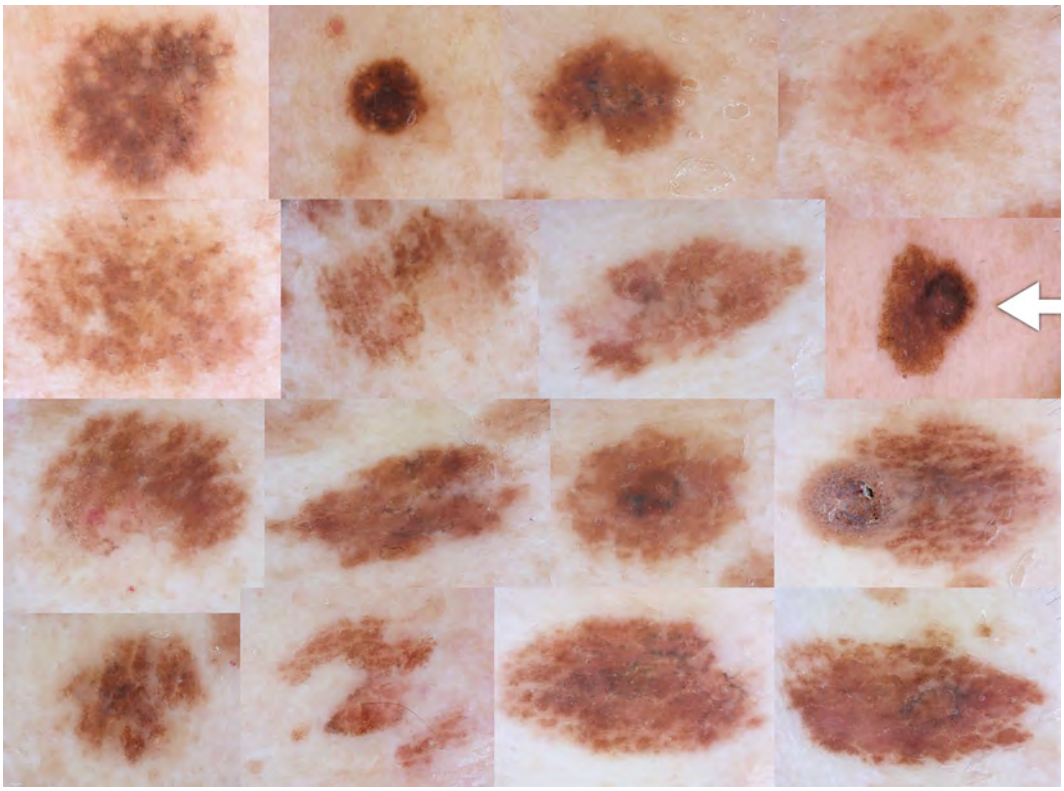


Figure 9. Dermoscopic images of some of the lesions of the patient in Figure 8. Many of these lesions are dermoscopically atypical. However, only the lesion indicated by the arrow was diagnosed histopathologically as a de novo melanoma in situ.

Conclusions and Practical Recommendations

The management of melanocytic tumors, particularly those falling into the so-called "intermediate" or "gray zone," remains one of the most challenging aspects of dermatology practice. While the latest WHO classification offers a refined framework rooted in molecular pathology, its clinical transposition is far from straightforward.

This review highlights how many of the assumptions underlying the nevus-to-melanoma transformation model are not corroborated by real-world evidence. Most melanomas arise de novo, not from pre-existing nevi, many so-called "high-grade dysplastic nevi" are biologically indolent, and some melanomas with bland histopathological features are misclassified as borderline lesions, delaying appropriate management.

Instead of rigidly adhering to histopathological labels or theoretical pathways, clinicians must embrace a case-by-case approach that prioritizes clinical scenario, dermoscopic morphology, lesion dynamics, and patient history. Only through this integrative method can we avoid both over- and undertreatment.

The ultimate goal should not be to fit every lesion into a predefined category but to provide patients with the most appropriate precision care based on the best available clinical, dermoscopic, and histopathological evidence, used in harmony, not in isolation.

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Dermatology Practical & Conceptual

Targeted Therapies and Pharmacologic Advances in Mucous Membrane Pemphigoid: A Comprehensive Review

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Key words: Autoimmune Bullous Dermatoses, Mucous Membrane Pemphigoid, Cicatricial Pemphigoid, Pemphigoid Antibodies, Novel therapies

Citation: Busol VN, Kudryashov NV. Targeted Therapies and Pharmacologic Advances in Mucous Membrane Pemphigoid: A Comprehensive Review. *Dermatol Pract Concept*. 2025;15(4):5749. DOI: https://doi.org/10.5826/dpc.1504a5749

Accepted: July 20, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Mucous membrane pemphigoid (MMP) is a rare autoimmune bullous dermatosis which predominantly affects the mucous membranes and, occasionally, the skin. The exact pathogenesis of MMP remains unclear and should be considered as a unique phenomenon, which involves the formation of subepithelial blisters and fibrosis.

Objectives: This narrative review aimed to summarize the pharmacological agents which showed efficacy in the management of MMP but that are not included in the guidelines.

Methods: We conducted a search on Google Scholar, PubMed, and the Web of Science databases concerning articles published in English on the management of MMP between January 2000 and February 2025; all the sourced articles were full-text reviewed.

Results: We included 13 articles. The studied pharmacological agents are classified as immunosuppressive agents (leflunomide, sirolimus, daclizumab) and biologics (daclizumab, dupilumab, omalizumab, bevacizumab, aflibercept, cenegermin); the immunosuppressant leflunomide and the antimalarial agent hydroxychloroquine are also classified as disease-modifying antirheumatic drugs. Other pharmacological agents (colchicine, corticotropin, varenicline, lifitegrast) exert miscellaneous mechanisms.

Conclusion: Considering the severity of the condition, progressive fibrosis, and resistance to therapy, more research is required in relation to the pathogenesis of MMP and the efficacy and safety profile of novel pharmacological options. Pharmacological agents should provide the achievement and maintenance of remission with minimal adverse effects. A broader spectrum of pharmacological agents will allow a personalized approach and more alternatives, in particular for recalcitrant cases, failure of the previous therapy, and in patients with MMP and malignancy.

Introduction

Mucous membrane pemphigoid (MMP) is a rare autoimmune bullous dermatosis (AIBD) which predominantly affects mucous membranes and the skin. Generally, MMP has a late onset, and the mean age of patients ranges from 60 to 80 years; the association between the condition and HLA-DQB1*0301, HLA-DRB1*1101, HLA-DQA1*0505 alleles has been notes noted.

The pathogenesis of MMP remains unclear and involves the formation of subepithelial blisters and fibrosis. The formation of blisters is linked to the production of antibodies (IgG and/or IgA) against the basement membrane proteins BP230 and BP180, α6 and β4 integrin subunits, laminin-332, laminin-6, type VII collagen. The activation of fibroblasts and hyperproduction of collagen may be associated with the dysregulation of immunity, excessive release of pro-inflammatory molecules, and proteolytic enzymes [1]. Transforming growth factor beta (TGF-β) plays a major role in fibrosis, and an increased expression of TGF-β and alpha-smooth muscle actin were observed in conjunctiva samples taken from patients with MMP [2].

MMP develops through three distinct phases: injury, acute inflammation and proliferation, and fibrosis. Subepithelial tense blisters precede erosions and scarring. Histologically, the separation of the epithelium from the underlying connective tissue, leukocyte infiltrates, granulation tissue, and fibrosis may be seen. Direct immunofluorescence demonstrates peculiar linear depositions of immunoglobulins (IgG and/or IgA) and/or complement C3 along the basal membrane; indirect immunofluorescence (salt-split) and immunoserological tests detect pathogenic autoantibodies [1].

Since 2002, several guidelines have evolved on the management of MMP. The First International Consensus on MMP [3] and the guidelines of the Brazilian Society of Dermatology [4] and the Japanese Dermatological Association [5] classify patients as low risk (oral and/or cutaneous lesions) or high risk (ocular, pharyngeal, laryngeal, esophageal, and/or genital involvement), with adapted treatment options depending on the risk category; the guidelines of the French Society of Dermatology [6] are based on the location and disease severity. The European Guidelines (S3) [7] and the S2k guideline [8] offer lines of therapy, alternative combinations, and treatment options, depending on the clinical course, location, and response. Given the risk of disease progression and complications, early initiation of immunosuppressive therapy is of vital importance; in severe cases, surgical treatment is considered. Nonetheless, there is no gold standard for treatment.

This narrative review aimed to summarize the pharmacological agents which showed efficacy in the management of MMP but that are not included in the earlier published guidelines.

We conducted a search on Google Scholar, PubMed, and the Web of Science databases concerning articles published in English on the management of MMP between January 2000 and February 2025, using the search terms “mucous membrane pemphigoid”, “cicatricial pemphigoid”, “Brunsting-Perry pemphigoid”, “management”, “guidelines”. All the sourced articles were full-text reviewed. The criteria for inclusion of the articles were publication in English and the use of pharmacological options not included in the published guidelines.

Drug Review

We included 13 articles in English in which the diagnosis of MMP was verified and the data on the capacity to induce disease control and improvement and the absence of reported severe adverse effects of the suggested pharmacological options were available (Table 1).

The studied pharmacological agents are classified as immunosuppressive agents (leflunomide, sirolimus, daclizumab) and biologics (daclizumab, dupilumab, omalizumab, bevacizumab, aflibercept, cenegermin); the immunosuppressant leflunomide and the antimalarial agent hydroxychloroquine are also classified as disease-modifying antirheumatic drugs. Other groups of pharmacological agents (colchicine, corticotropin, varenicline, lifitegrast) exert miscellaneous mechanisms, which are specified bellow.

Interleukin (IL)-2 is a pro-inflammatory cytokine, also known as T cell growth factor; positive expression of IL-2 is observed in T cells, infiltrating the MMP-affected conjunctiva [9]. Daclizumab, a monoclonal anti-CD25 antibody, binds to the human IL-2 receptor (IL-2Rα) in the IL-2Rα

Table 1. Pharmacological Agents Reported in the Management of Mucous Membrane Pemphigoid.

Drug	Drug class	Condition	No. of reported patients	No. of patients with improvement	References
Omalizumab	Monoclonal anti-IgE antibody	MMP	5	3	Alexandre et al. (2022)
Daclizumab	Monoclonal anti-CD25 antibody / IL-2R antagonist	OcMMP	1	1	Papaliodis et al. (2003)
Dupilumab	IL-4/IL-13-inhibitor	MMP BPP	1 1	1 1	Wang et al. (2024) Raef et al. (2021)
Cenegermin	rhNGF	OcMMP	1 1	1 1	Abbot et al. (2024) Surico et al. (2024)
Colchicine	Anti-mitotic agent	OrMMP MMP	6 12	5 8	Fribourg et al. (2024) Chaidemenos et al. (2011)
Leflunomide	Pyrimidine synthesis inhibitor	OcMMP MMP	1 1	1 1	Smichowski et al. (2020) Boedeker et al. (2003)
Hydroxychloroquine	Antimalarial agent	OcMMP BPP	1 1	1 1	Morel et al. (2022) Guerrero et al. (2025)
Corticotropin	Adrenocorticotropic hormone formulation	OcMMP	15	9	Sharon et al. (2022)
Varenicline	Selective nAChR partial agonist	OcMMP	4	1	Abbot et al. (2024)
Lifitegrast	ICAM-1 and LFA-1 antagonist	OcMMP	10	2	Abbot et al. (2024)

ectodomain, the binding site of IL-2 to immune cells, and inhibits B cell proliferation and IL-2-mediated T cell activation. Papaliodis et al. (2003) reported one patient diagnosed with ocular MMP (OcMMP) and successfully treated with daclizumab [10].

An increased expression of IL-4 was noted in conjunctival sections of patients with OcMMP and in isolated fibroblasts; IL-4 may exert a modulatory effect on macrophages via inducing m-CSF as well as uncontrolled extracellular matrix accumulation [11]. An elevated stromal expression of IL-13 is seen in active OcMMP, suggesting profibrotic and pro-inflammatory effects on human conjunctival fibroblasts [12]. Dupilumab, a recombinant fully human IgG4 monoclonal antibody, suppresses inflammatory signaling via binding to the IL-4Rα subunit of IL-4 and IL-13 receptor complexes. Dupilumab combined with systemic corticosteroids was reported as effective in a patient with multisite MMP (oral, genital, and cutaneous involvement) [13] and Brunsting-Perry pemphigoid [14].

The circulation of sera IgE autoantibodies against the BM components [15,16] as well as linear IgE depositions along BM on immunofluorescence [15,17] have been observed in patients with MMP. Omalizumab is a humanized monoclonal anti-IgE antibody which neutralizes total serum IgE via forming interactions with IgE Cε3 domains outside the FcεRI-binding site and inhibiting FcεRI and CD23 binding. Omalizumab was reported to induce complete remission in three out of 5 patients with MMP (with oral, laryngeal, and genital MMP-related lesions) [18].

Neutrophils are present in inflammatory infiltrates at the acute stage and persist in MMP-affected tissues even when inflammation is visually resolved [9,19], and the involvement of other mechanisms (i.e., neutrophil recruitment) has been suggested in the pathogenesis of MMP [20]. Colchicine, a bioactive plant alkaloid derived from *Colchicum autumnale*, is commonly used in gout flares, familial Mediterranean fever, Behçet's disease, psoriasis, Sweet's syndrome, and erythema nodosum [21]. Colchicine inhibits neutrophil recruitment and disrupts the NLRP3 inflammasome assembly in neutrophils and monocytes through the inhibition of cellular P2X7 receptors; the suppression of β-tubulin polymerization and synthesis of microtubules is related to anti-mitotic properties [22]. Colchicine has been offered as a second-line option in oral MMP [23]; earlier colchicine was also suggested as a first-line corticosteroid-sparing agent in MMP [24]. Adverse effects (AEs) of colchicine include cardiomyopathy, cytopenia, elevation of hepatic transaminases, maculopapular rash, and alopecia [21].

Hydroxychloroquine, an antimalarial and antirheumatic agent, exerts anti-inflammatory action via the disruption of antigen presentation in the background of intracellular pH alteration, processing of antigenic protein, and formation of the alpha and beta chains of major histocompatibility complex class II proteins, reducing T cell stimulation and immune responses [25]. Hydroxychloroquine has been reported to induce disease control in MMP [26] and Brunsting-Perry pemphigoid [27]; however, retinopathy, as well as cardiac and auditory toxicity [28] and dermatological AEs, in particular in autoimmune conditions [29], are linked to hydroxychloroquine.

Leflunomide is an isoxazole derivative and pyrimidine synthesis inhibitor used in MMP. The drug inhibits the mitochondrial enzyme dihydroorotate dehydrogenase, disrupting de novo synthesis of pyrimidine ribonucleotide uridine monophosphate, required for the progression from G1 to S phase in activated lymphocytes; these cytostatic and anti-proliferative effects may contribute to disease control in patients with MMP [30,31]. Diarrhea, elevation of liver enzymes, rash, and alopecia are the most frequent AEs of leflunomide in rheumatoid arthritis [32].

Melanocortins exert anti-inflammatory effects via the stimulation of glucocorticoid-dependent and glucocorticoid-independent pathways, reducing the release of pro-inflammatory cytokines and ROS. Repository corticotropin injection (RCI) was earlier offered for systemic lupus erythematosus, given the reduction of B cell proliferation (possibly, via suppressing the activity of IL-6 and B-cell-activating factor of the tumor necrosis factor (TNF) family signaling) [33]. Furthermore, RCI has been suggested as a safe and well-tolerated alternative or adjunctive option for patients with severe and refractory OcMMP, inducing improvement in 60% of cases; no serious AE has been reported [34].

The recombinant human nerve growth factor (rhNGF) cenegermin improves corneal healing via binding to the tyrosine kinase receptor TrkA and to p75NTR, promoting neuronal and epithelial cell growth. Abbot et al. (2024) reported the resolution of MMP-associated large, non-healing corneal defect in two patients treated with cenegermin [35,36], but Surico et al. (2024) highlighted patient monitoring due to the formation of corneal superficial plaque linked to posttreatment epithelial hyperplasia [36].

Sirolimus, a mammalian target of rapamycin (m-TOR) inhibitor, suppresses cytokine and growth factor receptor signaling and T cell progression from G1 to S [30]. Sirolimus was reported in combined and rotation therapy in OcMMP [37]. On the other hand, sirolimus-induced bullous pemphigoid was reported in two renal transplant recipients [38]; consequently, sirolimus should be employed with caution in autoimmune skin blistering diseases (AIBDs).

Vascular endothelial growth factor (VEGF) is involved in immune responses and proliferation, exerting signaling by binding to tyrosine kinase receptors, and bevacizumab and aflibercept neutralize VEGF via forming interactions with the receptor-binding regions. Subconjunctival and intravitreal injections of bevacizumab and aflibercept [39,40] have been reported in OcMMP; in the mentioned cases, these agents did not alter the severity of the disease course. However, hypothetically, given their capacity to suppress angiogenesis and tissue remodeling, these agents may represent an opportunity to improve quality of life of patients with MMP as adjuvant therapy, although clinicians must be aware of drug-induced MMP [1].

Dry eye disease is frequently associated with OcMMP. Varenicline, a selective nicotinic acetylcholine receptor (nAChR) partial antagonist, induces the basal tear film formation by the lacrimal gland via the stimulation of the trigeminal parasympathetic nerve pathway [41]. Lifitegrast binds to the integrin lymphocyte function-associated antigen-1, preventing its interaction with the intercellular adhesion molecule-1, blocking the formation of immunological synapse, T cell activation, and suppressing inflammatory cascades [42]. These agents are employed in dry eye disease; however, their efficacy was limited in OcMMP [35].

Mucous Membrane Pemphigoid and Malignancy

In MMP, malignancy is reported in 15.5% of cases [43], while in patients with sera anti-laminin 332 antibodies (anti-laminin-332 MMP), the malignancy rate is 21–21.8% [43,44]. Laminin-332 is a structural glycoprotein of BM which is involved in extracellular matrix formation, cell proliferation and migration; its elevation has been observed in some tumors and may trigger autoimmune reactions and cross-reactivity with BM proteins [45,46]; thus, various studies highlight an elevated malignancy risk in anti-laminin-332 MMP [44,47]. Another issue is MMP induced by malignancy treatment (e.g., radiation [48] and immune checkpoint inhibitors [49]).

The current guidelines do not contain sections on the management of anti-laminin-332 MMP or of MMP in patients with a history of previous or concurrent malignancy, and the selection of therapy depends on lesion location and severity of the disease course. The use of immunosuppressive agents raises concerns over tumorigenesis risks [43,50,51], and several studies warn about elevated malignancy risks [52]. On the other hand, malignancy was detected before establishing the diagnosis of MMP in 47.1% of patients [43], and immunosuppressive agents have also been reported to have antineoplastic effects [51,53,54,55]. Corticosteroids remain among the most frequently indicated drugs in oncological conditions [56]. In paraneoplastic pemphigus, another autoimmune blistering disease, the guidelines indicate systemic

corticosteroids and steroid-paring agents: cyclophosphamide, azathioprine, mycophenolate mofetil, rituximab, intravenous immunoglobulin (IVIG) [57,58]. The latter two were recently reported in anti-laminin-332 MMP [59,60,61], while cyclophosphamide is associated with bladder malignancy [62]. The use of mycophenolate mofetil raises concerns [52] but may also be associated with lower cancer risks [52,63]. Curiously, in inflammatory bowel disease, thiopurines (azathioprine) should be withdrawn in patients with active cancer, and the combination of thiopurines and TNF-alpha inhibitors is linked to a higher lymphoma risk, which should be considered before the therapy selection [64].

The pharmacological agents discussed in this review may also be of interest in the management of MMP and malignancy.

The antitumor effect of leflunomide has been confirmed in myeloma (NCT02509052) and will be examined in other clinical trials (NCT06540937, NCT04997993, NCT03709446, NCT04508790, NCT06229340, NCT06454383); the evaluation of the effect of hydroxychloroquine in melanoma and various cancer types in different regimes is planned for clinical trials (NCT04464759, NCT05647330, NCT0632 8387, NCT07061717, NCT06949982, NCT05518110, NCT06229340, NCT06408298, NCT05733000, NCT0584 3188, NCT04841148).

The expression of CD25 is observed in activated T cells and some malignancies; regulatory T lymphocytes (Tregs) constitute the tumor microenvironment, contributing to drug resistance via the suppression of immune surveillance [65]. Before its global withdrawal, daclizumab was reported in combination with chemotherapy and as an option to overcome the Tregs-mediated drug resistance [66,67]. Developing pharmacological agents which target CD25 may be of use for the management of both malignancy and MMP.

Given the link between the PI3K/mTOR signaling pathway and genetic mutations [51,68], sirolimus is a curious option.

Colchicine exerts anti-mitotic properties [69] and has been associated with a lower risk of colorectal cancer in immune-mediated inflammatory diseases [70].

Dupilumab is generally considered safe, but caution is required in patients with cutaneous T-cell lymphoma [71,72]. However, the initially incorrect diagnosis of atopic dermatitis was suggested as an explanation for the poor prognosis in such cases [52]. Patient monitoring is recommended for cenegermin, given its growth factor properties [73]. The anti-angiogenic agent bevacizumab is used in combination with immune and chemotherapy, but patient selection criteria should be developed due to the risk of hemorrhage and to high mortality rates [74].

The presence of IgE antibodies to BM proteins (e.g., laminin-332 [17]) were earlier reported in MMP, suggesting the potential of omalizumab; additionally, omalizumab can be employed in desensitization to chemotherapeutic agents [75].

The rarity of MMP and its comorbidity with malignancy complicates the collection of further data on the association between MMP and malignant tumors and the impact of immunosuppressive and other pharmacological agents on malignancy risks.

Future Perspectives

Considering that the mechanisms of action of the abovementioned agents are directed against the earlier discussed or hypothesized components of the pathogenesis of MMP and its complications, the studied drugs possess the potential for additional research concerning their efficacy and safety profile.

The analysis of the guidelines shows the susceptibility to therapeutic novelties. Azathioprine, cyclophosphamide, and mitomycin C were included in the First International Consensus on MMP, while mycophenolate mofetil, rituximab, intravenous immunoglobulin, ciclosporin A, and etanercept were introduced by the guidelines of the French Society of Dermatology; a broader term "TNF-inhibitors" was later included in the S3 and S2k guidelines, Janus kinase inhibitors were indicated by the S2k guidelines for severe and recalcitrant cases. Corticosteroids are the most frequently employed immunosuppressive agents owning to their availability and efficiency. However, the unacceptance of long-term use of systemic corticosteroids due to severe AEs (e.g., aseptic hip necrosis, uncontrolled diabetes mellitus, and hypertension) was earlier highlighted in patients diagnosed with OcMMP [76], and there is a wide range of both topical and systemic steroid-sparing immunosuppressants, which are included in the guidelines and which exert effects through various pathways, reduce proliferation of immune cells, and release of pathogenic autoantibodies, with the underlying risk of complications, therapy resistance, and recalcitrant disease course. The search for new options with minimal AEs continues, and time will show which pharmacological agents will be included in new guidelines; some options will remain outside the list of recommended agents (e.g., thalidomide), while others may fade away.

Furthermore, in preclinical studies, additional pharmacological targets have been proposed.

In a murine model of anti-laminin-332 MMP the inhibition of phosphodiesterase-4, responsible for cell signaling, resulted in the improvement of oral lesions [77].

Phosphatidylinositol-3-kinase-δ (PI3Kδ) is involved in cutaneous blistering following leukocyte activation after Fc gamma receptor-dependent binding to the skin-located immune complexes and subsequent production of proteases and ROS. Parsaclisib, a PI3Kδ-selective inhibitor, showed the amelioration of cutaneous lesions in the MMP-induced mouse model [78]. Additionally, laminin-332 is linked to

malignancy development through the activation of PI3K and the Rho family of small GTPases [45,46], with decreased signaling of the latter after the administration of IVIG demonstrated by Murthy et al. (2024) [20]. Thus, the role of these pathways should be further clarified in MMP.

MMP-associated fibrosis may be linked to the aldehyde dehydrogenase/retinoic acid (ALDH/RA)-mediated dendritic cell paracrine effect and activation of a pro-fibrotic phenotype of fibroblasts. Patzelt et al. (2021) concluded that the ALDH inhibitor disulfiram does not reduce fibrosis in ocular and oral lesions in MMP-induced mice but improved cutaneous lesions [79]. However, earlier disulfiram effectively alleviated fibrotic changes in human OcMMP fibroblasts and in a mouse model [80].

In patients with MMP, high serum levels of IL-1 [81] and IL-5 [82] and an elevated expression of IL-6, IL-12, IL-17 [83], and IL-5 mRNA [84] in biopsy samples were reported. IL-1, IL-5, IL-6, IL-12, and IL-17 inhibitors are employed in dermatology; IL-5, IL-12/23, and IL-17 inhibitors were used in bullous pemphigoid [85,86]. Nonetheless, these agents occasionally paradoxically induce BP [87,88]. Moreover, complement inhibitors have been suggested for BP [85,86]; no report on the use of these agents in MMP was found.

Summarizing the above-mentioned data, a broader spectrum of pharmacological agents will allow a personalized approach and more alternatives, in particular for recalcitrant cases and failure of previous therapy. Moreover, given the participation of mechanisms other than the formation of autoantibodies in the pathogenesis of MMP [20], it is advisable to collect more data on the impact of cytokines, complement, proteases, immune cells, and other agents in search of solutions to avoid severe complications and overcome therapy resistance.

Conclusion

We present the analysis of pharmacological agents used in the management of MMP but that are not included in earlier published guidelines. Considering the severity of the condition, progressive fibrosis, and resistance to therapy, more research is required in relation to the pathogenesis of MMP and the efficacy and safety profile of novel pharmacological options. Pharmacological agents should provide the achievement and maintenance of remission with minimal adverse effects. A broader spectrum of pharmacological agents will allow a personalized approach and more alternatives, in particular for recalcitrant cases, failure of the previous therapy, and patients with MMP and malignancy.

Abbreviations: Recombinant human nerve growth factor (rhNGF); Nicotinic acetylcholine receptor (nAChR); Lymphocyte function-associated antigen-1 (LFA-1); Intercellular adhesion molecule-1 (ICAM-1); Interleukin-2 receptor (IL-2R); IL-4 receptor alpha chain (IL-4Rα); Adrenocorticotropic hormone (ACTH); Tropomyosin receptor kinase A (TrkA); Nerve growth factor receptor (p75NTR); Mucous membrane pemphigoid (MMP); Ocular mucous membrane pemphigoid (OcMMP); Oral mucous membrane pemphigoid (OrMMP); Brunsting-Perry pemphigoid (BPP).

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Dermatology Practical & Conceptual

Advanced Skin Imaging Techniques for Patients with Skin of Color: Clinical and Technological Insights

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Key words: Skin imaging, Skin of color, Dermatoscopy, Artificial intelligence, Autoimmune bullous dermatoses

Citation: Guermazi D, Saliba E. Advanced Skin Imaging Techniques for Patients with Skin of Color: Clinical and Technological Insights. *Dermatol Pract Concept.* 2025;15(4):5762. DOI: https://doi.org/10.5826/dpc.1504a5762

Accepted: June 26, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Skin imaging has transformed dermatology by enabling non-invasive diagnosis, monitoring, and treatment of various skin conditions. However, imaging skin of color presents unique challenges and opportunities due to variations in melanin content and skin structure.

Objectives: By focusing on the unique aspects of skin of color, this review aims to promote equitable healthcare and encourage the adoption of advanced imaging technologies across all skin types.

Methods: This review paper provides a comprehensive overview of the current state of skin imaging technologies, including optical, non-optical, and hybrid modalities, and their specific applications in dermatology.

Results: We discuss the diagnostic complexities associated with skin cancers, inflammatory conditions, and infectious diseases in diverse skin tones, underscoring the need for tailored imaging techniques. The review also explores advances in artificial intelligence and machine learning, highlighting their potential to enhance image analysis and diagnostic accuracy for skin of color.

Conclusion: We address the technical limitations, biological variability, and ethical considerations in skin imaging, ultimately advocating for more inclusive research and development. Future directions include the development of innovative imaging modalities and personalized medicine approaches that consider the diverse spectrum of human skin.

Introduction

Background

The skin is the largest human organ and serves as a critical barrier and interface between the body and the external environment. The skin's appearance and characteristics vary widely among individuals, influenced by factors such as genetics, age, and environmental exposure. Among these variations, skin of color presents unique anatomical and physiological features, primarily due to differences in melanin content and distribution. Melanin, the pigment responsible for skin color, not only determines the visual appearance of the skin but also affects its response to external stimuli, disease manifestations, and healing processes [1].

Historically, dermatological evaluation relied on visual inspection and palpation. The introduction of photography in the 19th century enabled documentation of skin conditions. Major advancements occurred in the mid-20th century, with the emergence of dermatoscopy in the 1980s to enhance melanoma detection through visualization of sub-surface structures [2, 3]. In the 1990s, confocal laser scanning microscopy (CLSM) allowed for high-resolution in vivo cellular imaging.

Non-optical imaging methods like high-frequency ultrasound and MRI further expanded diagnostic capabilities by visualizing skin tumors and inflammatory conditions [4, 5]. In the 21st century, hybrid technologies such as photoacoustic imaging have combined optical and ultrasound modalities for improved visualization of vascular and pigmented lesions [2, 3]. Despite historical bias toward lighter skin tones in imaging research, recent efforts have aimed to improve representation and diagnostic equity for skin of color [4, 5]. Advances in digital dermatoscopy, multispectral imaging, and artificial intelligence (AI)-driven diagnostics continue to make skin imaging more precise, accessible, and inclusive [2, 3].

Importance of Skin Imaging

Skin imaging technologies facilitate early diagnosis, precise monitoring, and effective treatment of various dermatological conditions. Imaging techniques range from traditional methods like dermatoscopy to advanced modalities such as confocal laser scanning microscopy, ultrasound imaging, and emerging hybrid techniques [2, 4]. While these technologies have significantly improved dermatological care, their efficacy and accuracy can be influenced by the patient's skin tone. For instance, the higher melanin content in skin of color can affect the penetration and reflection of light-based imaging methods, potentially complicating the diagnosis and treatment of skin conditions [1, 5].

Literature Selection and Appraisal

We conducted a targeted literature search to identify relevant articles on skin imaging modalities, artificial intelligence applications, and equity considerations in dermatology. Sources were selected based on their relevance to the topic, with a focus on peer-reviewed studies, reviews, and consensus guidelines published in English. While this is not a systematic or scoping review, efforts were made to include diverse perspectives and recent advancements.

Although many imaging technologies are described in the literature, few have been rigorously validated across diverse skin tones. For example, dermoscopy and high-frequency ultrasound have been well studied, while newer modalities like photoacoustic imaging and AI-driven tools have often relied on preliminary or retrospective data. Notably, there remains a lack of standard imaging protocols and prospective validation studies specifically for skin of color.

Purpose of the Review

This review focused on the intersection between skin imaging technologies, artificial intelligence, and dermatological equity, with an emphasis on their application to skin of color (SoC). Rather than offering a broad survey, it critically examined how diagnostic tools, particularly AI-driven and noninvasive imaging modalities, perform across diverse skin types. It identified key limitations in dataset diversity, algorithmic bias, and the lack of standardized imaging protocols for melanin-rich skin. By synthesizing evidence across modalities and highlighting underexplored gaps, the review aimed to advance a central thesis: achieving diagnostic equity in dermatology requires not only technological innovation but also a fundamental redesign of how imaging tools are developed, validated, and deployed for all skin tones.

How Imaging Technologies Shape Dermatological Insight

Optical Imaging

Optical imaging techniques use light to visualize skin structures and offer both high resolution and noninvasiveness. These methods are widely used due to their ability to provide detailed images of the skin surface and superficial layers.

Dermatoscopy

Dermatoscopy uses a handheld device with a magnifying lens and a light source to examine skin lesions. This technique enhances the visualization of subsurface structures, aiding in the early detection of melanoma and other skin cancers. Dermatoscopy is particularly useful for evaluating pigmented lesions and vascular structures, which can appear differently in skin of color [6].

Confocal Laser Scanning Microscopy (CLSM)

CLSM provides real-time, high-resolution imaging of the skin at the cellular level. By using a laser to scan the skin and

a pinhole to eliminate out-of-focus light, CLSM produces clear images of the epidermis and upper dermis. This technique is valuable for diagnosing skin cancers, inflammatory conditions, and infections. Its ability to visualize individual cells and cellular structures makes it a powerful tool for both research and clinical practice [7].

Multiphoton Microscopy

Multiphoton microscopy (MPM) is an advanced optical imaging technique that uses multiple photons to excite fluorescent molecules within the skin. This method allows for deeper penetration and reduced photodamage, making it suitable for long-term imaging of living tissues. MPM is particularly effective in studying the dynamic processes of skin physiology and pathology at the molecular level [2, 8].

Non-Optical Imaging

Non-optical imaging techniques rely on other forms of energy, such as sound waves or magnetic fields, to visualize deeper skin structures. These methods are used for assessing conditions that affect the deeper layers of the skin and underlying tissues.

Ultrasound Imaging

High-frequency ultrasound (HFUS) uses sound waves to create detailed images of the skin and its underlying structures. HFUS is widely used to evaluate skin tumors, measure skin thickness, and monitor wound healing. This technique is non-invasive and widely accessible, and it provides real-time imaging, making it a valuable tool in dermatology. Additionally, the integration of color Doppler imaging with HFUS enhances the evaluation by providing information on blood flow within the skin and its underlying structures, further aiding in the diagnosis and management of vascular-related dermatological conditions [9]. This combined approach offers comprehensive insights into both the anatomical and functional aspects of skin health.

Magnetic Resonance Imaging (MRI)

MRI uses strong magnetic fields and radio waves to produce high-contrast images of the skin and subcutaneous tissues. While MRI is more commonly used for internal organs, it can be adapted for dermatological purposes, particularly for evaluating large or deep skin tumors and inflammatory conditions. MRI offers excellent soft tissue contrast, which is beneficial for detailed skin assessments [2].

Terahertz Imaging

Terahertz imaging uses terahertz radiation, a type of electromagnetic wave with frequencies between 0.1 and 10 terahertz, to penetrate the skin and visualize its internal structures. This technique is still in the experimental stage but shows promise for noninvasive skin cancer detection and other dermatological applications [10]. Terahertz imaging can differentiate between various tissue types based on their water content and molecular composition.

Hybrid Imaging Techniques

Hybrid imaging techniques combine multiple modalities to leverage their respective strengths, providing comprehensive and complementary information about the skin.

Photoacoustic Imaging

Photoacoustic imaging (PAI) combines optical and ultrasound imaging to produce high-resolution, high-contrast images of skin structures. In PAI, pulsed laser light is absorbed by the skin, causing thermoelastic expansion and generating ultrasound waves. These waves are then detected to create images. PAI is particularly useful for visualizing blood vessels, melanin, and other chromophores, making it suitable for assessing vascular and pigmented lesions, especially in skin of color, though there are still some biases present [11].

Optoacoustic Imaging

Similarly to PAI, optoacoustic imaging uses laser-induced ultrasound waves to create detailed images of the skin. This technique provides high contrast and resolution and is effective for visualizing both superficial and deeper skin layers. Optoacoustic imaging is valuable for studying skin cancer, vascular anomalies, and other dermatological conditions [12].

Overall, the advancements in skin imaging modalities have significantly enhanced the ability to diagnose, monitor, and treat various skin conditions (Figure 1).

Clinical Impact and Gaps in Skin Imaging Applications

Diagnosis of Skin Diseases

Melanoma and Non-melanoma Skin Cancers

Detecting melanoma and non-melanoma skin cancers in individuals with darker skin tones is challenging due to variations in lesion appearance and pigmentation, and most of the data we have to date are from white patients [13, 14]. Traditional imaging methods, which often rely on color contrast between lesions and surrounding skin, may not be as effective in detecting early-stage cancers or distinguishing malignant from benign lesions in darker skin tones. Advanced imaging technologies have been developed to address these challenges, as was discussed with the many examples given in Section 3 on 'Imaging Modalities'. These techniques enable dermatologists to visualize structures beneath the skin's surface, enhancing the

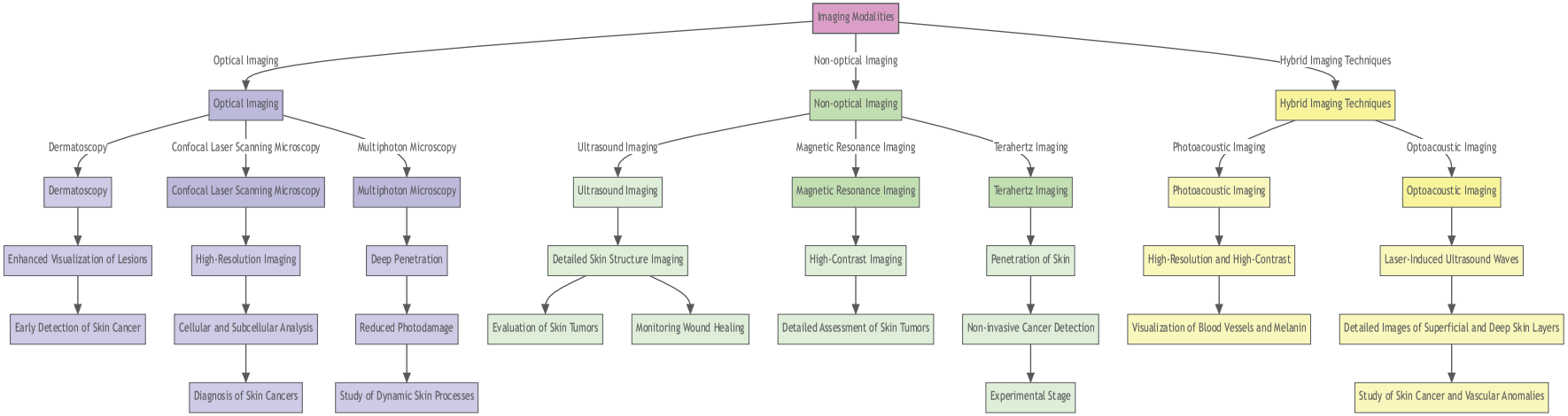


Figure 1. Key Imaging Modalities in Dermatology. This flowchart illustrates the primary imaging modalities used in dermatology, categorized into optical, non-optical, and hybrid techniques.

detection of subtle morphological changes associated with malignancy. By improving diagnostic accuracy, these technologies improve the chances that individuals with skin of color receive timely and appropriate treatment, thereby reducing disparities in cancer outcomes, which can be seen in Figure 2 below.

One such example is below, in a study done by Wang et al., where "melanoma moulages" were used to evaluate melanoma detection rates in training medical students in different skin types [15]. Though they did not find a significant difference in detection rates between whites and African Americans, they concluded that it is essential to educate students to consider sun exposure history and sun protection practices regardless of skin color [15].

Psoriasis and Eczema

Psoriasis and eczema can present differently in individuals with diverse skin tones, affecting both diagnosis and treatment strategies [16]. Skin imaging techniques such as high-resolution photography and optical coherence tomography help dermatologists assess the severity of these conditions and monitor response to therapy. For instance, psoriatic plaques may appear thicker or exhibit different patterns of erythema in darker skin tones compared to lighter skin tones [17]. By capturing detailed images of the affected areas, these technologies assist in tailoring treatment plans that take into account these variations, thereby optimizing outcomes for patients of all skin types.

Figure 3 is an example of psoriasis presentation in different skin colors [18, 19]. In fair-skinned individuals, psoriasis typically appears red or pink with a silvery-white scale, while Hispanic individuals may exhibit salmon-colored psoriasis with a silvery-white scale, and in African American patients it may appear violet with a gray scale. On dark skin, psoriasis can also be dark brown and may be more challenging to detect [20].

Infectious Diseases

The presentation and imaging outcomes of infectious dermatological diseases, such as fungal infections or viral rashes, can vary significantly based on skin color. Traditional imaging methods may struggle to differentiate between different types of skin lesions in individuals with darker skin tones due to similarities in color and texture. Advanced imaging modalities, including fluorescence microscopy and multispectral imaging, enhance the visualization of pathogens or inflammatory responses within the skin. By providing detailed insights into disease progression and treatment efficacy, these technologies aid dermatologists in improving the accuracy of diagnoses and guide appropriate therapeutic interventions for patients with skin of color.

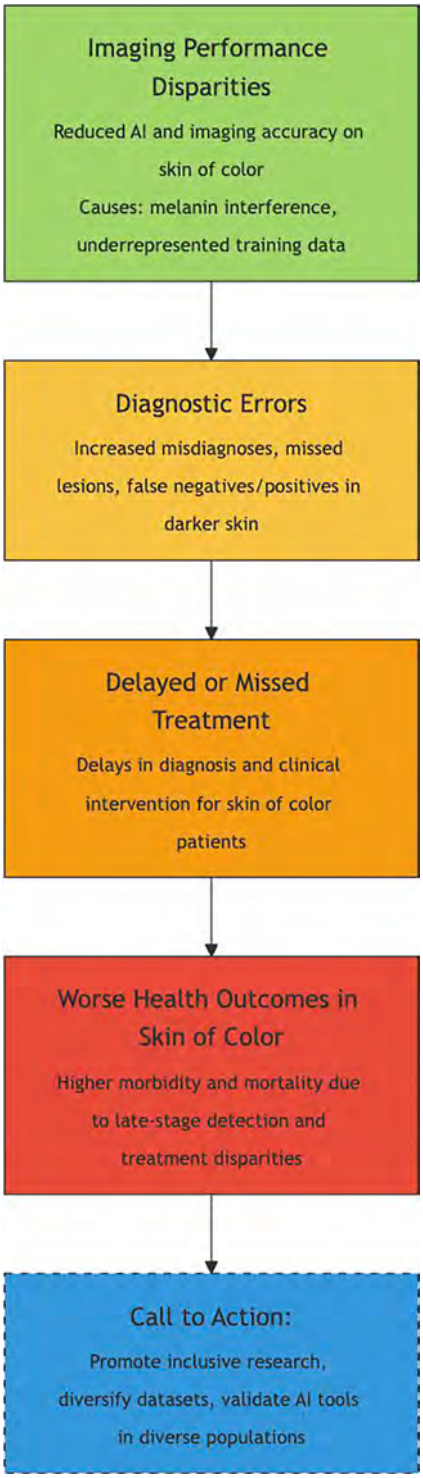


Figure 2. Clinical Impact Funnel Diagram.

Monitoring and Treatment

Wound Healing

The process of wound healing can vary in individuals with darker skin tones, presenting challenges in assessing tissue repair and identifying complications such as hypertrophic scars or keloids [21, 22]. Imaging techniques such as digital photography and ultrasound imaging enable dermatologists to monitor wound progression and evaluate treatment outcomes. These technologies provide objective measurements



Figure 3. On light skin, psoriasis typically appears red or pink (A) [18], while on dark skin, it often looks violet (B) [19].

of wound size, depth, and healing rates, facilitating early intervention and personalized care for patients of all skin types.

Laser Therapy Guidance

Laser treatments for dermatological conditions must be carefully tailored for individuals with darker skin tones to minimize the risk of adverse effects such as post-inflammatory hyperpigmentation or hypopigmentation [23]. Advanced imaging modalities, such as laser speckle imaging and thermal imaging, assist dermatologists in targeting treatment areas accurately and monitoring skin response in real time. By optimizing laser parameters based on individual skin characteristics, these technologies can enhance treatment efficacy and safety for patients of diverse ethnic backgrounds.

Cosmetic Dermatology

Aging and Pigmentation Analysis

Assessing skin aging and hyperpigmentation in diverse populations requires a nuanced approach to imaging [24, 25]. Techniques such as skin surface photography and spectrophotometry enable dermatologists to quantitatively measure melanin content and assess changes in skin texture and elasticity over time. These technologies capture detailed images of facial lines, wrinkles, and pigmentary changes, enabling personalized treatment planning and enhancing cosmetic outcomes for patients with diverse skin tones.

Scar and Wrinkle Assessment

Scars and wrinkles may appear differently in individuals with darker skin tones compared to lighter skin tones, necessitating specific imaging techniques for accurate assessment [25]. Modalities such as 3D skin imaging and laser scanning microscopy provide detailed visualizations of scar depth, texture, and vascularity [24]. By evaluating collagen deposition and tissue remodeling processes, these technologies help dermatologists select appropriate treatment modalities, including laser therapy or topical agents, to improve the appearance of scars and wrinkles in patients of all skin types.

Ultimately, skin imaging technologies play an increasingly important role in dermatology for their ability to enhance diagnostic accuracy, guide therapeutic interventions, and improve cosmetic outcomes across diverse patient populations. By addressing the unique challenges associated with skin of color, these advanced techniques ensure equitable access to high-quality care and personalized treatment strategies, thereby advancing dermatological practice towards more inclusive and effective patient management. We have illustrated a conceptual framework in Figure 4 below.

Barriers to AI Equity in Skin Imaging

Artificial Intelligence and Machine Learning

Artificial intelligence (AI) and machine learning (ML) are increasingly utilized to enhance the analysis and interpretation of skin images, particularly in populations with diverse skin tones [26]. Algorithms trained on extensive datasets encompassing varied pigmentation levels and dermatological conditions enable more accurate detection and classification of skin lesions, including melanomas and other skin cancers. By learning from a broad spectrum of skin types, these AI models improve diagnostic precision and reduce disparities in healthcare outcomes.

Wearable Skin Imaging Devices

Advancements in miniaturization and sensor technology have led to the development of wearable skin imaging devices. These portable devices allow for noninvasive, real-time monitoring of skin conditions and treatment responses. Designed to be worn comfortably by patients, wearable devices provide dermatologists with continuous access to high-resolution skin images, facilitating remote consultations and personalized treatment adjustments [27]. Their accessibility and convenience make them invaluable tools in managing chronic dermatological conditions, promoting patient engagement, and improving overall care outcomes across different ethnicities.

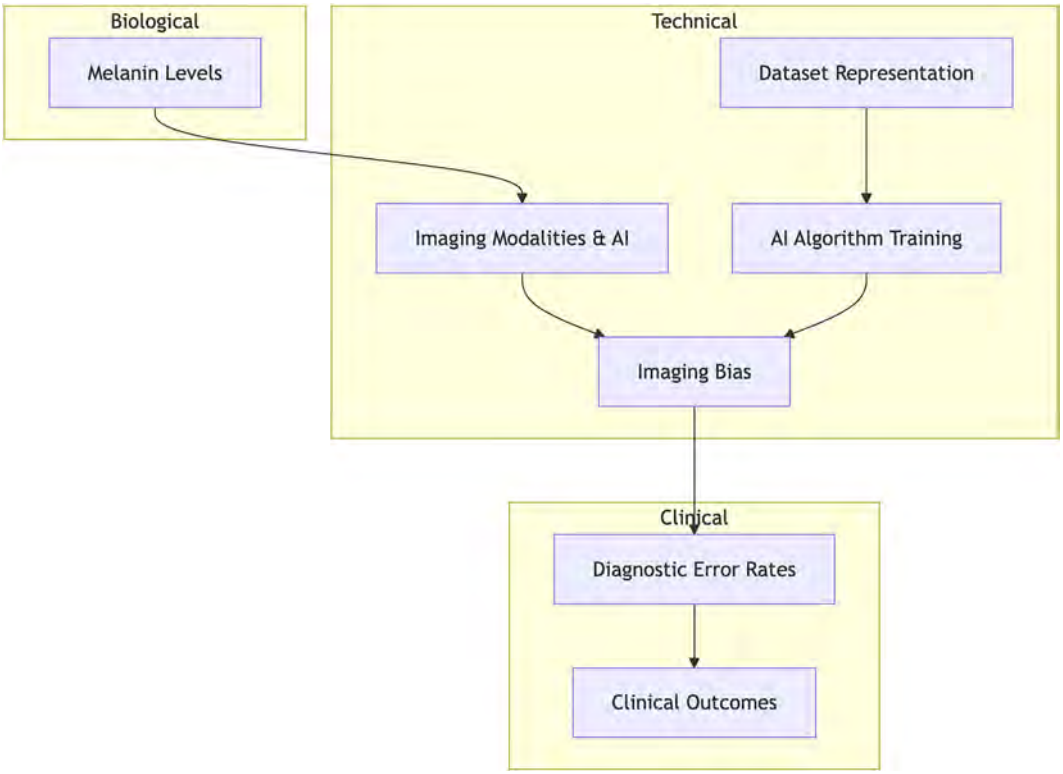


Figure 4. Conceptual Framework: interplay and directional relationships between AI, bias, melanin, and errors.

Portable and Point-of-Care Devices

Portable and point-of-care skin imaging devices are transforming dermatological practice by enabling rapid assessments in various clinical settings. These handheld devices, equipped with advanced optics and imaging modalities, deliver high-quality images of skin lesions and abnormalities [28]. Dermatologists can use these devices for on-the-spot evaluations during patient consultations, dermatology clinics, or community health screenings. Their ability to provide instant feedback and image documentation enhances diagnostic efficiency, supports timely interventions, and fosters equitable healthcare delivery for individuals with diverse skin tones [28].

Challenges and Limitations

One of the primary technical challenges in skin imaging, especially for darker skin tones, is achieving sufficient resolution and depth penetration [29]. Traditional imaging techniques may struggle to capture detailed structures and abnormalities in deeper layers of melanin-rich skin [30]. This limitation can affect the accuracy of diagnostic assessments and treatment monitoring, requiring advancements in optics and imaging modalities tailored to diverse pigmentation levels.

Moreover, the cost of advanced skin imaging technologies poses a significant barrier to equitable access, particularly in resource-limited settings. High-end imaging devices and AI-driven diagnostic systems may be prohibitively expensive for many healthcare facilities and patients [31]. Ensuring affordability and availability of these technologies across diverse socioeconomic backgrounds is essential to reducing disparities in dermatological care and improving health outcomes.

Future Directions

Emerging Technologies

A new computing method for four-dimensional (4D) spectral-spatial imaging in photoacoustic imaging (PAI), as discussed in section 3, has been developed to enable quantitative analysis and to optimize both structural and functional imaging of skin. This method accounts for the heterogeneous optical and acoustic properties of skin tissues, improving the accuracy of single-spectrum and multispectral imaging solutions [32]. The evolution from 2D to 3D and 4D imaging technologies represents a significant advancement in dermatological imaging. These technologies enable dermatologists to capture detailed three-dimensional representations of skin structures and dynamics over time [33]. By visualizing changes in skin texture, volume, and vascularization, 3D and 4D imaging enhance diagnostic accuracy and treatment planning, particularly for complex dermatological conditions and cosmetic procedures.

Table 1. Conceptual Heatmap Showing AI and Imaging Performance Across Skin Tones.

Imaging Modality / AI Model	Light Skin (Fitzpatrick I–III)	Medium Skin (Fitzpatrick IV)	Dark Skin (Fitzpatrick V–VI)
Dermoscopy AI	High (>85%)	Moderate (75-85%)	Low (<70%)
Clinical photography AI	High (>85%)	Moderate (70-80%)	Low (<65%)
Multispectral imaging AI	Moderate (75-85%)	Moderate (75-85%)	Moderate (70-80%)
Confocal laser scanning microscopy (CLSM)	High (90%)	High (85-90%)	Moderate (75-80%)
High-frequency ultrasound	High (85-90%)	Moderate (75-85%)	Moderate (70-80%)
Photoacoustic imaging AI	Moderate (80%)	Moderate (75-80%)	Moderate (70-80%)

Equity and Ethical Considerations

Despite technological progress, dermatological imaging and AI tools often lack equitable representation. Studies show that only 10–20% of images in major dermatology datasets represent Fitzpatrick skin types IV–VI [34] (Table 1). Many AI models trained on these datasets perform poorly on darker skin, risking misdiagnosis and delayed care [35]. Moreover, over 60% of AI dermatology studies fail to report skin type or race [36], limiting transparency and reproducibility.

These disparities raise ethical concerns around algorithmic bias and unequal access to innovation. Ensuring equity requires standardized reporting, deliberate inclusion of diverse skin tones in datasets, and a commitment to inclusive research design.

Research and Development Needs

Future research efforts should prioritize inclusivity in the development of skin imaging technologies. This includes expanding datasets to encompass diverse skin tones and conditions, ensuring that AI algorithms and imaging modalities are robust across different ethnicities [26]. By addressing biases and enhancing accuracy in diagnostic algorithms, researchers can mitigate disparities in dermatological care and promote equitable access to advanced imaging technologies worldwide.

Conclusion

The integration of skin imaging technologies has had a profound impact on dermatology and healthcare at large. By improving diagnostic accuracy and treatment outcomes, these technologies have reduced disparities in dermatological care and enhanced patient satisfaction. They have also streamlined clinical workflows, allowing for more efficient patient management and resource allocation in healthcare settings.

Looking ahead, the future of skin imaging in dermatology holds promising prospects for further innovation and advancement. Emerging technologies such as 3D and 4D imaging, along with enhanced data integration and AI applications, may enhance clinical practice, though further validation in diverse populations is needed. These developments will facilitate more personalized medicine approaches, improve predictive modeling, and continue to ameliorate dermatological care, ultimately improving the quality of life for patients worldwide.

Acknowledgements

AI tools were minimally utilized in the Abstract and Conclusions sections to enhance sentence clarity.

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Dermatology Practical & Conceptual

Evaluation of Clinical Studies of Patients With Dermatophyte Infections Caused by Trichophyton indotineae: Treatment Response and Resistance to Antifungal Medications

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Key words: Dermatophytosis, Treatment, *Trichophyton indotineae*

Citation: Tamer F, Polat M. Evaluation of Clinical Studies of Patients With Dermatophyte Infections Caused by Trichophyton indotineae: Treatment Response and Resistance to Antifungal Medications. *Dermatol Pract Concept.* 2025;15(4):5517. DOI: https://doi.org/10.5826/dpc.1504a5517

Accepted: June 5, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

ABSTRACT

Introduction: Dermatophytoses are the most frequent fungal infections of the skin. It has been reported that dermatophyte infections resistant to antifungal medications have increased in recent years. Therefore, superficial fungal skin infections that are difficult to treat have become a major health problem worldwide. *Trichophyton indotineae* is a newly described dermatophyte species that has been mainly isolated from patients with dermatophytosis characterized by widespread skin lesions and resistance to antifungal treatment and that causes outbreaks. *T. indotineae* leads to a pruritic rash that affects the large areas of the body surface such as the trunk, groin, and extremities, even in immunocompetent patients. Moreover, these patients usually do not respond to systemic terbinafine, which is the first-line treatment for dermatophyte infections and has fungicidal effects.

Objectives: Our aim was to determine the body sites affected by *T. indotineae* infection, the types of tinea caused by *T. indotineae*, the drugs to which it is particularly resistant, and the treatment regimens to which it responds.

Methods: Articles in the PubMed database published between December 2020 and September 2024 were investigated by searching the word *"Trichophyton indotineae"*.

Results: We reviewed 39 studies in the PubMed database that reported patients with *T. indotineae* infection to identify treatment regimens to which it is resistant or responsive.

Conclusion: Treatment guidelines should be established to select the appropriate alternative antifungal medication and determine the adequate drug dose and duration in treatment-resistant fungal skin infections caused by *T. indotineae*. Nevertheless, the data required to develop standard treatment regimens are insufficient.

Introduction

Trichophyton indotineae is a newly described dermatophyte species that is frequently isolated in patients with dermatophyte infections characterized by extensive skin lesions and antifungal treatment resistance [1-3]. Patients are usually unresponsive to systemic terbinafine, which is the first-line treatment for dermatophyte infections. In addition, topical or systemic administration of steroids due to misdiagnoses worsens *T. indotineae* infection. It has been reported that clinicians' awareness of treatment-resistant fungal infections caused by *Trichophyton indotineae* is inadequate and needs to be increased [2]. Moreover, treatment guidelines should be established to select the appropriate alternative antifungal medication and determine the adequate drug dose and duration in terbinafine-resistant skin infections caused by *T. indotineae*. Nevertheless, the data required to develop standard treatment regimens are insufficient [4].

Objectives

We evaluated articles reporting patients with dermatophytosis caused by *T. indotineae* to determine the body sites affected by the infection, the types of tinea caused by *Tindotineae*, and, in particular, the drugs to which it is resistant and the treatment regimens to which it responds.

Methods

The articles in the PubMed database published between December 2020 and September 2024 were investigated by searching the word "*Trichophyton indotineae*". After reviewing the titles and abstracts, human studies reporting patients with dermatophytosis caused by *T. indotineae* were included. Articles for which the full text was not available, non-English articles, laboratory studies without patient involvement, reviews, meta-analyses, in vitro studies, and animal studies were excluded from this review.

Results

The search steps are outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure 1) [5]. The initial PubMed search identified 98 articles; of these, 39 met the inclusion criteria and were further reviewed.

Studies on Patients with T. indotineae *Infections*

Original Articles

Kano et al. reported two patients with tinea corporis who had traveled to Nepal and India (Table 1). The patients had previously been treated with terbinafine but had not shown any clinical response. After performing internal transcribed spacer (ITS) region sequences analysis, *T. indotineae* was detected in skin lesions. Both patients recovered completely with itraconazole and fosravuconazole treatment [6].

Khurana et al. reported 40 patients with tinea corporis and tinea cruris caused by *T. indotineae*. Among these patients, 12 had previously used systemic antifungals, 24 had previously used topical antifungals, and 24 had used topical steroids. Patients were treated with itraconazole at different doses of 100 mg, 200 mg, or 400 mg daily. Complete clinical response was observed in 37 patients; treatment failure occurred in three patients. Khurana et al. stated that serum itraconazole levels lower than 0.2 µg/ml were associated with treatment failure, while successful treatment could be achieved with values above this level [7].

Pashootan et al. investigated the antifungal susceptibility of *T. indotineae* detected in samples obtained from five patients with tinea cruris, three patients with tinea pedis, and two patients with tinea corporis. Among the antifungals such as itraconazole, terbinafine, voriconazole, ketoconazole, fluconazole, posaconazole, and amphotericin B, terbinafine was reported to have the highest effect against *T. indotineae* [8].

Moreno-Sabater et al. evaluated the frequency of *T. indotineae* as an etiological agent and terbinafine resistance in patients with dermatophyte infections. Among the 580 samples, terbinafine resistance was observed in three samples, and *T. indotineae* was detected as the causative agent in one of them. This patient reportedly had traveled to India, had been diagnosed with tinea corporis, and had been treated with itraconazole 200 mg daily. On the other hand, *T. indotineae* was detected in a total of six specimens. *T. indotineae* was particularly characterized by inflammatory skin lesions and was detected in patients with tinea cruris and tinea corporis. However, in two patients, it was also associated with onychomycosis of the fingernails and tinea pedis [9].

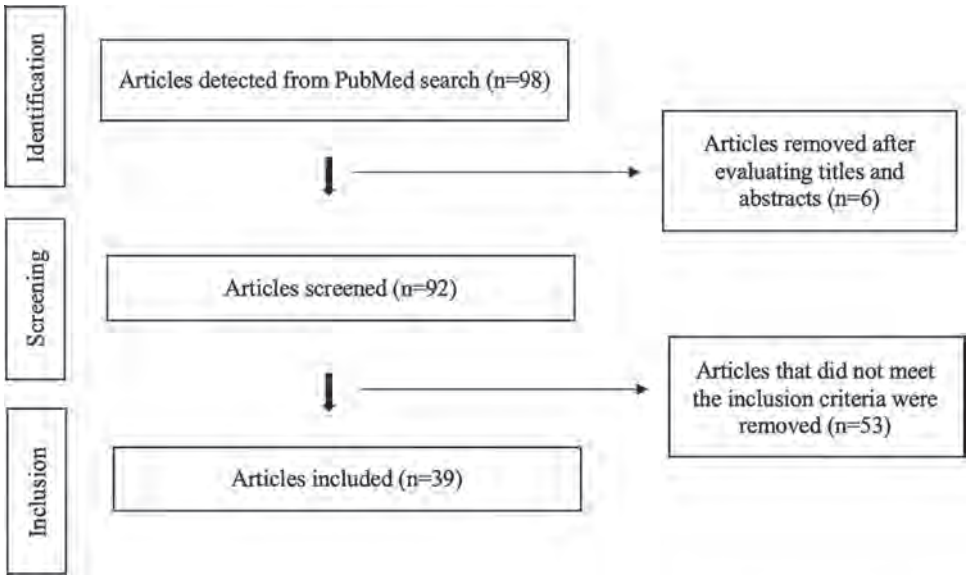


Figure 1. The search process for the articles is stated in the flow diagram.

Table 1. Articles Reporting Patients with Dermatophyte infections caused by *Trichophyton indotineae*.

Author	Infection	Treatment resistance	Effective treatment	Treatment duration
Kano et al.[6]	Tinea corporis	Terbinafine	Itraconazole, fosravuconazole	Not specified
Khurana et al.[7]	Tinea corporis, tinea cruris	Systemic terbinafine, griseofulvin, itraconazole, fluconazole, topical antifungals	Itraconazole	Until cure
Pashootan et al.[8]	Tinea corporis, tinea cruris, tinea pedis	Not specified	Not specified	Not specified
Moreno-Sabater et al.[9]	Tinea corporis, tinea cruris, tinea pedis, fingernail onychomycosis	Not specified	Oral itraconazole	1-3 months
Astvad et al.[10]	Not specified	Not specified	Not specified	Not specified
Posso-De Los Rios et al.[11]	Tinea corporis, tinea faciei Tinea corporis Tinea corporis Tinea corporis, tinea faciei Tinea corporis Tinea corporis, tinea faciei Tinea corporis, tinea pedis Tinea corporis	Oral terbinafine, fluconazole Clotrimazole cream, oral terbinafine Clotrimazole cream Terbinafine cream, ciclopirox cream, oral itraconazole Ketoconazole cream, oral fluconazole Oral terbinafine, itraconazole, topical terbinafine and ketoconazole Topical antifungal Clotrimazole cream	Referred to infectious disease department Oral itraconazole Ketoconazole cream Oral fluconazole* Referred to infectious disease department Referred to infectious disease department Oral fluconazole*, topical clotrimazole Ciclopirox cream*	Not specified 4 weeks Lost to follow-up 12 weeks Not specified Not specified 12 weeks Not specified

Table1 continues

Table 1. Articles Reporting Patients with Dermatophyte infections caused by *Trichophyton indotineae*. *(continued)*

Author	Infection	Treatment resistance	Effective treatment	Treatment duration
Jia et al.[12]	Tinea corporis, tinea cruris, tinea faciei	Oral fluconazole, miconazole nitrate cream	Oral itraconazole, bifonazole cream, ketoconazole lotion	4 weeks
Bortoluzzi et al.[13]	Tinea corporis, tinea cruris	Systemic and topical terbinafine	Oral itraconazole	14 days
Kong et al.[14]	Tinea corporis, tinea cruris	Oral itraconazole, terbinafine, topical terbinafine, econazole and ketoconazole	Oral itraconazole+ and topical naftifine hydrochloride/ ketoconazole Itraconazole pulse therapy	3 weeks 5 weeks
Tamimi et al.[15]	Tinea corporis, tinea cruris	Oral terbinafine, itraconazole	Oral terbinafine, itraconazole, voriconazole, topical clotrimazole	Not specified
Caplan et al.[16]	Tinea corporis, tinea cruris, tinea faciei	Oral terbinafine, fluconazole, griseofulvin, voriconazole, topical antifungal medication	Oral fluconazole, griseofulvin, itraconazole	2 weeks-2 months
Ngo et al.[17]	Tinea corporis, tinea cruris, tinea pedis	Not specified	Not specified	Not specified
Hiruma et al.[18]	Tinea corporis	Not specified	Not specified	Not specified
Dellière et al.[19]	Tinea corporis Tinea corporis Tinea corporis Tinea corporis, tinea faciei Tinea corporis Tinea corporis Tinea corporis	Oral terbinafine, griseofulvine Oral terbinafine Oral terbinafine Oral terbinafine None None Oral terbinafine, topical bifonazole	Oral itraconazole+ Oral itraconazole+ Oral itraconazole Oral itraconazole Oral terbinafine, topical ciclopirox Oral fluconazole+, topical terbinafine Oral terbinafine+	12 weeks 12 weeks 8 weeks 12 weeks Lost to follow-up 16 weeks 8 weeks
Jabet et al.[20]	Tinea corporis, tinea cruris	None None None Terbinafine, griseofulvin, econazole Terbinafine None None None None Terbinafine, griseofulvin	Oral and topical terbinafine Terbinafine Terbinafine None None Ciclopirox olamine Terbinafine, bifonazole+ Omoconazole, miconazole Terbinafine Itraconazole	1 month 1 month 2 months Lost to follow-up Lost to follow-up 1 month 6 weeks 2 months 1 month 2 months
Ngo et al.[21]	Tinea corporis	None	Oral itraconazole Topical ketoconazole	1 week 2 weeks
Durdu et al.[22]	Tinea cruris Tinea corporis	Oral terbinafine, itraconazole, topical antifungals Oral and topical terbinafine, resveratrol	Oral fluconazole+ Resveratrol tablet Oral itraconazole+ Oral itraconazole	Not specified 4 weeks 2 months

Table 1. Articles Reporting Patients with Dermatophyte infections caused by *Trichophyton indotineae*. *(continued)*

Author	Infection	Treatment resistance	Effective treatment	Treatment duration
Caplan et al.[23]	Tinea corporis, tinea cruris Tinea corporis, tinea cruris	Oral terbinafine Oral terbinafine, clotrimazole and terbinafine cream	Oral itraconazole Griseofulvin	4 weeks 4 weeks
Russo et al.[24]	Tinea corporis Tinea corporis, tinea cruris	Topical econazole, ketoconazole lotion None	None Oral terbinafine, topical ketoconazole	Lost to follow-up 4 months
Dashti et al.[25]	Tinea corporis, tinea cruris, tinea faciei	Oral terbinafine, griseofulvin, itraconazole, topical terbinafine, miconazole	Oral voriconazole	3 months
Messina et al.[26]	Tinea corporis	Oral fluconazole, terbinafine, topical antifungals	SUBA itraconazole	4 weeks
Crotti et al.[27]	Tinea corporis, tinea cruris, tinea faciei, tinea manuum, onychomycosis	Oral fluconazole, topical ketoconazole	Oral terbinafine, topical ciclopirox nail solution	12 weeks
Thakur et al.[28]	Tinea universalis	None	Oral itraconazole, topical luliconazole	2 months
Pavlović et al.[29]	Tinea corporis, tinea cruris, tinea faciei	Oral terbinafine, fluconazole, topical terbinafine	Oral itraconazole	8 weeks
Teo et al.[30]	Tinea cruris Tinea cruris	Not specified Topical miconazole	Not specified Oral itraconazole, topical terbinafine, ketoconazole	Not specified Under follow-up
Fukada et al.[31]	Tinea faciei	Topical ketoconazole	Oral itraconazole	5 weeks
Spivack et al.[32]	Tinea genitalis	Oral terbinafine, fluconazole, topical econazole and ketoconazole	Oral itraconazole	8 weeks
Tamimi et al.[33]	Tinea incognito Tinea incognito Tinea incognito Tinea incognito	Terbinafine Terbinafine Terbinafine Terbinafine, topical clotrimazol	Not specified	Not specified
Madarasingha et al.[34]	Extensive dermatophytosis	None Oral terbinafine None Oral terbinafine None	Oral itraconazole^{+} Oral itraconazole^{+} Oral itraconazole^{+} Oral itraconazole^{+} Oral itraconazole^{+}	6 weeks 4 weeks 8 weeks 6 weeks 10 weeks
Chua et al.[35]	Tinea cruris	Oral fluconazole, topical terbinafine, clotrimazole	Oral itraconazole	8 weeks

Table1 continues

Table 1. Articles Reporting Patients with Dermatophyte infections caused by *Trichophyton indotineae*. *(continued)*

Author	Infection	Treatment resistance	Effective treatment	Treatment duration
Smith et al.[36]	Tinea corporis	Oral fluconazole, terbinafine, itraconazole, griseofulvin, topical terbinafine, topical ketoconazole, nystatin	Not specified	Not specified
Mochizuki et al.[37]	Tinea corporis	Topical luliconazole	Oral itraconazole, topical lanoconazole[+]	1 month
Tan et al.[38]	Tinea cruris	None	Oral itraconazole, topical sertaconazole	4 weeks
Carroll et al.[39]	Tinea cruris, tinea faciei, tinea capitis	Oral terbinafine, itraconazole, topical antifungals	Topical griseofulvin	6 weeks
Gueneau et al.[40]	Tinea corporis	Systemic terbinafine and griseofulvin, topical terbinafine, econazole and bifonazole	Voriconazole cream	6 months
Villa-Gonzalez et al.[41]	Tinea corporis	Oral terbinafine	Oral itraconazole	6 months
Xie et al.[42]	Tinea corporis, tinea cruris, tinea faciei	Oral voriconazole, terbinafine	Oral itraconazole	1-8 weeks
Abdolrasouli et al.[43]	Tinea corporis, tinea cruris	Betamethasone dipropionate/ clotrimazole cream, terbinafine cream	Oral itraconazole	2 months
Bui et al.[44]	Tinea corporis, tinea cruris	Oral terbinafine, griseofulvin, fluconazole, topical clotrimazole	Oral itraconazole, topical ketoconazole	7 weeks

SUBA: Super bioavailable. [*] Treatment response was still being monitored. [+] Relapse was observed after treatment.

Astvad et al. examined the susceptibility tests performed on samples taken from patients with dermatophyte infection. *T. indotineae* was detected in six of the 59 patients. Terbinafine resistance was observed in all specimens obtained from these patients [10].

Posso-De Los Rios et al. evaluated eight Canadian patients with fungal skin infections due to *T. indotineae* who had traveled to India. All patients had previously used oral or topical antifungal medications without a complete clinical response. Three patients were started on oral itraconazole or fluconazole treatment, two patients were started on only topical antifungal treatment, and three patients were referred to the infectious diseases department [11].

Jia et al. reported the first case of *T. indotineae*-associated dermatophytosis in China. After four weeks of treatment with oral itraconazole 200 mg/day, bifonazole 1% cream twice daily, and ketoconazole 2% lotion, the lesions healed completely, leaving post-inflammatory hyperpigmentation [12].

Bortoluzzi et al. investigated five patients infected with *T.* species who were unresponsive to terbinafine treatment. ITS region sequences analysis identified *T. rubrum* in one patient and *T. indotineae* in four patients. They recovered with 14 days of oral itraconazole treatment, and the lesions did not recur during the 12-week follow-up [13].

Kong et al. described complete healing in a patient with *T. indotineae* infection three weeks after treatment with oral itraconazole 200 mg/day and naftifine hydrochloride/ ketoconazole cream. Nevertheless, the lesions recurred two weeks after discontinuation of the medications. The patient was initiated itraconazole pulse therapy (200 mg twice daily) for five weeks. The lesions did not recur at the 3-month follow-up [14].

Tamimi et al. evaluated 72 patients with tinea corporis and tinea cruris; *T. indotineae* was the causative agent in 53 patients. Of all patients, 47 had treatment-resistant infection, 42 of whom were infected with *T. indotineae*. Thirty patients with *T. indotineae* infection were unresponsive to terbinafine, 20 to itraconazole, and eight to both itraconazole and terbinafine. Refractory cases were treated with oral terbinafine, itraconazole, and voriconazole alone or in combination, with or without topical antifungal drugs such as clotrimazole [15].

Caplan et al. evaluated the characteristics of 11 patients infected with *T. indotineae*. All patients except two had traveled to Bangladesh. None of the patients responded to topical antifungals. Seven patients received oral terbinafine, and two received voriconazole, without a complete response. Four patients received oral fluconazole; two improved, and two were unresponsive to treatment. Of the five patients who received griseofulvin, two showed a clinical response to treatment, while three did not respond. Of the seven patients who received oral itraconazole, five responded to treatment, one was lost to follow-up, and one discontinued treatment due to side effects [16].

In a study by Ngo et al., *T. indotineae* was the causative agent in four of 114 patients with dermatophytosis. In vitro, *T. indotineae* was susceptible to itraconazole and voriconazole in all patients, while resistance to terbinafine was detected in half of them [17].

Short Reports

In a study by Hiruma et al., *T. indotineae* was detected in two patients with tinea corporis in Japan. In addition to terbinafine resistance, *T. indotineae* was found to be resistant to eficonazole and luliconazole [18].

Case Series

Dellière et al. reported seven patients with tinea corporis who were generally started on itraconazole due to terbinafine resistance. However, relapse was observed five months after treatment in one patient and one year after treatment in three patients [19]. Jabet et al. described 10 patients with *T. indotineae* infections; most were treated with oral terbinafine. Complete clinical response was observed only in three patients; two patients did not respond to antifungal therapy. One of the patients who showed clinical improvement had a relapse, while three were lost to long-term follow-up [20].

Case Reports

Ngo et al. reported a male patient with a 2-month history of tinea corporis due to *T. indotineae*. After one week of 200 mg/day of oral itraconazole and two weeks of topical ketoconazole treatment, almost complete improvement was observed in the lesion [21]. Durdu et al. described two patients with *T. indotineae* infection. As the first patient was unresponsive to oral terbinafine and itraconazole, oral fluconazole 200 mg/day treatment was started. Although the patient healed completely, the lesions recurred when itraconazole was stopped. The patient was started on resveratrol tablet, and the lesions regressed without the need for antifungal treatment. The other patient was a female with terbinafine-resistant tinea corporis. She recovered completely with oral itraconazole 200 mg/day for four weeks; however, the lesions recurred one month after the treatment was discontinued. She was started on resveratrol; however, unlike the first patient, there was no clinical response. The patient was started on oral itraconazole again, and no recurrence was observed after two months of treatment [22].

Caplan et al. reported two patients; the first was a female with a terbinafine-resistant but itraconazole-sensitive *T. indotineae* infection that began during pregnancy. The other patient had a *T. indotineae* infection that started while she was in Bangladesh, and most of the lesions resolved after one month of griseofulvin treatment [23].

Russo et al. described two patients with tinea corporis and tinea cruris. The first was a breastfeeding female and was therefore able to use only topical therapy such as ketoconazole. However, there was no response to treatment. The second patient was treated with oral terbinafine and topical ketoconazole; oral terbinafine treatment was extended to four months, and a complete clinical response was achieved [24].

Dashti et al. presented a dermatology nurse with disseminated dermatophytosis which was unresponsive to terbinafine, griseofulvin, and itraconazole. The patient was successfully treated with oral voriconazole. Voriconazole was given at a dose of 800 mg for the first two days, then was reduced to 400 mg per day for three months [25].

Messina et al. reported rapid, complete clinical response to super bioavailable (SUBA) itraconazole treatment in a patient with tinea corporis caused by *T. indotineae* which was unresponsive to systemic fluconazole and terbinafine treatment. SUBA itraconazole was preferred because it allows rapid attainment of therapeutic blood levels and was given at a dose of 50 mg twice a day for four weeks [26].

Crotti et al. reported a dermatophyte infection with skin and nail involvement due to *T. indotineae* in an Indian immigrant. Since the lesions were unresponsive to oral fluconazole, the patient was initiated on oral terbinafine and ciclopirox nail solution, and the lesions regressed after 12 weeks [27]. Thakur et al. reported a disseminated dermatophyte infection due to *T. indotineae*. The cure was achieved in two months with oral itraconazole 200 mg/day and topical 1% luliconazole [28].

Pavlović et al. presented a case of a treatment-resistant tinea cruris associated with *T. indotineae* that spread to the

face, trunk, and extremities. Skin lesions improved in eight weeks with oral itraconazole 200 mg/day and topical clotrimazole treatment [29]. Teo et al. investigated the antifungal resistance of *T. indotineae* obtained from the skin samples of two patients with tinea cruris. While no detailed clinical information was given about the female patient in the study, it was stated that the male patient's lesions recurred after topical miconazole treatment and that he was followed up with systemic itraconazole, topical terbinafine, and ketoconazole treatment [30].

Fukada et al. described a case of tinea faciei caused by *T. indotineae* that may have been facilitated by topical steroid use. Although the patient recovered completely after four weeks of treatment with oral itraconazole 100 mg/day, the lesions recurred after treatment. The infection was controlled with itraconazole 400 mg/day for another week. Fukada et al. stated that *T. indotineae* was not a terbinafine-resistant strain. Although the minimal inhibitory concentration (MIC) for terbinafine was low, they recommended itraconazole to the patient since the MIC does not always correlate with clinical response [31].

Spivack et al. presented a female who developed dermatophytosis due to *T. indotineae* in the genital area after sexual intercourse with a person with similar complaints. The patient had not responded to multiple systemic and topical antifungal treatments. Moreover, the topical steroids she had used with the misdiagnosis of dermatitis exacerbated the lesions. The patient transmitted the disease to her new partner after sexual intercourse. She was started itraconazole at a dose of 400 mg/day. After eight weeks of treatment, skin lesions completely regressed, and no recurrence was observed [32]. Tamimi et al. presented four females with tinea incognito who were misdiagnosed as having dermatitis and had used topical steroids. The causative agent was *T. indotineae* and showed resistance to terbinafine both in vivo and in vitro [33].

Madarasingha et al. presented five patients with extensive dermatophyte infection caused by *T. indotineae*; two patients were started on oral terbinafine. However, they were switched to itraconazole due to inadequate response. The remaining patients were treated with itraconazole; however, they still required systemic antifungal therapy for up to 10 weeks. However, relapse was observed in all patients. Terbinafine and fluconazole resistance was detected in skin samples obtained from all patients, whereas the MIC value for itraconazole was low except for one patient [34].

Chua et al. reported treatment-resistant tinea cruris in an Afghan patient living in Australia. *T. indotineae* was detected by ITS region sequences analysis, and antifungal susceptibility test revealed low MIC levels for itraconazole. The patient responded to eight weeks of oral itraconazole treatment. The authors also noted that they had detected *T. indotineae* in another patient from Sri Lanka who had yet to commence treatment [35]. Smith et al. presented a case of tinea corporis that developed after travel to India. The patient did not respond to systemic terbinafine, fluconazole, itraconazole, or griseofulvin. The lesion progressed even after increasing the dose of itraconazole to 400 mg/day [36].

Mochizuki et al. reported *T. indotineae* infection in a Vietnamese patient working in Japan. The patient was started on oral itraconazole 100 mg daily and lanoconazole cream and recovered completely after four weeks of treatment. The lesions recurred eight weeks after the cessation of medications. Therefore, the patient was started on the same treatment again [37].

Letters to the Editor

Tan et al. described a female with extensive dermatophytosis who was treated with oral itraconazole and sertaconazole cream. The clinical response was good in the first month. Terbinafine-resistant *T. indotineae* was identified as the etiological agent, which also revealed low MIC levels of itraconazole, posaconazole, and voriconazole and high MIC levels of fluconazole [38].

Carroll et al. reported *T. indotineae* infection in a Bangladeshi patient residing in Ireland. The patient was unresponsive to itraconazole and terbinafine. Although the patient was prescribed liquid griseofulvin to be taken orally, the patient mistakenly applied griseofulvin topically to the skin lesions. Nevertheless, the patient recovered after six weeks of treatment [39].

Gueneau et al. described a patient with treatment-resistant tinea corporis who was initiated on voriconazole 1% cream once daily. The lesions regressed with six months of treatment; however, they recurred six months after discontinuation of the treatment. Voriconazole cream was restarted, and the cure was achieved after two months of treatment [40].

Villa-Gonzalez et al. presented a Bangladeshi female in Spain who developed tinea corporis unresponsive to oral terbinafine. The patient recovered completely with three months of itraconazole 200 mg/day treatment. The lesions recurred one week after the treatment was stopped. The patient was given 100 mg of itraconazole daily for three more months, and no new lesion was observed afterwards [41].

Xie et al. described 14 patients with *T. indotineae* infection. Clinical and mycological cure was achieved in two patients who received oral itraconazole and topical antifungal medication. In addition, skin lesions improved in five patients with oral itraconazole. Recurrence was observed in two patients after itraconazole treatment. None of the seven patients who received oral terbinafine adequately responded to treatment. Two patients received oral voriconazole, but

treatment was discontinued due to poor response and side effects [42].

Abdolrasouli et al. described a patient with tinea corporis who had recently traveled to Central and South America and who did not adequately respond to topical antifungal medications. However, he was successfully treated with oral itraconazole 200 mg/day for two months [43].

Bui et al. reported a case of an extensive *T. indotineae* infection which was unresponsive to terbinafine, griseofulvin, and fluconazole. The patient was initially started on oral itraconazole 200 mg twice a day and topical 2% ketoconazole. After four days, the evening dose of itraconazole was adjusted to 300 mg to increase its trough level [44].

Discussion

T. indotineae is a novel dermatophyte species, first described in 2020 in India. Thereafter, *T. indotineae* infections spread rapidly outside India and were observed throughout the world, including in Europe and North America [45, 46]. Although isolating *T. indotineae* and determining the antifungal medication to which it is sensitive is crucial for effective treatment, performing laboratory tests for this purpose routinely and widely remains challenging [46]. *T. indotineae* is highly resistant to terbinafine, and this resistance is gradually increasing. Patients who are resistant to terbinafine are usually started on oral itraconazole therapy [45]. However, it has recently been shown that *T. indotineae* is also frequently resistant to azole antifungal drugs such as itraconazole and fluconazole [47]. On the other hand, experience in the usefulness of combination treatments containing different systemic antifungal medications for the management of *T. indotineae* infections is insufficient [45].

Conclusion

In the medical literature, articles on *T. indotineae* infection have been published from different countries all over the world. However, the number of clinical studies involving human participants is limited, and they are usually in the form of case reports describing one or a few patients. Within this review, we evaluated 39 clinical studies including 12 original articles, one short report, two case series, 17 case reports, and seven letters which described patients with different types of tinea caused by *T. indotineae*. In these publications, the most common dermatophyte infections detected in patients were tinea corporis and tinea cruris. Besides widespread skin involvement, the infection was usually resistant to treatment, and some patients required receiving various topical and systemic antifungal treatments, either in combination, at increased doses, or for prolonged periods, to achieve complete healing. Although *T. indotineae* has been reported to be resistant to terbinafine treatment, cases that respond to oral terbinafine have also been revealed. Further comprehensive clinical studies are required to determine the appropriate antifungal medications as the first-line treatment and treatment steps for superficial fungal skin infections caused by *T. indotineae* as well as the effective dose and duration of the treatment and the sufficient follow-up time to establish treatment guidelines.

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Dermatology Practical & Conceptual

Sleep Disturbances and Acne: A Comprehensive Review

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Key words: Acne, Sleep, Sleep quality, Psychodermatology, Skin health

Citation: Samaniego M, Alonso M, Sohail N, Mostaghimi L. Sleep Disturbances and Acne: A Comprehensive Review. *Dermatol Pract Concept*. 2025;15(4):5530. DOI: https://doi.org/10.5826/dpc.1504a5530

Accepted: May 1, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Acne, a common inflammatory skin disorder, is influenced by factors like hormones, age, and stress. Sleep also affects acne, as poor sleep quality can exacerbate skin issues.

Objective: This review aimed to explore the relationship between acne and sleep quality, examining the mechanisms, extent, and implications of this connection.

Methods: A systematic review of 18 studies was conducted to assess the link. Studies were retrieved from PubMed using predefined search criteria and evaluated for relevance.

Results: The findings indicate a bidirectional relationship between acne and sleep. Acne is associated with poor sleep quality, insomnia, and increased stress, while sleep deprivation exacerbates acne through hormonal imbalances, inflammation, and immune dysregulation.

Conclusion: There is a complex, bidirectional link between acne and sleep, requiring further research. Standardized metrics and behavioral interventions such as cognitive-behavioral therapy for insomnia could improve acne and sleep outcomes.

Introduction

Acne vulgaris is a common inflammatory skin disorder that occurs when hair follicles become clogged with sebum and dead skin cells, leading to outbreaks of lesions, including comedones, inflammatory papules, and pustules. Factors that may increase the risk of developing acne include hormonal alterations, age, medications, and family history, while diet, stress, pressure, and environmental irritants can exacerbate the condition [1].

Given the role of factors like hormonal alterations, age, medications, and family history in skin health, it is crucial to recognize sleep as another critical component in maintaining skin integrity. Sleep is a period during which the skin undergoes a process of repair and regeneration, which preserves its elasticity and firmness. The impact of poor sleep quality on skin health is evident in increased signs of intrinsic aging, compromised skin barrier function, and reduced satisfaction with appearance [2]. This underscores the importance of understanding the connection between sleep disorders and skin conditions, making it an emerging area of research with significant implications for dermatological patient care.

Objectives

This review surveyed the existing evidence on the intricate relationship between acne and sleep quality to better understand the mechanisms, extent, and implications of this connection.

Materials and Methods

Data Sources and Eligibility Criteria

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines [3] (Table S1), a systematic search was conducted in August 2024 of the PubMed database using the following search phrase: (sleep OR sleep quality) AND (acne OR acne vulgaris). Two researchers independently screened titles and abstracts based on the selection criteria. Full-text articles were then retrieved and assessed for inclusion, with reasons for exclusion documented. The inclusion criteria for this review included both clinical studies and reviews, with no publication date restrictions. Studies were excluded if they were not published in English, did not directly address acne in relation to sleep, or lacked sufficient data for analysis.

Data Extraction and Analysis

The information extracted from each of the included studies consisted of the study characteristics (authors, year, study design), population characteristics (sample size), measures of acne (severity), measures of sleep quality (e.g., Pittsburgh Sleep Quality Index [PSQI], self-reported sleep quality), and key findings on the relationship between acne and sleep quality.

Results

Characteristics of Included Studies

Figure 1 illustrates the study selection process. Of the 149 articles reviewed, 18 studies met the inclusion criteria: three reviews, two cohort studies, two case-control studies, nine cross-sectional studies, and two letters to the editor (Table 1). Collectively, these studies reported on over 4,498 patients with acne, excluding one study that did not specify the total number of acne patients.

Impact of Acne on Sleep

Acne is strongly associated with poor sleep and mood disturbances, including depression and anxiety [4,5]. A case-control study involving 81 acne patients found that they

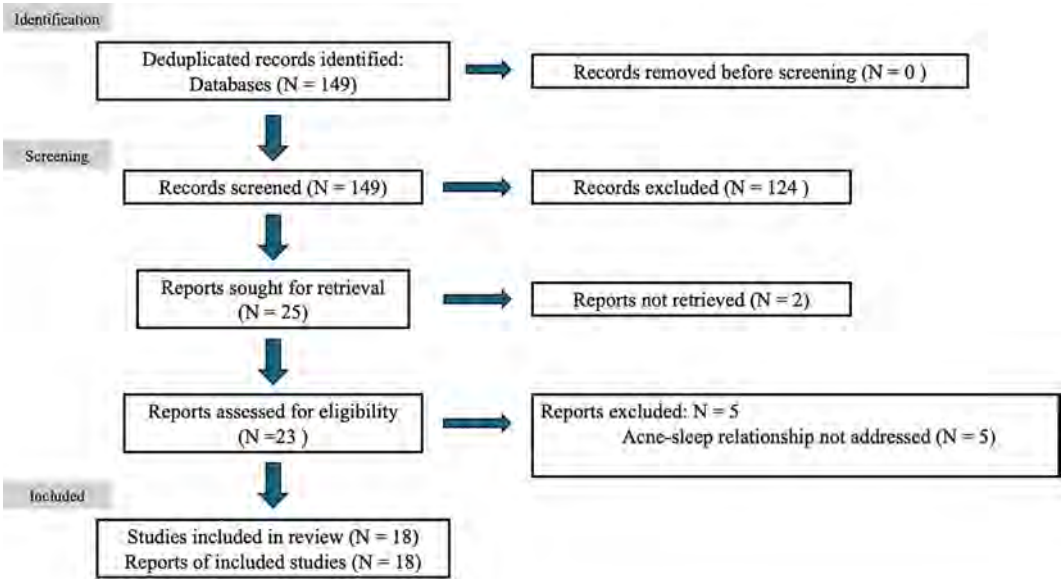


Figure 1. Flow Diagram of Study Selection.

Table 1. Study Characteristics.

Authors [Year]	Sample size	Study design	Sleep measures	Dermatologic measures	Key findings
Zhu J *et al.* (2023)	157 (81 acne, 76 control)	Case-control	PSQI; STAI; MEQ; ESS	IGA	Acne is highly associated with poor sleep and mood.
Pärna E, Aluoja A, Kingo K. (2015)	80 (40 acne, 40 control)	Cross-sectional	EST-Q	DLQI; RAND-36 (for health-related QoL)	Insomnia is significant among acne patients.
Arakaki FH *et al.* (2020)	NA	Letter to editor	NA	NA	Sleep loss may worsen acne; acne-related stress disrupts sleep.
Misery L *et al.* (2015)	1,375	Case-control	Self-reported questionnaire	CADI	Acne was linked to sleep issues and morning fatigue.
Suh DH *et al.* (2011)	657	Cross-sectional	Self-reported questionnaire	Self-reported questionnaire	Stress and limited sleep trigger and aggravate acne.
Wisuthsarewong W *et al.* (2020)	330	Cross-sectional	Self-reported questionnaire	Dermatologist-rated acne severity	Inadequate sleep and stress worsen acne.
Schrom KP *et al.* (2019)	40	Cohort	PSQI; sleep journal	GAGS; DLQI	Acne is correlated with worse QoL and depression.
Dashti HS *et al.* (2021)	16,509 (979 acne, 15,530 control)	Cross-sectional	Self-reported questionnaire	ICD-9 and ICD-10 codes	Sleep debt is strongly associated with acne.
Lu F *et al.* (2019)	384	Cross-sectional	Global PSQI scores	Self-reported questionnaire	Acne was more prevalent among poor sleepers.
Güler D, Soylu S, Güler HA. (2023)	151	Cross-sectional	ISI; MEQ	GAGS; VAS; AQLS	Insomnia is correlated with QoL in acne patients.
Khormi G *et al.* (2024)	1,427	Cross-sectional	Self-reported sleep duration	Self-reported acne severity	Stress and sleep contribute to acne development.
Hua H *et al.* (2024)	83	Cohort	PSQI	ECCA scale	Sleep quality affects CO_2 laser efficacy for acne scars.
Albuquerque RG *et al.* (2014)	NA	Review	NA	NA	Sleep distress may worsen acne.
Passeron T *et al.* (2021)	NA	Review	NA	NA	Sleep deprivation increases stress-related hormones.
Jusuf NK, Putra IB, Sutrisno AR. (2021)	60 (30 acne, 30 control)	Cross-sectional	Holmes-Rahe stress scale questionnaire	Serum substance P level	Sleep habit changes cause stress in acne patients, linked to increased substance P.
Xerfan EMS *et al.* (2021)	NA	Letter to editor	NA	NA	Poor sleep may trigger acne development.
Bilgiç Ö, Bilgiç A, Altinyazar HC. (2016)	85	Letter to editor	PSQI	Sebumeter® (SM815)	Sebum promotes acne but also has protective effects.
Yang J *et al.* (2020)	NA	Review	PSQI	TEWL	Poor sleep quality can negatively impact acne.

Abbreviations: Pittsburgh Sleep Quality Index (PSQI); State-Trait Anxiety Inventory (STAI); Morningness and Eveningness Questionnaire (MEQ); Epworth Sleepiness Scale (ESS); Investigator's Global Assessment (IGA); Emotional State Questionnaire (EST-Q); Dermatology Life Quality Index (DLQI); Research and Development (RAND); Not Applicable (NA); Cardiff Acne Disability Index (CADI); Global Acne Grading Scale (GAGS); Quality of life (QoL); International Classification of Diseases (ICD); Insomnia Severity Index (ISI); Visual Analogue Scale (VAS); Acne Quality of Life Scale (AQLS); échelle d'évaluation clinique des cicatrices d'acné (ECCA); Carbon dioxide (CO_2); Transepidermal water loss (TEWL)

scored higher on the Pittsburgh Sleep Quality Index (PSQI) and State-Trait Anxiety Inventory than did control patients, indicating poorer sleep quality and elevated anxiety levels [4]. Acne severity, evaluated with the Investigator's Global Assessment, was associated with sleep quality (β=0.33), depression (β=0.66), and anxiety (State: β=1.73; Trait: β=1.21) [4]. Those with acne often exhibit elevated levels of stress and emotional distress, mainly manifesting as insomnia and general anxiety. The stress and anxiety triggered by acne negatively impacts sleep quality [6]. Individuals with acne are more likely to experience difficulties falling asleep. In a survey of 1,375 individuals with acne, fatigue upon waking was strongly associated with the presence of acne (65.4% vs. 58.4%) [7].

Impact of Sleep on Acne

Sleep quality has a significant impact on acne severity and overall skin health. Poor sleep quality can exacerbate acne, as highlighted by one cross-sectional study, which identified psychological stress (82% of acne patients) and lack of sleep (75.2% of acne patients) as primary triggers or aggravating factors.[8] Furthermore, a cross-sectional study involving 330 acne patients revealed that 65% of respondents felt inadequate sleep worsened their acne and believed it significantly impacted their quality of life [9]. When controlling for individuals' perception of quality of life and depressive symptoms, it was found that subjective sleep quality worsened as the objective acne severity score, measured by the Global Acne Grading System (GAGS), increased, and vice versa [9]. This finding aligns with several studies that demonstrate a strong positive correlation between acne severity and poor sleep quality [7,10-12].

Specifically, associations have been found between acne and various aspects of sleep quality, such as sleep debt [11] and fatigue upon waking, even when adjusting for age (P<0.0001) [7]. Additionally, stressed patients tend to experience more fatigue upon waking and are more prone to developing acne [7]. One cross-sectional study also reported a significantly positive correlation between the Insomnia Severity Index (ISI) and Acne Quality of Life Scale (ALQS) scores, indicating that insomnia symptoms are prevalent among acne patients and constitute a significant source of distress [13]. Similarly, sleep disorder symptoms were found to be a significant form of distress for these patients [5].

Both stress and poor sleep quality contribute to acne through disrupted hormonal balance and immune function [14]. These factors increase inflammation and a higher likelihood of acne flare-ups. Additionally, insufficient sleep can reduce the effectiveness of acne treatments, resulting in less favorable outcomes. For example, one study found a negative correlation between Pittsburgh Sleep Quality Index (PSQI) scores and the postoperative effectiveness of fractional CO2 laser treatment for facial atrophic acne scars (r= -0.5130, P<0.05) [15].

Physiological Mechanisms

Poor sleep significantly affects acne pathogenesis, disrupting endocrine regulation and skin homeostasis and contributing to acne development. Sleep deprivation is associated with dysregulation of the hypothalamus-pituitary-adrenal (HPA) and neuroendocrine axes (NNA). It may act as a stressor, leading to elevated stress-related hormones such as cortisol [16], increased production of proinflammatory cytokines [16], and higher levels of substance P [17,18], a neuropeptide involved in transmitting pain signals and modulating inflammatory responses in the skin. One cross-sectional study conducted on 30 acne patients demonstrated a significantly positive correlation between stress and serum substance P level in acne patients with moderate strength (r=0.446; P=0.014) [19].

These physiological changes have been observed to exacerbate acne by promoting inflammation and sebum production [16,17,19]. Insufficient sleep has been linked to facial sebum dysregulation, which may lead to acne development [19]. Excess sebum contributes to acne by clogging pores, promoting bacterial growth, and triggering inflammation. However, the results of one study of 85 females with acne showed that good sleep quality was associated with elevated sebum levels, measured using a Sebumeter® over the T-zone, as sebum also has some protective and antimicrobial effects over the body (P=0.007) [20]. Additionally, sleep disturbance (PSQI >5, sleep duration ≤5 hours) increases transepidermal water loss (TEWL) [21], impairs skin barrier recovery [16], and weakens the skin's defenses against external stimuli, further exacerbating the effects of both stress and sleep deprivation [21].

Discussion

The general trend of the literature suggests a bidirectional relationship between acne and sleep that involves a complex interaction between physiological and psychological mechanisms. Poor sleep exacerbates acne through various physiological mechanisms, such as hormonal imbalances and increased inflammation, and impacts emotional well-being and skin health.

Similarly, prior research found that dermatology patients are more subjectively sleep-disturbed, primarily due to skin-related issues [22]. More specifically, one study revealed that patients with inflammatory skin conditions report significantly more fatigue and have an increased risk of developing insomnia compared to patients with noninflammatory skin disorders [23]. Moreover, previous studies have demonstrated a link between sleep and other dermatological

conditions, including atopic dermatitis [24,25], chronic spontaneous urticaria [26,27], psoriasis [24,28,29], and rosacea [30].

Sleep and the immune system are interconnected in a feedback loop. While sleep is believed to play a role in regulating immune memory formation, the activity of the immune system influences sleep parameters such as latency, efficiency, and architecture [31]. Previous research has shown that inadequate sleep can stimulate inflammatory responses, increasing secretion of pro-inflammatory cytokines (such as TNF and IL-6) and excessive cortisol production [30,32].

While the evidence suggests a reciprocal relationship between acne and sleep quality, additional studies are necessary to clarify the underlying mechanisms involved for a more comprehensive understanding of the acne-sleep connection. Further investigation is also required to determine the effectiveness of behavioral interventions such as cognitive-behavioral therapy for insomnia (CBT-I) for patients with moderate-to-severe acne with sleep disturbances. Previous research has found CBT effective for other skin conditions such as atopic dermatitis [33] and psoriasis [34]. Therefore, these interventions should also be evaluated for their efficacy in acne patients, as they may improve both sleep quality and acne outcomes, offering new therapeutic approaches.

Limitations

The limitations of this review include data heterogeneity across studies, which may affect the consistency of the results. This discrepancy may be due to several factors, including variations in study design, differences in the populations studied, and the various tools and scales used to measure sleep quality and acne severity, making comparisons difficult. When comparing results across studies, the lack of uniform outcome measures may lead to conflicting or inconclusive findings. Nonetheless, the review offers valuable insights into the relationship between acne and sleep, proposing potential physiological mechanisms involved.

Conclusion

This review highlights the complex relationship between acne and sleep, potentially exacerbating each condition. Despite existing research, significant gaps still need to be filled in our understanding, particularly regarding the causal mechanisms and long-term impact of this interplay. Addressing these gaps through longitudinal studies, standardized metrics, and targeted interventions like cognitive-behavioral therapy could pave the way for more effective, personalized treatment strategies. Research in these areas could improve sleep quality and acne outcomes, thereby enhancing the overall quality of life for affected individuals.

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Supplemental Materials

Table S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) Checklist

Section	Item	PRISMA-ScR Checklist Item	Reported on page #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	NA
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/ objectives lend themselves to a scoping review approach.	1-2
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	1-2
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	NA
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	3
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	3
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	3
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	3
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	3

Table S1 continues

Table S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) Checklist. *(continued)*

Section	Item	PRISMA-ScR Checklist Item	Reported on page #
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	3
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	NA
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	3-4
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Figure 1
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Table I
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	NA
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Table I
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	4-6
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	6-7
Limitations	20	Discuss the limitations of the scoping review process.	7
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	8
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	1 (None)

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).
From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

Dermatology Practical & Conceptual

Meta-Research Study on the Quality of Randomized Controlled Trials Evaluating Drug Therapy for Impetigo

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Key words: Impetigo, Drug therapy, Randomized controlled trials, Methodological quality, Meta-research

Citation: Rodrigues JC, Sá KMM, Lopes GCM, Piovesan MC, Santos EM, Martimbianco ALC. Meta-Research Study on the Quality of Randomized Controlled Trials Evaluating Drug Therapy for Impetigo. *Dermatol Pract Concept.* 2025;15(4):5668. DOI: https://doi.org/10.5826/dpc.1504a5668

Accepted: June 11, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Impetigo is a common, highly contagious bacterial skin infection primarily affecting children. Treatment usually involves topical or oral antibiotics, and numerous clinical trials have been published to support these therapeutic approaches.

Objectives: To evaluate the methodological quality of randomized clinical trials (RCTs) on the pharmacological treatment of impetigo in children and adolescents.

Methods: This meta-research evaluated RCTs on systemic or topical pharmacological treatments for impetigo in children and adolescents. A comprehensive literature search was conducted in September 2024 across MEDLINE, Embase, CENTRAL, and LILACS databases. The methodological quality of the included RCTs was assessed using the Cochrane Risk of Bias tool. Data are presented as percentages.

Results: Twenty-one RCTs on pharmacological treatments for impetigo were identified and assessed. The findings identified some methodological concerns: i) 53% to 57% of RCTs had an unclear risk of selection bias due to insufficient information on randomization and allocation concealment; ii) 71% were at high risk of bias for blinding of participants and personnel, while 57% had a high risk for

blinding of outcome assessors; iii) 24% exhibited a high risk of attrition bias due to significant participant losses without justification; iv) 81% had an unclear risk of bias due to the lack of registered protocols available.

Conclusions: Based on the methodological quality of the assessed RCTs, this study highlights the need for more rigorous design and reporting standards in future research on pharmacological treatments for impetigo to enhance the reliability and validity of the evidence, thereby supporting more informed clinical decision-making.

Introduction

Randomized controlled trials (RCTs) are the gold standard for generating high-quality evidence on the effects of healthcare interventions. Their methodological rigor, particularly in minimizing bias, ensures more accurate and valid estimates of treatment effects. As a result, RCTs play a pivotal role in informing clinical practice and shaping healthcare policies, either directly or through their integration into systematic reviews and meta-analyses [1–3].

However, the reliability and applicability of RCT findings are highly dependent on their methodological quality. Across diverse medical fields, persistent deficiencies such as inadequate randomization, poor allocation concealment, insufficient blinding, high attrition without appropriate handling, and the absence of prospective protocol registration remain prevalent. These shortcomings introduce various sources of bias, leading to distorted effect estimates and ultimately compromising the credibility of the evidence base [1,4–6].

The evidence on pharmacological treatments is well established in the context of impetigo, a common and highly contagious superficial bacterial skin infection that predominantly affects children [7,8]. Numerous RCTs have evaluated the efficacy and safety of both topical and systemic antibiotics for this condition. However, despite the substantial body of research, no prior study has systematically examined the methodological quality of these trials. This represents a critical gap, as deficiencies in trial design and reporting can undermine not only the validity of individual studies but also the reliability of evidence syntheses and the clinical guidelines derived from them. Moreover, systematically identifying recurring methodological limitations can inform improvements in the design, conduct, and reporting of future trials, ultimately contributing to more transparent, rigorous, and trustworthy research that underpins evidence-based clinical practice [1,4].

Objective

This meta-research study aimed to evaluate the methodological quality of the RCTs on the pharmacological treatment of impetigo in children and adolescents.

Methods

This meta-research study adheres to the methodological guidance proposed by Murad et al. [9] and the relevant items of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10] to enhance the quality and transparency of the study report.

Criteria for Inclusion of Studies

Randomized clinical trials (RCTs) that evaluated the efficacy of systemic or topical pharmacological interventions, including antimicrobial and antiseptic agents, for treating impetigo in children and adolescents, regardless of dosage, treatment duration, or route of administration. Studies were eligible if the authors identified them as "randomized clinical trials." Studies employing quasi-randomized methods, such as allocation based on date of birth, medical record number, or alternation, were not considered due to the high risk of selection bias associated with these designs.

Search Strategy

A comprehensive literature search was conducted on 19 September 2024 to identify the RCTs using the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE), by PubMed; Excerpta Medica Database (Embase), by Elsevier; The Cochrane Central Register of Controlled Trials (CENTRAL) (by Wiley); Latin American Literature on Health Sciences and the Caribbean - LILACS (Biblioteca Virtual em Saúde - BVS) (Table S1).

Selection of Studies and Data Collection

Two independent reviewers screened the titles and abstracts using the Rayyan platform [11]. References that met the eligibility criteria were then selected for a more detailed analysis through full-text reading. A third author resolved disagreements between reviewers about the inclusion or exclusion of studies. Data extraction was conducted by two independent reviewers who collected the following information from the included RCTs: year, participants' characteristics, intervention, comparator groups, outcomes assessed, and funding sources.

Assessment of the Methodological Quality of the Included Studies

Two reviewers independently assessed the methodological quality (risk of bias) of each included RCT, using the Cochrane Risk of Bias (RoB) tool (version 1.0) following the recommendations of the Cochrane Handbook of Systematic Reviews of Interventions [12]. This tool is composed of seven domains that assess potential sources of bias that could affect the study's validity, as follows:

- Random sequence generation (selection bias): evaluate the method used to generate the random sequence for assigning participants to intervention or control groups. It assesses whether the process was genuinely random, helping to ensure that any systematic factors did not influence group allocation.
- Allocation concealment (selection bias): examines whether the allocation of participants to intervention or control groups was concealed from those assigning participants. Proper concealment prevents selection bias by ensuring the researchers cannot predict or influence the group assignment.
- Blinding of participants and personnel (performance bias): assesses whether participants and personnel were blinded to the administered intervention. Blinding helps prevent performance bias, where knowledge of the intervention may influence how participants or staff behave or interact, potentially skewing the study results.
- Blinding of outcome assessors (detection bias): evaluates whether those assessing outcomes were blinded to the intervention received by participants. Blinding of outcome assessors helps prevent detection bias, where knowledge of the intervention might influence outcome assessment.
- Incomplete outcome data (attrition bias): analyses how incomplete outcome data (e.g., losses and withdrawals) were handled. It covers the difference in the number of participants withdrawn from each group (intervention and control) and how the losses were considered in the data analyses.
- Selective reporting: assesses whether the study reported all intended outcomes. This domain identifies any selective reporting of results that could skew findings, as published studies are more likely to report analyses showing significant differences between groups rather than those with non-significant differences.
- Other sources of bias: examines any other potential sources of bias not covered by the previous domains. It includes factors such as baseline data imbalance and other factors affecting the study's validity.

Blinding and incomplete outcome data were evaluated separately for each outcome, as recommended. However, since all outcomes of interest in this meta-research study were subjective (cure response, bacteriological response, adverse events, and quality of life), the lack of blinding in these domains could have potentially influenced the results, which were assessed together. The judgment of risk of bias for each domain is categorized into three levels: (1) low risk of bias, when the method is adequately addressed in the study; (2) high risk of bias, when the method is inadequately addressed; (3) unclear risk of bias, when there is insufficient information to make a definitive assessment.

Data Synthesis

The risk of bias assessments were reported as absolute frequencies and proportions for each domain of the RoB tool. In addition, 95% confidence intervals (95% CI) for proportions were calculated using the Wilson score interval, in the binomial R® software package (version 4.5).

Results

Search Results

The database search yielded 907 references. After removing six duplicates and screening the titles and abstracts, 878 studies were excluded for not meeting the inclusion criteria. Twenty-nine studies were assessed in full text, and eight were excluded [7,13-17] because they were not randomized clinical trials (RCTs). Consequently, 21 studies were included in this meta-analysis [18-38] (Figure 1).

Characteristics of the Included Studies

The 21 randomized controlled trials (RCTs) published between 1986 and 2023 included 2,876 participants diagnosed with impetigo. The most common interventions were macrolide antibiotics, bacterial protein synthesis inhibitors, penicillins, cephalosporins, quinolones, sulfonamides, and antifungals. These interventions were compared regarding their effects via topical versus oral administration or against a placebo (Table 1).

Risk of Bias Assessment

The methodological quality of the included RCTs was assessed using the Cochrane Risk of Bias (RoB) tool following the assessment recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Figure 2 presents the overall assessment, while Table S2 provides detailed judgments for each study.

Only one RCT (5%, 95% CI: 0.85%–23%) was classified as having low risk of bias across all domains assessed [35], while three trials (14%, 95% CI: 0.5%–35%) demonstrated low risk in six out of the seven domains of the RoB tool [26,29,30].

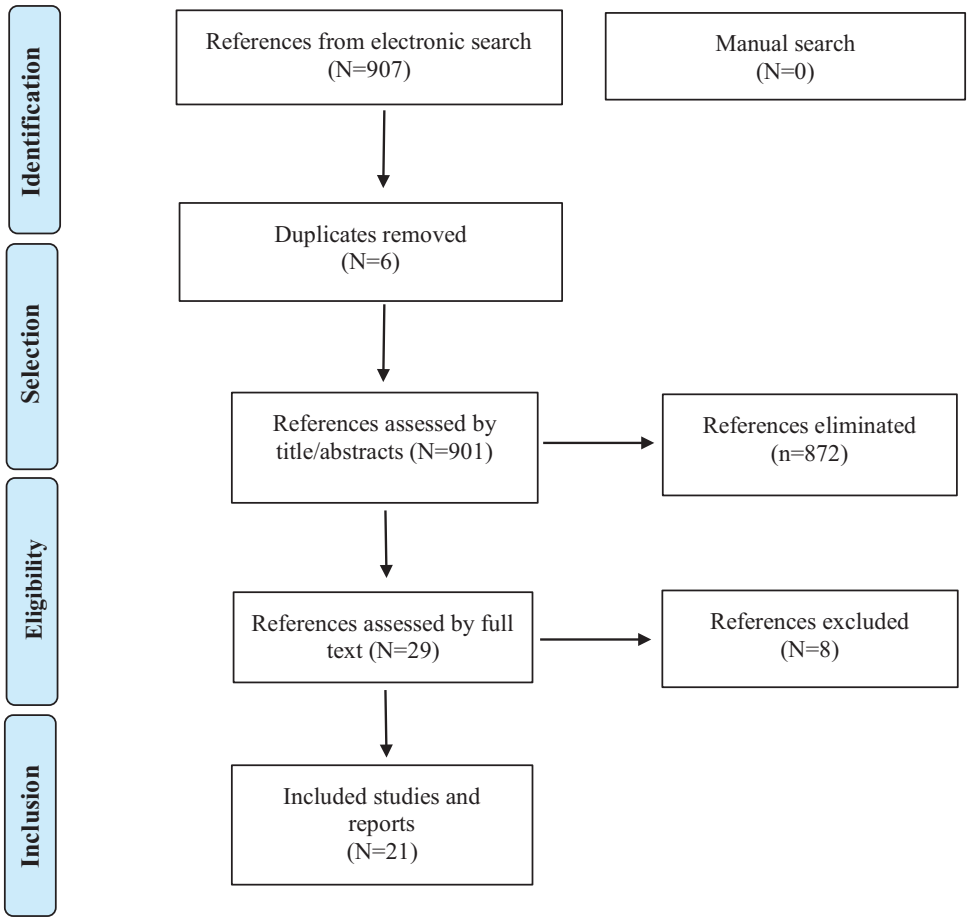


Figure 1. Flowchart of the study selection process.

Table 1. Characteristics of the Included Studies.

Study, year	Intervention / Number of participants (N)	Control / Number of participants (n)	Outcomes of interest	Funding sources
Anusharani 2019[18]	Topical 2% fusidic acid cream (N=50)	Topical 2% mupirocin ointment (n = 50)	• Clinical response • Adverse events	No sources
Barton 1988[19]	Oral erythromycin (40 mg /kg/day) (n = 29)	Oral dicloxacillin (25 mg/kg/day) (n = 30)	• Bacteriological response • Adverse events	Warner-Lambert Corporation
Ciftci 2002[20]	Mupirocin (Bactroban 2% ointment, 3 times/ day for 10 days) (n=25)	Terbinafine (Lamisil 1% cream topically, 3 times/day, for 10 days) (n=23)	• Clinical response • Bacteriological response • Adverse events	NR
Dagani 1992[21]	Oral erythromycin (50 mg/kg daily) + placebo ointment (n=51)	2% mupirocin ointment in polyethylene glycol + oral placebo suspension (n=51)	• Clinical response • Adverse events	Beecham Pharmaceuticals
Dash 2023[22]	Topical 1% ozenoxacin cream (n=16)	Topical 2% mupirocin cream (n=17)	• Clinical response • Bacteriological response	NR

Table 1. Characteristics of the Included Studies. *(continued)*

Study, year	Intervention / Number of participants (N)	Control / Number of participants (n)	Outcomes of interest	Funding sources
Demidovich 1990[23]	Oral penicillin V potassium (40 a 50mg/kg, daily for 10 days) (n=25)	Oral cephalexin monohydrate (40 a 50 mg/kg, daily for 10 days) (n=23) Oral erythromycin (30 a 40 mg/kg, daily for 10 days) (n=25)	• Clinical response • Adverse events	NR
Eells 1986[24]	15g of 2% mupirocin in polyethylene glycol (3 times/day for 12 days) (n=18)	15 g of the vehicle alone (3 times/day for 12 days) (n=20)	• Clinical response • Bacteriological response • Adverse events	NR
Goldfarb 1988[25]	2% mupirocin ointment (3 times/day, for 8 days) (n=30)	Oral erythromycin (40 mg/kg, daily, for 8 days) (n=32)	• Clinical response • Bacteriological response	Beecham Laboratories and Children's Research Foundation of Cleveland
Gropper 2014[26]	Topical ozenoxacin 1% cream (twice daily, for 5 days) (n=155)	Topical retapamulin 1% ointment (twice daily, for 5 days) (n=154) Placebo (twice daily, for 5 days) (n=156)	• Clinical response • Bacteriological response • Adverse events	Ferrer Internacional SA, Barcelona, Spain
Iovino 2011[27]	NVC-422 topical gel 0.1% (n=43)	NVC-422 topical gel 0.5% (n=45) NVC-422 topical gel 1,5% (n=41)	• Clinical response • Bacteriological response • Adverse events	NR
Jeffrey 1990[28]	Oral erythromycin (40 mg/kg/day, 4 times/day) + topically applied placebo (3 times/day) (n= 30)	Topical mupirocin 15g 2% (3 times/day) + orally administered placebo (4 times/day) (n= 24)	• Clinical response • Bacteriological response	United States Navy Bureau of Medicine and Surgery Clinical Investigation Program
Koning 2002[29]	Topical fusidic acid cream 2% (3 times/day, for 14 days) (n=78)	Placebo (3 times/day, for 14 days) (n=82)	• Clinical response • Bacteriological response	Fonds Alledaagse Ziekten of the Dutch College of General Practitioners
Koning 2008[30]	Topical retapamulin ointment 1% (twice daily for 5 days) (n=139)	Topical placebo (twice daily for 5 days) (n=71)	• Clinical response • Bacteriological response • Adverse events	GlaxoSmithKline
Kuniyuki 2005[31]	Topical 3% Oxytetracycline-hydrochloride (n=28)	Topical tetracycline and oral antibiotics (cefdinir, fosfomycin and minocycline) (n=21)	• Clinical response • Bacteriological response	NR

Table 1. Characteristics of the Included Studies. *(continued)*

Study, year	Intervention / Number of participants (N)	Control / Number of participants (n)	Outcomes of interest	Funding sources
Mclinn 1990[32]	Topical mupirocin ointment 2% (3 times/day) (n=29)	Oral erythromycin (30 to 40 mg/kg/day) (n=30)	• Clinical response • Bacteriological response • Adverse events	NR
Mertz 1989[33]	Topical 15g mupirocin ointment 2% (3 times/day, for 8 days) (n=28)	Oral erythromycin (30 to 50 mg/kg/day) (n=25)	• Clinical response • Bacteriological response	Beecham Laboratories, Bristol, Tenn
Nolting 1998[34]	Topical sulconazole nitrate 1% cream (twice daily, for 14 days) (n=32)	Topical miconazole nitrate 2% cream (twice daily, for 14 days) (n=34)	• Clinical response • Bacteriological response	NR
Oranje 2007[35]	Topical retapamulin ointment 1% (twice daily for 5 days) (n=345)	Topical sodium fusidate ointment 2% (3 times daily for 7 days) (n=172)	• Clinical response • Bacteriological response	GlaxoSmithKline
Rosen 2018[36]	Topical ozenoxacin cream 1% (twice daily for 5 days) (n=206)	Placebo (twice daily for 5 days) (n=206)	• Clinical response • Bacteriological response	Ferrer Internacional, SA.
Sudha 2017[37]	Oral azithromycin (10 mg/kg/day) (n=50)	Oral azithromycin (10 mg/kg/day) + Probiotic (n=50)	• Clinical response	No sources
Tong 2010[38]	Oral trimethoprim-sulfamethoxazole (4+20 mg/kg up to 160 + 800 mg) (n=7)	Intramuscular benzathine penicillin (45 mg/kg up to 900 mg) (n=6)	• Clinical response • Bacteriological response	Australian National Health and Medical Research Council, Australian National Heart Foundation, Cooperative Research Centre for Aboriginal Health, Ian Potter Foundation, and the Rio Tinto Aboriginal Foundation.

Abbreviations: N: number of participants, NR: not reported, NVC-422: N, N-dichloro-2, 2-dimethyltaurine.

Regarding the randomization process, which assesses the method by which participants were assigned to ensure comparable groups, 53% (11/21, 95% CI: 32%–72%) [18-23,25,27,31,32,37,38] of the RCTs presented an unclear risk of bias due to insufficient information provided for judgment. In contrast, 47% (10/21, 95% CI: 28%–68%) [21,24,26,28-30,33-36] clearly described the randomization process, which was typically carried out using a computer-generated randomization code, schedule, or list of random set numbers. No study was classified as having a high risk of bias in this domain. Similar proportions were observed regarding allocation concealment, where 57% (12/21, 95% CI: 37%–76%) [18-20,22-25,27,38,31,32,37] of the RCTs had an unclear risk of bias. In comparison, 43% (9/21, 95% CI: 24%–63%) [21,26,29,30,33-35,28] had a low risk of bias, with most studies describing methods such as the use of sequentially sealed opaque envelopes to ensure proper allocation concealment.

The assessment of the blinding domains evaluates whether participants and outcome assessors were aware of the intervention assigned to each group. This awareness can influence the results, especially when outcomes are measured subjectively or rely on patients' perceptions. Among the RCTs, 71% (15/21, 95% CI: 50%–86%) [18,20,22-25,27,31-28] were classified as high risk of bias for blinding of participants and personnel, and 57% (12/21, 95% CI: 37%–76%) [18-21,24,25,27,31,32,34,36,37] were at high risk of bias for blinding of outcome assessors. This indicates either knowledge of the intervention or insufficient information to assess blinding. The lack of blinding of participants and assessors

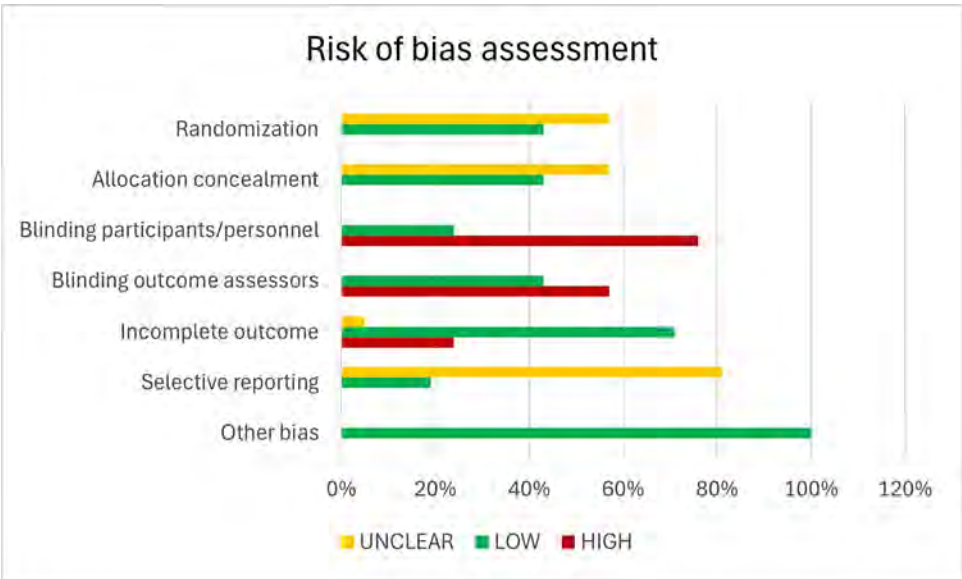


Figure 2. Risk of bias assessment.

can significantly impact the results since clinically relevant efficacy and safety outcomes were measured subjectively. With a low risk of bias, 29% (6/21, 95% CI: 14%–50%) [19,21,26,28-30] had adequate blinding of participants, and 43% (9/21, 95% CI: 24%–63%) [22,23,26,28-30,33,35,38] had adequate blinding of assessors. In these studies, the compared medications were identical in appearance and characteristics, or participants received a placebo that closely resembled the intervention, such as a placebo ointment for the oral administration group versus the topical treatment.

The incomplete outcome data domain assesses how results are reported, including participant losses or withdrawals during the study, and examines the impact of these losses on the final analysis. Among the included RCTs, 76% (16/21, 95% CI: 55%–89%) [18,19,21-23,25-27,29,31,32,34-38] were considered to have a low risk of bias, as they reported losses of less than 20% of participants and provided appropriate justifications. In contrast, 24% (5/21, 95% CI: 11%–45%) [20,24,28,30,33] had a high risk of bias due to losses exceeding 20% and lacking justification.

The selective reporting domain revealed that 81% (17/21, 95% CI: 60%–92%) [18-29,31-34,37] of the studies had an unclear risk of bias, as most did not provide a registered protocol, making it impossible to assess the differences between reported and unreported outcomes and results. No other source of bias was identified in the evaluated RCTs.

Discussion

This meta-research evaluated the methodological quality and risk of bias in randomized clinical trials (RCTs) concerning pharmacological treatments for impetigo in children and adolescents. Impetigo, a highly contagious skin infection, is a common condition requiring effective treatment options, yet evidence supporting various interventions remains uncertain. This study aimed to assess the reliability and applicability of current RCTs, mapping the methodological flaws to clinical practice and providing recommendations for future research. The results revealed that a significant proportion of the included RCTs exhibited unclear or high risks of bias, particularly in domains related to randomization, blinding, and handling of incomplete outcome data.

A significant proportion of the included studies presented an unclear or high risk of bias regarding the randomization process, with 53%–57% of studies lacking sufficient details. Randomization is critical to ensuring that participants are allocated to treatment groups without bias, guaranteeing comparability. Inadequate or poorly described randomization methods can lead to selection bias, potentially affecting the generalizability of the results and distorting the perceived treatment effect. Rigorous randomization procedures are essential to ensuring baseline comparability and to reducing the risk of bias [1,5,39].

Most studies had a high risk of bias concerning the blinding of participants and outcome assessors. This lack of blinding can introduce performance and detection biases. When participants or researchers know the treatment allocation, it may influence participant behavior and the interpretation of outcomes. For example, participants aware of receiving a placebo might report subjective outcomes differently from those receiving the active treatment. Similarly, unblinded assessors may unintentionally assess outcomes in a biased manner. Such biases can lead to overestimations or underestimations of treatment effects, affecting the reliability of study results [6].

Over 70% of the RCTs were classified as having a low risk of bias regarding participant losses or withdrawals during study follow-up. Incomplete outcome data can compromise the validity of the results and introduce bias if not adequately managed. It is crucial that future studies employ rigorous methods for dealing with missing data and that they provide transparent reporting to allow for accurate assessments of treatment efficacy [39].

Finally, regarding selective reporting bias, 81% of the evaluated RCTs were classified as having unclear risk of bias, mainly due to the lack of prospective protocol registration. The absence of a publicly available protocol compromises the ability to verify whether predefined outcomes were altered, selectively reported, or omitted, which may distort study conclusions by overestimating benefits or underestimating harms. This issue is particularly critical in impetigo clinical trials, in which outcomes are largely subjective and prone to bias. Mandatory prospective registration of clinical trials in international registries such as ClinicalTrials.gov and the WHO ICTRP should be strictly enforced to mitigate this bias. This practice is widely recognized as an essential safeguard for research integrity, as it increases transparency, reduces reporting bias, and ensures that all prespecified results are publicly accessible for verification [40-42].

The methodological weaknesses identified in the included RCTs are consistent with patterns observed in dermatology research. A meta-research study [42] assessed dermatological RCTs included in Cochrane reviews and reported a high prevalence of unclear risk of bias, particularly for allocation concealment (79%) and random sequence generation (64%), which closely reflects the findings of our study. Similarly, another recent meta-research study [43] evaluating systematic reviews of RCTs on vesiculobullous skin diseases found that over half (55.5%) of the reviews were rated as critically low quality according to the AMSTAR-2 tool assessment. This reinforces that the methodological limitations observed in impetigo trials are not isolated but are part of a widespread challenge.

This meta-research study has some limitations that should be acknowledged. First, although a comprehensive literature search was conducted, the possibility of missing relevant studies cannot be entirely excluded. Second, the risk of bias assessment depended on the quality and completeness of the reports provided by the original studies. Third, the wide confidence intervals observed in some risk of bias domains reflect the uncertainty associated with the relatively small number of included trials.

Another important consideration in our study was the choice of the Cochrane Risk of Bias tool version 1.0 rather than the updated version 2.0. Despite the methodological improvements introduced by RoB 2.0, particularly its outcome-level assessment framework, the choice to use RoB 1.0 was made because it includes a dedicated domain for selective reporting, a critical issue not explicitly assessed in RoB 2.0. Selective reporting bias is a significant concern in clinical research, occurring when pre-specified outcomes are omitted, reported incompletely, or presented selectively, leading to biased effect estimates with overestimation of benefits and underestimation of harms. The decision also reflects growing concerns in the literature regarding the complexity and operational challenges associated with RoB 2.0, which has demonstrated lower inter-rater reliability and considerable implementation challenges, even when applied by experienced systematic reviewers [44–46].

The methodological shortcomings identified in this meta-research have important implications for both clinical practice and future research. For clinicians, the variability and potential biases in the current evidence base emphasize the need for cautious interpretation of studies on impetigo treatments. Evidence derived from trials with a high risk of bias may not accurately represent the true efficacy and safety of pharmacological interventions, potentially leading to suboptimal treatment decisions. For researchers, these findings highlight the urgent need to strengthen methodological rigor in future RCTs. Key areas for improvement include robust randomization procedures, proper allocation concealment, adequate blinding, and appropriate handling of incomplete outcome data. Equally important is the commitment to transparency through prospective protocol registration and adherence to standardized reporting guidelines.

In this context, future RCTs should comply with the SPIRIT checklist for comprehensive and transparent protocol development [47,48] and the CONSORT statement to ensure complete and accurate reporting of trial findings [49], and they should incorporate the Cochrane Risk of Bias tool to guide risk of bias assessment and improve internal validity [12]. These practices are essential to enhancing the credibility, reproducibility, and utility of clinical research on impetigo. Ultimately, improving the methodological quality of trials will support more reliable evidence synthesis, inform guideline development, and guide decision-making about which treatments should be prioritized, recommended, or funded in clinical practice.

Conclusion

This meta-research study evaluated the methodological quality of 21 RCTs on pharmacological treatments for impetigo. The findings identified critical areas of concern: i) 53% to 57% of RCTs had an unclear risk of selection bias due to insufficient information on randomization and allocation concealment; ii) 71% were at high risk of bias for blinding of participants and personnel, while 57% had a high risk of blinding of outcome assessors; iii) 24% exhibited a high risk

of attrition bias due to significant participant losses without justification; iv) 81% had an unclear risk of bias due to the lack of registered protocols. These methodological weaknesses highlight the need for more rigorous design and reporting standards in future RCTs on impetigo treatments, adopting the SPIRIT checklist for protocol development, the CONSORT statement for reporting, and the Cochrane RoB 2.0 tool for bias assessment, to enhance the transparency, validity, and consistency of evidence to better support clinical decision-making.

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Supplementary file

Table S1. Search Strategies (run on 19 September 2024).

Databases	Search strategy	Results
MEDLINE (Pubmed)	#1 "Impetigo"[Mesh] OR Impetigo OR Impetigos OR (Impetigo Contagiosa) OR (Contagiosa, Impetigo) OR (Contagiosas, Impetigo) OR (Impetigo Contagiosas) #2 (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]))	77
Embase	#1 'impetigo'/exp OR Impetigo OR Impetigos OR 'Impetigo Contagiosa' OR 'Contagiosa, Impetigo' OR 'Contagiosas, Impetigo' OR 'Impetigo Contagiosas' #2 'randomized controlled trial' OR 'controlled clinical trial' OR 'pragmatic clinical trial' OR 'equivalence trial' OR 'clinical trial, phase iii' #3 'randomized controlled trial'/exp #4 'randomized controlled trials as topic'/exp OR 'randomized controlled trial (topic)' #5 'controlled clinical trial'/exp OR 'controlled clinical trial' #6 'controlled clinical trial (topic)'/exp OR 'controlled clinical trial (topic)' #7 'randomization'/exp OR randomization #8 'random allocation'/exp OR 'random allocation' #9 'double blind procedure'/exp OR 'double blind procedure' #10 'double-blind method'/exp OR 'double-blind method' #11 'double-blind studies'/exp OR 'double-blind studies' #12 'single-blind method'/exp OR 'single-blind method' #13 'single blind procedure'/exp OR 'single blind procedure' #14 'single-blind studies'/exp OR 'single-blind studies' #15 'placebo'/exp OR placebo OR placebos #16 'control group'/exp OR 'control group' OR 'control groups' #17 random* OR sham OR placebo* #18 (singl* OR doubl*) NEAR/2 (blind* OR dumm* OR mask*) #19 (tripl* OR trebl*) NEAR/2 (blind* OR dumm* OR mask*) #20 control* NEAR/3 (study OR studies OR trial* OR group*) #21 (nonrandom* OR non) AND random* OR 'non random*' OR 'quasi random*' OR quasirandom* #22 allocated OR allocate* #23 (equivalence OR superiority OR 'non inferiority' OR noninferiority) NEAR/3 (study OR studies OR trial*) #24 'pragmatic study' OR 'pragmatic studies' #25 (pragmatic OR practical) NEAR/3 trial* #26 (quasiexperimental OR 'quasi experimental') NEAR/3 (study OR studies OR trial*) #27 phase NEAR/3 (iii OR '3') NEAR/3 (study OR studies OR trial*) #28 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 #29 #28 AND #1 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	335

TableS1 continues

Table S1. Search Strategies (run on 19 September 2024). *(continued)*

Databases	Search strategy	Results
CENTRAL	#1 MeSH descriptor: [Impetigo] explode all trees #2 Impetigo OR Impetigos OR (Impetigo Contagiosa) OR (Contagiosa, Impetigo) OR (Contagiosas, Impetigo) OR (Impetigo Contagiosas) #3 #1 OR #2 (In Trials)	307
Biblioteca Virtual em Saúde (BVS)	#1 MH:Impetigo OR Impétigo OR Impetigo OR (Impetigo Contagioso) OR Impetigo OR Impetigos OR (Impetigo Contagiosa) OR (Contagiosa, Impetigo) OR (Contagiosas, Impetigo) OR (Impetigo Contagiosas) OR C01.150.252.410.868.951.360 OR C01.150.252.410.890.587 OR C01.150.252.819.770.360 OR C01.800.720.770.360 OR C17.800.838.765.770.360 AND (db:("LILACS" OR "BDENF" OR "LIPECS" OR "SES-SP" OR "BINACIS" OR "CUMED" OR "HANSENIASE" OR "BBO" OR "MINSAPERU" OR "MTYCI" OR "colecionaSUS"))	188

Table S2. Risk of Bias Judgments for Each Included RCT.

Study/Year	Randomization		Allocation concealment		Blinding participants/personnel (subjective outcomes)		Blinding outcome assessors (subjective outcomes)		Incomplete outcome		Selective reporting		Other bias	
Anusharani 2019	UNCLEAR	Quote: "*Patients were randomly allocated to two treatment groups*" Comment: No sufficient information on random sequence generation.	UNCLEAR	No sufficient information to judge.	HIGH	Quote: "*open-label study*'.	HIGH	Quote: "*open-label study*'.	LOW	Comment: No losses during the follow-up.	UNCLEAR	No study protocol registry available.	LOW	No other sources of bias were identified.
Barton 1988	UNCLEAR	Quote: "*Patients were randomly assigned in a double-blind manner by the hospital pharmacists to receive 10 days of either erythromycin or dicloxacillin.*" Comment: No sufficient information on random sequence generation.	UNCLEAR	No sufficient information to judge.	LOW	Quote: "*Patients were randomly assigned in a double-blind manner by the hospital pharmacists to receive 10 days of either erythromycin or dicloxacillin.*" Comment: No sufficient information on random sequence generation.	HIGH	Comment: The blinding of outcome assessors was not confirmed, and this lack of blinding can indeed influence the results.	LOW	Comment: lost less than 20% (12%), with reasons.	UNCLEAR	No study protocol registry available.	LOW	No other sources of bias were identified.
Ciftci 2002	UNCLEAR	Quote: "*the patients were randomized into two groups.*" Comment: No sufficient information on random sequence generation.	UNCLEAR	No sufficient information to judge.	HIGH	Comment: Insufficient information is available to make a judgment. Nonetheless, the absence of blinding among participants and personnel can significantly impact the outcomes.	HIGH	Comment: The blinding of outcome assessors was not confirmed, and this lack of blinding can indeed influence the results.	HIGH	Comment: lost more than 20% (22%).	UNCLEAR	No study protocol registry available.	LOW	No other sources of bias were identified.

Table S2 continues

Table S2. Risk of Bias Judgments for Each Included RCT. *(continued)*

Study/Year	Randomization		Allocation concealment		Blinding participants/personnel (subjective outcomes)		Blinding outcome assessors (subjective outcomes)		Incomplete outcome		Selective reporting		Other bias	
Dagani 1992	LOW	Quote: "*The randomized code was prepared by Beecham Pharmaceuticals and was not known to the investigators until after the raw data were tabulated.*	LOW	Quote: "*The randomized code was prepared by Beecham Pharmaceuticals and was not known to the investigators until after the raw data were tabulated.*"	LOW	Quote: "*prospective double-blind controlled study comparing topical mupirocin with oral erythromycin in the treatment of impetigo to determine; the erythromycin group, which received a placebo ointment (ointment containing polyethylene glycol only)*" Comment: blinding of participants and personnel was adequately done.	HIGH	Comment: The blinding of outcome assessors was not confirmed, and this lack of blinding can indeed influence the results.	LOW	Comment: lost less than 20% (11.7%), with reasons.	UNCLEAR	No study protocol registry available.	LOW	No other sources of bias were identified.
Dash 2023	UNCLEAR	Quote: "*the subjects were randomly allotted to treatment groups*." Comment: No sufficient information on random sequence generation.	UNCLEAR	No sufficient information to judge.	HIGH	Quote: "*in a single-centre, open-label, random allocation st udy*" Comment: lack of blinding of participants and personnel probably influences the results (subjective outcomes).	LOW	Quote: "*Evaluation of clinical and bacteriologic efficacy was determined by a blinded observer, a consultant from our department, not involved in this study*." Comment: blinding of outcome assessors was adequately performed.	LOW	Comment: no losses during the follow up.	UNCLEAR	No study protocol registry available.	LOW	No other sources of bias were identified.
Demidovich 1990	UNCLEAR	Quote: "*The pharmacist randomly assigned them to one of three treatment regimens*" Comment: No sufficient information on random sequence generation.	UNCLEAR	No sufficient information to judge.	HIGH	Comment: Insufficient information is available to make a judgment. Nonetheless, the absence of blinding among participants and personnel can significantly impact the outcomes.	LOW	Quote: "*Patients were reevaluated 3 to 5 and 8 to 10 days after beginning therapy by one of the authors (CD. or M.R.), both of whom were blinded to the treatment each child was receiving*."	LOW	Comment: lost less than 20% (2.6%), with reasons.	UNCLEAR	No study protocol registry available.	LOW	No other sources of bias were identified.

Eells 1986	LOW	Quote: "*Patients were randomized between the two treatment groups by a computer-generated set of random numbers in blocks of five per group.*"	UNCLEAR	No sufficient information to judge.	HIGH	Comment: Insufficient information is available to make a judgment. Nonetheless, the absence of blinding among participants and personnel can significantly impact the outcomes.	HIGH	Comment: The blinding of outcome assessors was not confirmed, and this lack of blinding can indeed influence the results.	HIGH	Quote: "*Of the 52 patients enrolled, 38 were evaluable*" Comment: Loss of more than 20% of the sample. (27%)	UNCLEAR	No study protocol registry available.	LOW	No other sources of bias were identified.
Goldfarb 1988	UNCLER	Quote "*Enrolled children were randomly assigned to groups that received either mupirocin topical therapy in a 2% polyethylene glycol ointment or oral erythromycin ethylsuccinate.*" Comment: No sufficient information on random sequence generation.	UNCLEAR	No sufficient information to judge.	HIGH	Quote: "*Parents or legal guardians of the children in the mupirocin group were instructed to apply the 2% mupirocin ointment three times per day, using the cotton swabs provided. Parents or legal guardians of children in the erythromycin group were given instructions and medication to administer erythromycin ethylsuccinate at 40 mg/kg of body weight per day in four doses.*" Comment: Different forms of interventions (oral and topical) prevent masking.	HIGH	Comment: The blinding of outcome assessors was not confirmed, and this lack of blinding can indeed influence the results.	LOW	Comment: lost less than 20% (14%), with reasons.	UNCLEAR	No study protocol registry available.	LOW	No other sources of bias were identified.

Table S2 continues

Table S2. Risk of Bias Judgments for Each Included RCT. *(continued)*

Study/Year	Randomization		Allocation concealment		Blinding participants/personnel (subjective outcomes)		Blinding outcome assessors (subjective outcomes)		Incomplete outcome		Selective reporting		Other bias	
Gropper 2014	LOW	Quote: "*Patients were allocated unique identification numbers and randomization was performed by an independent statistician using an interactive web response system and they were stratified into age subsets, thus ensuring a 1:1:1 distribution in each age group without selection bias.*"	LOW	Quote: "*Patients were allocated unique identification numbers and randomization was performed by an independent statistician using an interactive web response system and they were stratified into age subsets, thus ensuring a 1:1:1 distribution in each age group without selection bias.*"	LOW	Quote: "*Double-blind for ozenoxacin versus placebo comparison (ozenoxacin and placebo did not differ in color, smell or consistency and they were presented in identical aluminum tubes) and investigator-blinded for retapamulin versus placebo comparison because of the different formulation appearances (since retapamulin is formulated as an ointment, it could not be included in the double-blind design, but was administered in investigator-blinded fashion)*" Comment: blinding of participants and personnel was adequately done.	LOW	Quote: "*Double-blind for ozenoxacin versus placebo comparison (ozenoxacin and placebo did not differ in color, smell or consistency and they were presented in identical aluminum tubes) and investigator-blinded for retapamulin versus placebo comparison because of the different formulation appearances (since retapamulin is formulated as an ointment, it could not be included in the double-blind design, but was administered in investigator-blinded fashion)*" Comment: blinding of outcome assessors was adequately performed.	LOW	Comment: lost less than 20% (2%), with reasons.	UNCLEAR	No study protocol registry available.	LOW	No other sources of bias were identified.
Iovino 2011	UNCLEAR	Quote: "*children aged 2-12 years with micro-biologically documented primary non-bullous impetigo were enrolled and randomized into a dose-ranging parallel group study testing 3 different doses*" Comment: No sufficient information on random sequence generation.	UNCLEAR	No sufficient information to judge.	HIGH	Comment: Insufficient information is available to make a judgment. Nonetheless, the absence of blinding among participants and personnel can significantly impact the outcomes.	HIGH	Comment: The blinding of outcome assessors was not confirmed, and this lack of blinding can indeed influence the results.	LOW	Quote: "A *total of 120 subjects (96%) completed all 7 days of treatment and were assessed at end of treatment.*"	UNCLEAR	No study protocol registry available.	LOW	No other sources of bias were identified.

Jeffrey 1990	LOW	Quote: *"Using a random numbers table, the hospital pharmacy randomly assigned each patient to one of two groups"*	UNCLEAR	No sufficient information to judge.	LOW	Quote: *"The child's group assignment was not known to parents or investigators."* Comment: blinding of participants and personnel was adequately done.	LOW	Quote: *"The child's group assignment was not known to parents or investigators."* Comment: blinding of outcome assessors was adequately performed.	HIGH	Quote: *" 12 losses (22.2%), two were dropped when misdiagnosis was suspected and antifungal therapy begun, and one was removed from the study after the development of S. pyogenes pharyngitis, leading to treatment with intramuscular penicillin."* Comment: Loss of more than 20% of the sample (22.2%)	UNCLEAR	No study protocol registry available.	LOW	No other sources of bias were identified.
Koning 2002	LOW	Quote: *"An independent statistician provided a computer generated list of random set numbers in permuted blocks of six. The hospital pharmacist packed the study medication in identical blank tubes with a code number according to the randomisation list. We randomised the patients in blocks and stratified them for presence of pre-existing eczema at the site of the impetigo."*	LOW	Quote: *"The research nurse, who was unaware of the treatment allocation, allocated patients to the first available number of study cream in the corresponding block. The pharmacist kept the list of code numbers in a sealed envelope and was not involved in analysis of data or assessment of outcome."*	LOW	Quote: *"The placebo cream, prepared by the pharmacist, did not differ in colour, smell, or consistency from the fusidic acid cream. Unblinding took place after the primary statistical analysis had been done."* Comment: blinding of participants and personnel was adequately done.	LOW	Quote: *"The research nurse, who was unaware of the treatment allocation, allocated patients to the first available number of study cream in the corresponding block...as assessed by the research nurse."* Comment: blinding of outcome assessors was adequately done.	LOW	Comment: lost less than 20% (3.7%), with reasons.	UNCLEAR	No study protocol registry available.	LOW	No other sources of bias were identified.

Table S2 continues

Table S2. Risk of Bias Judgments for Each Included RCT. *(continued)*

Study/Year	Randomization		Allocation concealment		Blinding participants/personnel (subjective outcomes)		Blinding outcome assessors (subjective outcomes)		Incomplete outcome		Selective reporting		Other bias	
Koning 2008	LOW	Quote: *"Randomization was centre based and performed using an automated telephone system."*	LOW	Quote: *"Randomization was centre based and performed using an automated telephone system."*	LOW	Quote: *"The packaging and labelling of study medication was identical for the active medication and its placebo counterpart. All efforts were made to make the study medication and placebo identical with respect to appearance and smell. Only in the case of an emergency, when knowledge of the investigational product was essential for the clinical management or welfare of the patient, could the investigator unblind a patient's treatment assignment."* Comment: blinding of participants and personnel was adequately done.	LOW	Quote: *"The packaging and labelling of study medication was identical for the active medication and its placebo counterpart. All efforts were made to make the study medication and placebo identical with respect to appearance and smell. Only in the case of an emergency, when knowledge of the investigational product was essential for the clinical management or welfare of the patient, could the investigator unblind a patient's treatment assignment."* Comment: blinding of outcome assessors was adequately performed.	HIGH	Quote: *"48 losses (22.5%), lack of efficacy, disease progression, decided to withdraw, adverse event, protocol violation, lost of follow-up" Comment: Loss of more than 20% of the sample. (22.5%)*	LOW	Study protocol registry available (NCT00133848). Comment: No differences were identified between the study and the protocol.	LOW	No other sources of bias were identified.
Kuniyuki 2005	UNCLEAR	Quote: *"Forty-nine patients participated in a bacterio-logically controlled, randomized, open-label, parallel group comparison"* Comment: No sufficient information on random sequence generation.	UNCLEAR	No sufficient information to judge.	HIGH	Quote: *"open-label study"*.	HIGH	Quote: *"open-label study"*.	LOW	Comment: no losses during the follow up.	UNCLEAR	No study protocol registry available.	LOW	No other sources of bias were identified.

Mclinn 1990	UNCLEAR	QUOTE: "*Sixty patients participated in a bacteriologically controlled, randomized, open-label, parallel group comparison ...*" Comment: No sufficient information on random sequence generation	UNCLEAR	No sufficient information to judge.	HIGH	Quote: "*open-label study*'.	HIGH	Quote: "*open-label study*'.	LOW	Comment: lost less than 20% (1.7%), with reasons.	UNCLEAR	No study protocol registry available.	LOW	No other sources of bias were identified.
Mertz 1989	LOW	Quote: "*This was an investigator-blinded randomized study. Patients were randomized between the two treatment groups according to a computer-generated schedule having a block size of four.*"	LOW	Quote: "*This was an investigator-blinded randomized study. Patients were randomized between the two treatment groups according to a computer-generated schedule having a block size of four.*"	HIGH	Quote: "*Parents or guardians were instructed to either gently rub the mupirocin ointment into all the affected areas three times daily (morning, noon, and evening) for 8 ± 1 days (mean ± SD) or to give the patient 30 to 50 mg per kilogram (divided into two daily doses) of erythromycin ethylsuccinate suspension, chewable tablets, or capsules for 8 ± 1 days.*" *Comment: Different forms of interventions (oral and topical) prevent masking.*	LOW	Quote: "*The randomization was predetermined by the sponsor (Beecham Laboratories, Bristol, Tenn) and the schedule for distribution of medications was entrusted to team member whose assignment was to dispense medication.*" "*The identity of the patient assignment to each treatment was known to the support team but unknown to the physician evaluators.*"	HIGH	Comment: lost less than 20% (29%), with reasons.	UNCLEAR	No study protocol registry available.	LOW	No other sources of bias were identified.

Table S2 continues

Table S2. Risk of Bias Judgments for Each Included RCT. *(continued)*

Study/Year	Randomization		Allocation concealment		Blinding participants/personnel (subjective outcomes)		Blinding outcome assessors (subjective outcomes)		Incomplete outcome		Selective reporting		Other bias	
Nolting 1988	LOW	Quote: "*When patients enrolled in the trial, they were allocated, according to a computer-generated randomization code, to receive either sulconazole nitrate 1% cream or miconazole nitrate 2% cream.*"	LOW	Quote: "*When patients enrolled in the trial, they were allocated, according to a computer-generated randomization code, to receive either sulconazole nitrate 1% cream or miconazole nitrate 2% cream.*"	HIGH	Comment: Insufficient information is available to make a judgment. Nonetheless, the absence of blinding among participants and personnel can significantly impact the outcomes.	HIGH	Comment: The blinding of outcome assessors was not confirmed, and this lack of blinding can indeed influence the results.	LOW	Quote: "*All patients completed the 2-week study.*" Comment: no losses during the follow up.	UNCLEAR	No study protocol registry available.	LOW	No other sources of bias were identified.
Oranje 2007	LOW	Quote: "*Subjects were assigned randomly to retapamulin or sodium fusidate by means of a predetermined, center-based 2: 1 schedule using the telephone-based, interactive, central Registration and Medication Ordering System. Randomization was also stratified according to the following age groups: 9 months to 5 years, 6–12 years and 6 13 years.*"	LOW	Quote: "*Subjects were assigned randomly to retapamulin or sodium fusidate by means of a predetermined, center-based 2: 1 schedule using the telephone-based, interactive, central Registration and Medication Ordering System. Randomization was also stratified according to the following age groups: 9 months to 5 years, 6–12 years and 6 13 years.*"	LOW	Quote: "*observer-blinded*" "*In addition, subjects and, where appropriate, their parents/guardians were instructed not to discuss any details of the study medication with clinical assessors*" Comment: no blinding of participants and personnel.	LOW	Quote: "*The blinded assessor was responsible for performing all clinical activities in assessing the subjects' lesion(s) following treatment. To maintain observer blinding, an unblinded person (other than the investigator) at the study site was responsible for dispensing the study medication, maintaining the patients' study treatment records and ensuring that the clinical assessor remained blinded to treatment assignments at all visits. In addition, subjects and, where appropriate, their parents/guardians were instructed not to discuss any details of the study medication with clinical assessors*"	LOW	Comment: lost less than 20% (7.9%)	LOW	Study protocol registry available (NCT001 33874). Comment: No differences were identified between the study and the protocol.	LOW	No other sources of bias were identified.

Rosen 2018	LOW	Quote: "*Central randomization via an interactive web response system was used to allocate patients to treatment groups, stratified by age subset, to ensure a 1:1 distribution and avoid selection bias*."	LOW	Quote: "*Central randomization via an interactive web response system was used to allocate patients to treatment groups, stratified by age subset, to ensure a 1:1 distribution and avoid selection bias*."	HIGH	There is insufficient information available to make a judgment. Nonetheless, the absence of blinding among participants and personnel can significantly impact the outcomes.	HIGH	Quote: "*This randomized clinical trial was a multicenter, double-blind, vehicle-controlled, parallel group*," Comment: The blinding of outcome assessors was not confirmed, and this lack of blinding can indeed influence the results.	LOW	Quote: "*Overall, 13 patients in the placebo group discontinued the study owing to worsening of condition. Four patients withdrew owing to adverse events (1 in the ozenoxacin group and 3 in the placebo group), 4 were lost to follow-up (2 in each group), 3 withdrew consent (2 in the ozenoxacin group and 1 in the placebo group), and 2 discontinued for other reasons (1 in each group)*." Comment: lost less than 20% (6.3%)	LOW	Study protocol registry available (NCT02090764). Comment: No differences were identified between the study and the protocol.	LOW	No other sources of bias were identified.

Table S2 continues

Table S2. Risk of Bias Judgments for Each Included RCT. *(continued)*

Study/Year	Randomization		Allocation concealment		Blinding participants/personnel (subjective outcomes)		Blinding outcome assessors (subjective outcomes)		Incomplete outcome		Selective reporting		Other bias	
Sudha 2017	UNCLEAR	Quote: "*They were randomly divided into two groups with 50 patients in each group.*" Comment: No sufficient information on random sequence generation	UNCLEAR	No sufficient information to judge.	HIGH	Quote: "*This is a prospective, randomized, single blinded interventional study*" Comment: The blinding of participants was not confirmed, and this lack of blinding can indeed influence the results.	HIGH	Quote: "*This is a prospective, randomized, single blinded interventional study*" Comment: The blinding of outcome assessors was not confirmed, and this lack of blinding can indeed influence the results.	LOW	Comment: no losses during the follow up.	UNCLEAR	No study protocol registry available.	LOW	No other sources of bias were identified.
Tong 2010	UNCLEAR	Quote: "*Participants were randomised to receive either a single dose of IM BPG (45 mg/kg up to 900 mg) or TMP-SMZ*" Comment: No sufficient information on random sequence generation	LOW	Quote: *"Allocation was concealed by using sealed, sequentially marked, opaque envelopes.*"	HIGH	There is insufficient information available to make a judgment. Nonetheless, the absence of blinding among participants and personnel can significantly impact the outcomes.	LOW	Quote: *"Assessment was by clinical examination and also by review of photographs by two investigators blinded to treatment allocation.*"	LOW	Comment: no losses during the follow up.	LOW	Study protocol registry available (ACTRN 12607000 592448). Comment: No differences were identified between the study and the protocol.	LOW	No other sources of bias were identified.

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Tretinoin for Photodamaged Facial Skin: Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Key words: Tretinoin, Photodamaged skin, Facial skin, Systematic review, Meta-analysis

Citation: Huang HY, Lee LTJ. Tretinoin for Photodamaged Facial Skin: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Dermatol Pract Concept.* 2025;15(4):5172. DOI: https://doi.org/10.5826/dpc.1504a5172

Accepted: June 22, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Randomized controlled trials have suggested that tretinoin, a topical retinoid, can improve wrinkling in photodamaged skin; however, its overall effectiveness remains subject of debate.

Objectives: This study evaluated the efficacy and safety of tretinoin in treating facial wrinkles induced by photodamage.

Method: We systematically searched the PubMed, EMBASE, and Cochrane CENTRAL databases from their inception to 16 January 2024 to identify randomized controlled trials comparing topical tretinoin with vehicle treatments. Data were synthesized using a random effects model, and sensitivity analyses were performed to evaluate the robustness of the results in the presence of potential bias.

Results: This study identified eight trials (1,361 patients; median age range 29–76 years; average follow-up duration, 16 weeks to 2 years) that met the inclusion criteria. Compared with the vehicle, topical tretinoin significantly improved clinical signs of facial photodamage. Improvements were observed in both fine wrinkles (mean difference [MD]: 0.412; 95% confidence interval [CI]: 0.233–0.590; $P<0.001$) and coarse wrinkles (MD: 0.245; 95% CI: 0.119–0.370; $P<0.001$). Sensitivity analyses confirmed the robustness of these findings.

Conclusion: Topical tretinoin is a safe and effective treatment for fine and coarse facial wrinkles resulting from photodamage.

Introduction

The widespread use of social media has increased people's self-consciousness regarding their facial appearance. Many individuals consider facial skin aging to be undesirable and thus seek medical treatment for it. Such aging can be either intrinsic or extrinsic. Intrinsic aging results from unknown endogenous factors and genetically programmed skin cell deterioration, which can lead to epidermal or dermal atrophy. Skin affected by intrinsic aging typically exhibits thinning, decreased elasticity, and deeper expression lines. By contrast, extrinsic aging is caused by environmental factors, such as sun exposure. The extrinsic aging caused by chronic sun exposure is referred to as photoaging or photodamage, and it involves epidermal dysplasia, dermal damage, substantial elastosis, and collagen loss [1]. Facial manifestations of photoaging include fine and coarse wrinkles, irregular pigmentation, and changes in skin texture, elasticity, and thickness; they result from environmental influences rather than the natural progression of intrinsic aging [2].

Photodamage is associated with both undesirable cosmetic outcomes and pathological changes, including the development of benign and malignant tumors [2]. Many individuals seek treatment to address these aesthetic concerns and manage the underlying pathological problems related to photodamage to facial skin. Facial wrinkles are a common manifestation of skin aging and are one of the most prominent features of photoaging. Such wrinkles are generally categorized into two types: fine wrinkles and coarse wrinkles. Fine wrinkles appear as small folds in the superficial epidermal layers and are typically caused by skin dryness and photoaging. By contrast, coarse wrinkles are deeper folds within the dermal layer and primarily result from collagen and elastin loss.

Topical retinoids, which are derivatives of vitamin A, promote collagen synthesis and inhibit matrix metalloproteinase (MMP) activity by binding to and activating retinoic acid receptors. These receptors regulate the transcription of genes responsive to retinoic acid, thereby facilitating cell proliferation and differentiation. Topical retinoids are widely used to treat various dermatological conditions, including photoaging, acne vulgaris, psoriasis, cutaneous T-cell lymphoma, and Kaposi's sarcoma. Currently, six classes of topical retinoids are approved for clinical use: tretinoin (all-trans-retinoic acid), adapalene, tazarotene, trifarotene, alitretinoin, and bexarotene [3]. Among these, tretinoin is the only one that is effective at treating photoaging and wrinkles. Tretinoin operates through two distinct but synergistic molecular mechanisms. First, when applied prior to exposure to ultraviolet light, tretinoin inhibits activator protein-1 (AP-1) activity, which is a key driver of collagen-degrading MMPs. Second, topical application of tretinoin stimulates collagen synthesis by upregulating the expression of type I procollagen [3].

Unlike intrinsic aging, photoaging can be prevented by limiting sun exposure and applying sunscreen regularly [1,4,5]. Several alternative therapies have been developed for managing photoaging, including those involving non-retinoid topical agents, chemical peels, and laser resurfacing. Non-retinoid topical agents such as vitamin C, peptides, and growth factors have demonstrated potential in addressing photoaging; however, their effectiveness in reversing structural skin damage remains limited [9,10]. In addition, chemical peels and laser resurfacing may improve photoaging symptoms but are associated with risks such as irritation, prolonged recovery time, and outcome variability related to skin type [11,12]. Contemporary developments have indicated that injectable treatments, including treatment with hyaluronic acid and botulinum toxin, may help reduce the visibility of blood vessels in photodamaged skin [13,14]. This is particularly relevant for individuals with the atrophic photoaging phenotype, who commonly exhibit vascular features such as telangiectasias resulting from chronic sun exposure [13,15]. These injectables offer a noninvasive approach to addressing vascular changes commonly observed in the photoaged skin. In addition, individuals with the hypertrophic photoaging phenotype, characterized by deep and pronounced wrinkles, may benefit from injectables such as hyperdilute calcium hydroxylapatite, which stimulates collagen remodeling and improves overall skin texture [13,15-17]. These therapies are both cosmetic enhancers and targeted treatments for specific photoaging phenotypes. However, larger clinical trials are required to validate their efficacy and safety in treating photoaging and to clarify their role in personalized approaches to skin aging.

Large-scale trials have demonstrated that topical tretinoin is a safe and effective means of reducing facial wrinkling, mottled hyperpigmentation, and skin roughness. Tretinoin has also been reported to partially reverse skin photodamage [1,2,4-8]. Although topical tretinoin may have adverse effects, it remains the most promising therapeutic option for photoaged skin.

Objective

The present systematic review and meta-analysis evaluated the efficacy and adverse effects of topical tretinoin in the treatment of facial wrinkles.

Methods

General Guidelines

This meta-analysis was conducted in accordance with the latest version of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines

[18]. The PROSPERO registration number of this study is CRD42024511094.

Search Strategy and Study Selection

One investigator (HH) conducted a systematic search of three electronic databases, namely, PubMed, Embase, and Cochrane CENTRAL, for randomized controlled trials by using the following keywords: (topical retinoid) OR (retinoic acid) OR (all-trans-retinoic-acid) AND (photoaging) OR (photodamaged) AND (improvement) AND (wrinkle). The search included all records from the inception of each database to 16 January 2024. The complete search strategy is outlined in Supplementary Table S1. All identified trials were recorded in an Excel spreadsheet for review by a second investigator (LTL).

Two investigators (HH and LTL) independently screened the titles and abstracts of the retrieved studies for eligibility, and any discrepancies were resolved through discussion. Only full-text articles published in English were included.

Eligibility Criteria: Inclusion and Exclusion Criteria

The inclusion criteria for the trials were as follows: i) randomized, vehicle-controlled design; ii) use of tretinoin in a single formulation with variations in dosage, base, and application method as the primary treatment for photoaging; iii) evaluation of tretinoin's effects on facial skin wrinkles (fine wrinkles, coarse wrinkles, or both), with results reported as percentage improvements in wrinkle appearance; iv) inclusion of participants aged 18 years or older with mild, moderate, or severe skin photodamage.

In trials that employed multiple treatment dosages, data extraction was performed separately for each dosage to ensure analytical precision. Percentage improvements in wrinkle appearance were individually recorded for each dosage group. When trials reported aggregated outcomes without providing dosage-specific data, the corresponding authors were contacted to obtain detailed information. If these data were unavailable, results were included in the meta-analysis on the basis of the most relevant available information, and sensitivity analyses were conducted to evaluate the potential impact of data inconsistencies.

The following types of studies were excluded: i) nonrandomized controlled trials; ii) trials without a vehicle control; iii) studies assessing photoaging outcomes other than facial wrinkles; iv) trials using treatment regimens other than topical tretinoin; v) studies lacking data on percentage improvements in wrinkle appearance following therapy. Detailed reasons for article exclusion are provided in Table S2.

Outcomes and Data Extraction

The first reviewer (HH) conducted the initial data extraction on the basis of the inclusion criteria and recorded the results in Excel spreadsheets and tables. The second reviewer (LTL) independently extracted the data and compared their results with those of the first reviewer, and any discrepancies were resolved through discussion. Extracted data included study design, baseline demographics, tretinoin intervention details, treatment duration, and primary, secondary, and tertiary outcome values.

The primary outcome of interest was the percentage improvement in wrinkle appearance (fine or coarse) from baseline to the endpoint, as assessed by professional investigators in the included trials. Data were extracted separately for each wrinkle type, and percentages were manually calculated when only the number of patients exhibiting improvement was reported [1,6]. All relevant data were included from trials that reported multiple results either because multiple treatment dosages were used [5,19] or because the study was conducted at multiple centers [2]. If data were missing in a study (e.g., when the effect on coarse wrinkling was reported as nonsignificant, but no supporting data were provided, as in Weinstein et al. [19]), the corresponding author was contacted through email to obtain the original data. The secondary outcome of interest was the overall improvement in facial wrinkling caused by photodamage, as self-assessed by participants. The primary outcome was objective, whereas the secondary outcome was subjective. Percentage improvements for both outcomes were extracted and are presented in Table S3. The tertiary outcome involved adverse events, and event rates were calculated and are reported using odds ratios (OR).

Study Quality and Risk of Bias Assessments

The quality of the included studies was independently assessed by two reviewers (HH and LTL) by using the Cochrane Risk of Bias Tool for Randomized Trials (version 2, RoB 2, London, UK). Six domains of bias were evaluated: i) randomization process; ii) intervention adherence; iii) missing outcome data; iv) outcome measurement; v) selective reporting; vi) overall risk of bias [20]. Each domain was rated as low risk, some concerns, or high risk. On the basis of these ratings, each trial was categorized as having a low risk of bias, some concerns, or a high risk of bias. Any disagreement between reviewers was resolved through discussion and until a consensus was reached.

Statistical Analysis

A random effects model was used to analyze the data through Comprehensive Meta-Analysis software (version 4, Biostat, Englewood, NJ, USA). A two-tailed p-value of <0.05 was considered significant.

The primary and secondary outcomes were quantified using mean differences (MD) with corresponding 95% confidence intervals (CI). The tertiary outcome was quantified using OR and their associated 95% CI. Heterogeneity among the included trials was evaluated using the I^2 and Cochran's Q statistics, with I^2 values of 30%, 50%, and 75% indicating moderate, substantial, and considerable heterogeneity, respectively [18]. To validate the robustness of the findings, sensitivity analyses were performed using the one-study-removal method. This approach is used to determine whether the exclusion of any single trial results in significant changes in the overall effect size [18]. Potential publication bias was evaluated using funnel plot analysis and Egger's regression tests.

Results

A total of 128 relevant randomized controlled trials were identified through the database search, of which eight met the inclusion criteria and were included in the qualitative and quantitative syntheses (Figure 1). These eight trials were published between 1988 and 2006. Their characteristics are summarized in Table 1 and Supplementary Table S4. Collectively, the trials enrolled 1,361 patients aged between 29 and 76 years. All trials were conducted in the United States, with the exception of one conducted in Australia. The baseline severity of photoaging among the participants ranged from mild to severe. The average follow-up duration varied from 16 weeks to two years. Study quality assessments are presented in Table S5, and detailed data on clinical improvements and patient-reported outcomes from all trials are provided in Table S3.

Primary Outcome: Improvement in Fine Facial Wrinkles After Treatment With Tretinoin Compared With a Vehicle

All eight trials assessed clinical improvement in fine wrinkles by comparing tretinoin treatment with a vehicle. A significant improvement in fine facial wrinkles was observed following tretinoin treatment (MD: 0.412; 95% CI: 0.233–0.590; $P<0.001$; $I^2=35.438\%$; Figure 2). Moderate heterogeneity was noted in the included trials. To examine the robustness of the findings, a sensitivity analysis was performed using the one-study-removal method; the significant effect of tretinoin on fine wrinkle improvement remained consistent ($P<0.001$; Figure S1). Exclusion of any individual trial did not affect the overall significance of the findings. However, Egger's test indicated potential publication bias in the studies evaluating improvements in fine wrinkles ($P<0.001$; Figure S2).

Primary Outcome: Improvement in Coarse Facial Wrinkles After Treatment With Tretinoin Compared With a Vehicle

Six trials, excluding those conducted by Olsen et al. [5] and Weinstein et al. [19], evaluated the efficacy of tretinoin in improving coarse facial wrinkles. Consistent with the findings for fine wrinkles, tretinoin treatment led to a significant improvement in coarse wrinkles (MD:0.245; 95% CI: 0.119–0.370; $P<0.001$; $I^2=0\%$; Figure 3). No significant heterogeneity was detected. In a sensitivity analysis using the one-study-removal method, the significant effect of tretinoin on coarse wrinkle improvement remained unchanged ($P<0.001$; Figure S3). In addition, Egger's test indicated no significant publication bias in the studies assessing improvements in coarse wrinkles ($P=0.457$; Figure S4).

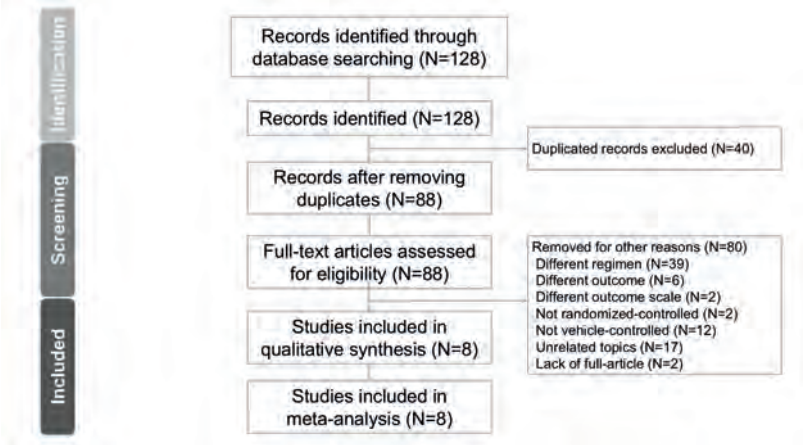


Figure 1. PRISMA flow diagram.

Table 1. Retrieved Trials Investigating the Effectiveness of Topical Retinoid Treatment in Improving Photodamage-Induced Wrinkles.

First author and year	Country	Population	Patient number (tretinoin/ vehicle), N	Sex (male/ female), N	Age [1]	Study design	Allocation concealment	Randomization	Funding/grants/support
Weiss 1988	USA	Healthy White patients	15/15	Sex not mentioned	50 (35–70)	RCT, double-blind	Not mentioned	Table of random numbers	- Ortho Pharmaceutical Corp. - Babcock Dermatologic Endowment
Weinstein 1991	USA	Healthy White patients	200/99	34/265	41 (29–50)	RCT, double-blind	Not mentioned	Randomization code	R. W. Johnson Pharmaceutical Research Institute
Olsen 1992	USA	Healthy White patients	224/72	Tretinoin 0.05%: 55/21 Vehicle: 50/22	42.5 (30–58)	RCT, double-blind	Double-blind tubes	Not mentioned	R. W. Johnson Pharmaceutical Research Institute
Andreano 1993	USA	White patients	17/17	Total: 28/6	41 (31–50)	RCT, double-blind	Not mentioned	Not mentioned	Ortho Pharmaceutical Corporation
Lowe 1994	Australia	Healthy White patients	62/63	Total: 115/10	46 (30–65)	RCT, double-blind	Not mentioned	Computer-generated randomization code	Janssen-Cilag Pty Ltd.
Nyirady 2001	USA	White patients	Study 1: 77/83 Study 2: 82/86	Study 1[2]: Tretinoin 0.02%: 78/12 Vehicle: 80/9 Study 2[2]: Tretinoin 0.02%: 79/10 Vehicle: 80/10	Study 1: 58.4 (45–69) Study 2: 58.6 (43–70)	RCT, double-blind	Not mentioned	Not mentioned	Ortho Dermatological Division of Ortho-McNeil Pharmaceutical, Inc.
Kang 2005	USA	Healthy patients	101/103	Tretinoin 0.05%: 91/10 Vehicle: 92/11	Tretinoin: 63.2 (40–76) Vehicle: 62.4 (43–75)	RCT, double-blind	Not mentioned	Computer-generated randomization lists	OrthoNeutrogena
Weiss 2006	USA	Healthy White patients	22/23	Total: 44/1	(38–73)	RCT, double-blind	Not mentioned	Not mentioned	OrthoNeutrogena

RCT: randomized controlled trial. USA: United States of America. [1] Age is presented as means (ranges) or as (ranges) only. [2] Sex was assessed in studies evaluating safety instead of efficacy.

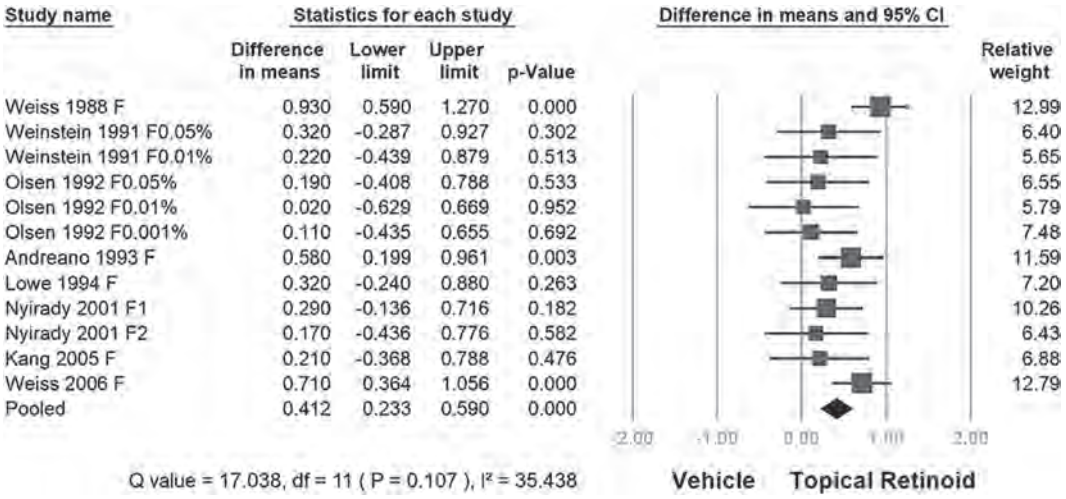


Figure 2. Forest plot illustrating the effects of topical tretinoin on fine wrinkles on photodamaged facial skin compared with placebo (vehicle). This figure summarizes the results of clinical studies evaluating the effectiveness of tretinoin, a topical retinoid, in reducing fine facial wrinkles caused by sun damage. The plot reveals that tretinoin led to a significantly greater improvement in wrinkle appearance than the placebo treatment did. (CI = confidence interval; F = fine wrinkles)

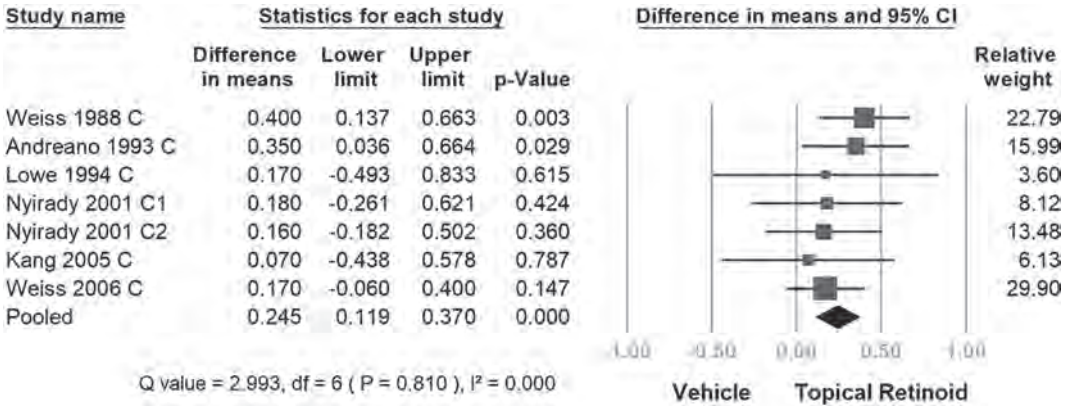


Figure 3. Forest plot illustrating the effects of topical tretinoin on coarse wrinkles in photodamaged facial skin compared with placebo (vehicle). This figure summarizes the results of clinical studies evaluating the effectiveness of tretinoin, a topical retinoid, in reducing coarse facial wrinkles caused by sun damage. The plot reveals that tretinoin led to a significantly greater improvement in wrinkle appearance than the placebo treatment did (C = coarse wrinkles; CI = confidence interval).

Secondary Outcome: Patient Self-Assessments of Overall Improvement in Photodamage Severity of Facial Skin After Treatment With Tretinoin Compared With a Vehicle

Six of the eight included trials reported data on patient self-assessments of overall improvement in photoaging, including with respect to skin appearance and texture, following treatment with tretinoin compared with a vehicle [2,5-8,19]. Patients who received tretinoin provided significantly higher ratings for overall improvement (MD: 0.270; 95% CI: 0.033–0.508; *P*=0.026; I^2=0%; Figure S5). The sensitivity analysis revealed consistent results (*P*=0.026; Figure S6). No significant heterogeneity was observed among the trials. Additionally, Egger's test revealed no significant publication bias in studies evaluating patient self-assessments (*P*=0.284; Figure S7).

Tertiary Outcome: Adverse Event Rates Associated With Treatment

Among the 1,361 patients included in the trials, 822 received tretinoin treatment. A total of 492 treatment-related adverse events were reported in this group. Meta-analysis of adverse event rates revealed a significant increase in the likelihood of experiencing adverse events following tretinoin treatment

(OR: 3.140; 95% CI: 1.819–5.419; P<0.001; I^2=73.261%; Figure S8).

Discussion

This systematic review and meta-analysis is the first to comprehensively evaluate both the safety and the efficacy of tretinoin in treating photodamage-induced facial wrinkles. The results revealed significant improvements in both fine and coarse facial wrinkles following tretinoin treatment compared with after the use of a vehicle. These findings remained robust in sensitivity analyses conducted using the one-study-removal method. In our meta-analysis, no significant heterogeneity was noted among studies assessing the efficacy of tretinoin for coarse wrinkles, and only moderate heterogeneity was observed in those evaluating fine wrinkles, suggesting consistent therapeutic benefits across different patient populations and study designs. This homogeneity may be attributed to the relatively standardized treatment protocols and objective efficacy measurements, such as global photographic assessment and lesion count reduction.

Photoaging is an extrinsic factor that contributes to the development of wrinkles. Ultraviolet light exposure leads to histologic damage to the skin, including epidermal dysplasia and atrophy, substantial elastosis in the dermis, increased melanocyte activity, and high levels of glycosaminoglycans and inflammatory infiltrates [1,4]. Additionally, the degradation of collagen and accumulation of elastotic material in the dermal extracellular matrix reduce mechanical support to the epidermis [4], ultimately contributing to photodamage-induced facial wrinkling [7].

Five of the eight trials included in this review assessed histological changes in skin biopsies before and after tretinoin treatment [1,4,5,7,19]. Across these studies, tretinoin consistently induced epidermal thickening, compaction of the stratum corneum, granular layer expansion, and reduced melanin content, changes associated with improved skin texture and reduced wrinkle appearance [1,5,7,19]. One study also reported increased levels of procollagen 1 C-terminal (PIC) and N-terminal (SP1) levels, suggesting enhanced collagen synthesis as a mechanism for wrinkle reduction [4].

The epidermal response observed following topical tretinoin application is mediated by well-established biochemical pathways in keratinocytes. Tretinoin regulates epidermal cell proliferation and differentiation by interacting with cellular retinoic acid–binding proteins, which function as receptors for all-trans-retinoic acid. Upon binding to specific cytosolic receptors, tretinoin translocates to the nucleus, where it modulates protein synthesis and enhances the features of photodamaged skin [1,5].

Tretinoin exerts its primary therapeutic effects through retinoic acid receptors (RARs), with RAR-γ being the predominant isoform in human skin [21]. The binding of tretinoin to RARs triggers a cascade of gene expression that regulates keratinocyte proliferation and differentiation [21]. Animal studies have demonstrated that RAR-γ activity, in coordination with retinoid X receptor alpha (RXRα), is essential to tretinoin-induced epidermal thickening [22]. Several molecular biomarkers have been identified as potential predictors of treatment response, including RAR-γ expression, Ki-67, and epidermal growth factor receptor (EGFR) pathway activation. Ki-67 is a nuclear protein expressed during active phases of the cell cycle, making it a widely used marker of cellular proliferation [23]. Increased Ki-67 expression following tretinoin treatment indicates increased keratinocyte turnover, which often correlates with visible improvements in skin appearance [23]. Additionally, tretinoin upregulates EGFR ligands such as amphiregulin (AR) and heparin-binding epidermal growth factor–like growth factor (HB-EGF), which further promote keratinocyte activity and epidermal hyperplasia [24]. These molecular effects support tretinoin's role in reversing photodamage and may guide personalized treatment strategies.

In the current analysis, in addition to the significant improvements in facial wrinkles noted by professional investigators, the study participants reported noticeable enhancements in the overall appearance and texture of their photodamaged skin following treatment (P=0.026). The sensitivity analysis conducted using the one-study-removal method confirmed the robustness of these findings. The significant improvement in the patient self-assessments further confirms the therapeutic effect of tretinoin on both objective and subjective measures. The results confirm that tretinoin significantly improves fine and coarse wrinkles; however, its impact on quality of life is also a critical concern. The patient-reported outcomes in this study indicated improvements in skin appearance and texture, suggesting potential psychological and emotional benefits associated with treatment.

Although tretinoin demonstrated significant efficacy in improving photodamaged skin (P<0.001), patients were frequently affected by adverse reactions. Across the included trials, individuals receiving tretinoin experienced various forms of cutaneous irritation, such as dryness, erythema, peeling, burning, and stinging, particularly during the initial weeks of treatment [1,2,4-8,19]. The severity of these effects was generally mild [2,4,7,8,19] or mild-to-moderate [5,6]. It is worth noting that considerable heterogeneity was observed in the tertiary outcome related to adverse events. This variability is likely attributable to differences in study duration, tretinoin concentrations, vehicle formulations, and the subjective nature of reporting symptoms such as irritation or dryness, which are heavily influenced by individual tolerance and study-specific factors. In some cases, these adverse

reactions were sufficiently bothersome to result in temporary discontinuation or modification of the treatment regimen. Previous studies have suggested that irritation may be mitigated by gradually escalating the dose, using moisturizers concurrently, or applying topical corticosteroids for short-term relief [1,5,6]. Nonetheless, further research is required to optimize treatment protocols that improve long-term adherence without reducing therapeutic efficacy. Patient adherence remains a key challenge in tretinoin treatment because of the high frequency of adverse effects. Because patient adherence is a critical determinant of clinical outcomes, education and individualized management strategies are essential. Ensuring that patients anticipate and are able to manage transient irritation may enhance treatment persistence. Additional investigations identifying alternative formulations, such as those with lower tretinoin concentrations or newer retinoid derivatives with improved tolerability, could help address this.

In the current study, common adverse reactions to topical tretinoin were generally resolved with continued use or appropriate supportive care. Some have speculated that the irritation and inflammation induced by topical retinoids may contribute to wrinkle improvement because mild swelling could temporarily reduce the appearance of wrinkles [1]. However, findings from the trial by Weiss et al. [1] indicated that no edema was observed in post-treatment skin biopsy specimens, and no improvement in photoaging was noted in areas affected by tretinoin-induced dermatitis. Additional controlled trials reported that the application of other irritants, such as salicylic acid, did not produce similar improvements in photodamaged skin [7]. Moreover, Olsen et al. [5] identified no clinical correlation between irritation and treatment response. In that study, only half of the patients who experienced satisfactory-to-excellent improvement rated their irritation level as 5 or higher on a 9-point grading scale [5].

The long-term safety of tretinoin treatment was assessed in a trial conducted by Kang et al. [4]. Over a 2-year treatment period, minimal histological changes were observed in the skin of most patients (≥85%). The evaluated histological parameters included keratinocytic dysplasia, melanocytic dysplasia, dermal elastosis, and the stratum corneum. The findings demonstrated that topical tretinoin is safe for long-term use of up to two years and does not induce cellular atypia within that timeframe.

In addition to retinoids, agents such as peptides, antioxidants, and growth factors have garnered interest for their anti-aging properties. Peptides and growth factors, in particular, have demonstrated an ability to stimulate collagen production and improve photodamaged skin with minimal adverse effects [9,10,25,26]. However, many of the studies that support the use of these treatments are limited by small sample sizes and nonrandomized designs, which reduce the overall strength of the evidence because of the potential for bias [9,10]. Cosmetic procedures such as microneedling and laser therapy, either as standalone treatments or in combination with tretinoin, are also effective options for individuals seeking rejuvenation strategies with reduced irritation. Although tretinoin remains a widely used and effective intervention, emerging therapies may offer advantages over tretinoin in terms of efficacy and tolerability. Future research should include larger, long-term clinical trials to compare these therapies and identify optimal treatment regimens for managing photoaging.

To assist clinicians in translating these findings into daily practice, Table 2 summarizes practical considerations and recommendations for the safe and effective use of topical tretinoin in treating photodamaged facial skin.

Limitations

Our study has several limitations. First, the randomized controlled trials included in this meta-analysis exhibited variability in terms of their design and methodology, including differences in treatment formulation, dosage, and duration. These inconsistencies may have contributed to heterogeneity in the reported outcomes and could affect the interpretability of their findings. Although this study standardized outcome measurements by using percentage improvements in wrinkle appearance, the initial assessment scales varied across the trials. Additional variations in dosages, treatment durations, and drug vehicles may have influenced the observed heterogeneity in fine wrinkle outcomes and affected the consistency of estimated treatment effects. To address this, we employed a random effects model and conducted sensitivity analyses. Second, the potential for reporting or publication bias cannot be excluded. Publication bias occurs when positive results are more likely to be published than are negative or null findings, leading to an overestimation of treatment efficacy. In our analysis, evidence of publication bias was observed in trials assessing improvements in fine wrinkles, suggesting that these results should be interpreted with caution. Third, most included trials lacked long-term follow-up data. The longest treatment duration reported was two years, thus limiting our ability to evaluate the sustained effectiveness and long-term safety of topical retinoids for treating fine and coarse wrinkles.

Although patient-reported outcomes indicated satisfaction with tretinoin treatment, the trials did not capture specific quality-of-life feedback, such as that regarding skin comfort or psychological and emotional impacts. Future studies should incorporate validated QoL instruments, such as the Dermatology Life Quality Index, to better assess the real-world impact of tretinoin therapy.

Table 2. Practical Takeaways for Clinicians: Topical Tretinoin Use.

Clinical Consideration	Recommendation
Patient Selection Based on Photodamage Severity	• Select patients with **mild-to-moderate photodamage** for best response • Use a **standardized 9-point photodamage scale**[1] to assess severity • **Avoid initiating** tretinoin in patients with severe photodamage until **skin barrier is optimized**
Initiation in Sensitive or Reactive Skin	• Start with **lower concentration** (e.g., ≤0.02%) • **Titrate gradually** as tolerated • Reduce application frequency to **every other night** if needed • Help improve **adherence** and **reduce discontinuation** due to irritation
Strategies for Mitigating Adverse Reactions	• Apply **moisturizer** before or after tretinoin to minimize irritation • Educate patients on **adaptation period** (typically 2–4 weeks) • Avoid **harsh skincare products** (e.g., alcohol-based toners, exfoliants) • Use **short-term topical corticosteroids** for severe irritation to control inflammation without reducing efficacy

[1] Please refer to: C.E. Griffiths, T.S. Wang, T.A. Hamilton, J.J. Voorhees, C.N. Ellis, A photonumeric scale for the assessment of cutaneous photodamage, *Arch Dermatol*, 128 (1992) 347-351. PMID: 1550366.

Despite these limitations, our findings indicate that tretinoin, across various dosages and treatment durations, significantly improves fine and coarse wrinkles on photodamaged facial skin. Findings of patient satisfaction, as reflected in subjective assessments, further support the clinical value of tretinoin treatment. However, such treatment's association with skin irritation highlights a need for continued research to determine optimal dosing strategies and to develop approaches to minimizing adverse reactions, which can improve the efficacy and safety of treatment.

Conclusion

Tretinoin treatment has been demonstrated to significantly improve facial wrinkling caused by photodamage, including both fine and coarse wrinkles, relative to a vehicle. Although some patients experience skin irritation in response to treatment, overall satisfaction with the improvements in photoaging was frequently reported following tretinoin therapy. These findings underscore the therapeutic value of topical tretinoin in addressing visible signs of photoaging. However, because of the potential for irritation and the variability in individual responses, additional research should be conducted to develop safer and more effective tretinoin formulations that better accommodate patient needs. Long-term follow-up studies are also necessary to evaluate the durability of treatment effects and to assess the long-term safety of topical retinoids. Additionally, such studies should investigate the broader impact of tretinoin on overall skin health and provide research that contributes to the development of evidence-based guidelines for its integration into clinical skin care regimens.

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Supplementary file

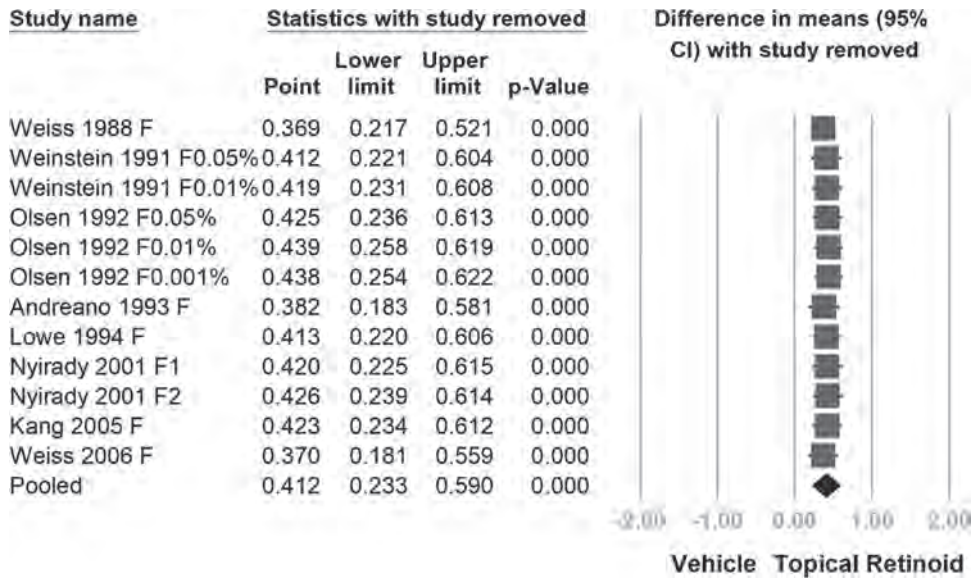


Figure S1. Sensitivity analysis using the one-study-removal method. The results indicated a statistically significant improvement in facial fine wrinkling, even after removing any one of the included trials. CI: confidence interval. F: fine wrinkles.

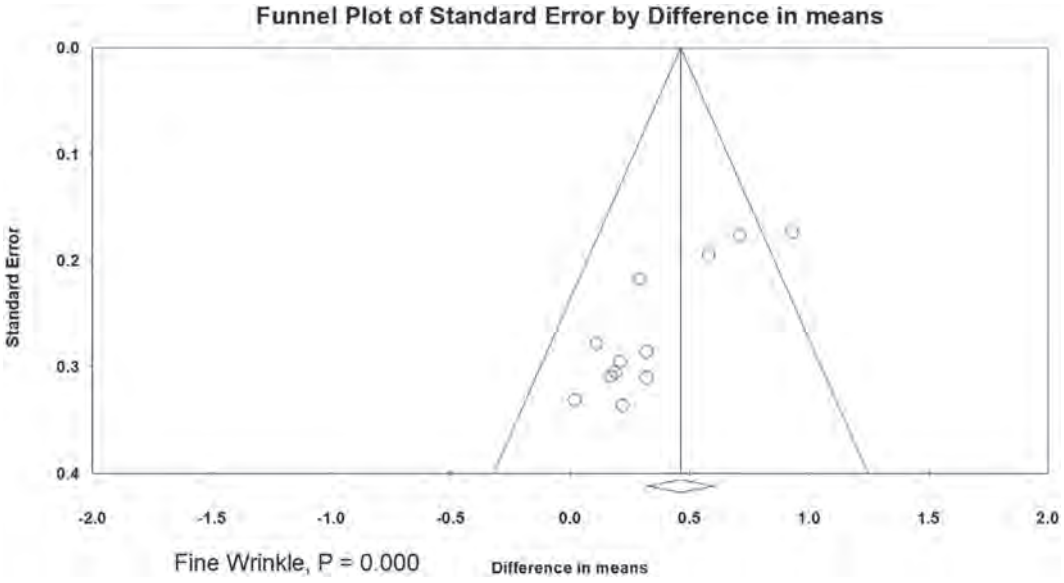


Figure S2. Funnel plot of all eight trials that were included in the analysis of fine wrinkles. Egger's test revealed a p-value of 0.000, indicating some publication bias.

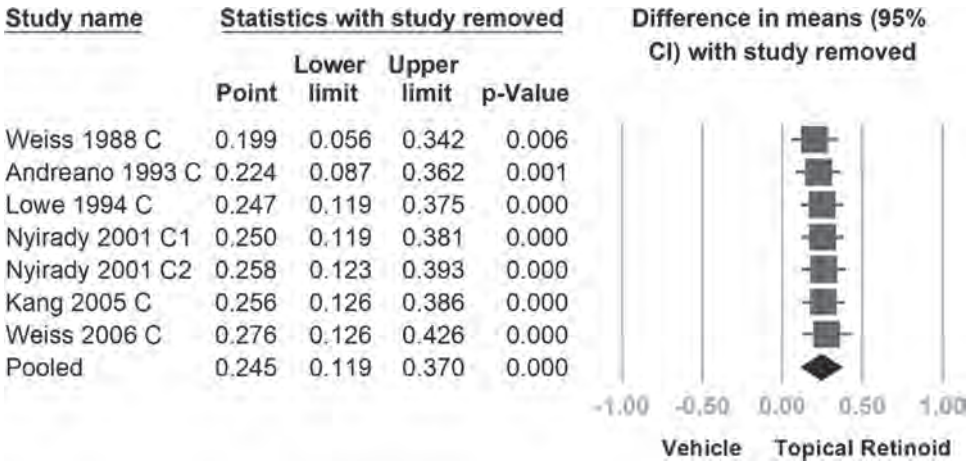


Figure S3. Sensitivity analysis using the one-study-removal method. The results indicated statistically significant improvement in facial coarse wrinkling even after removing any one of the included trials. CI: confidence interval. C: coarse wrinkles.

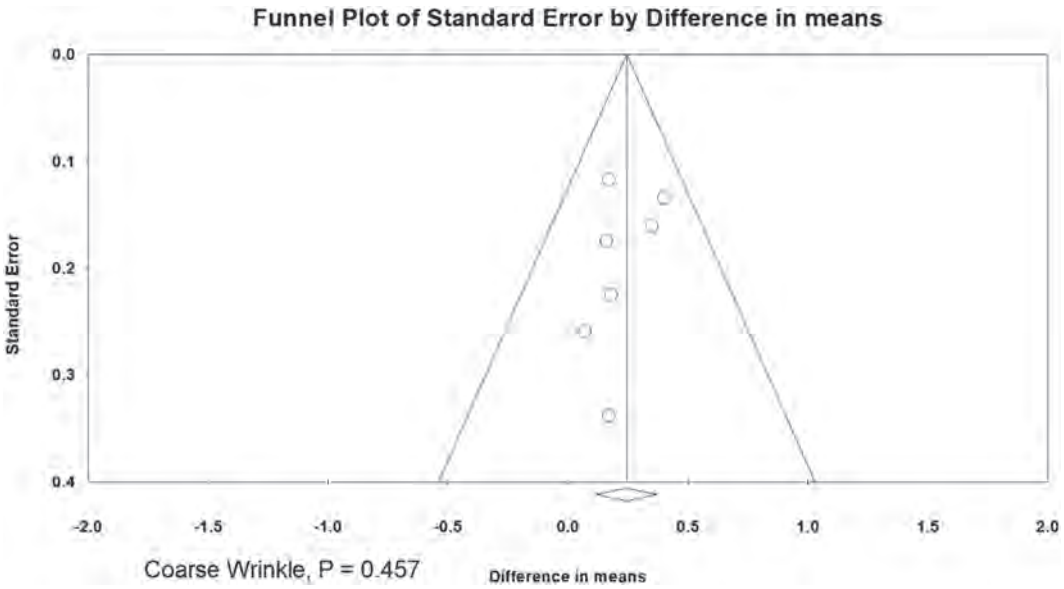


Figure S4. Funnel plot of six out of eight trials that were included in the analysis of coarse wrinkles. Egger's test revealed a p-value of 0.457, indicating no notable publication bias.

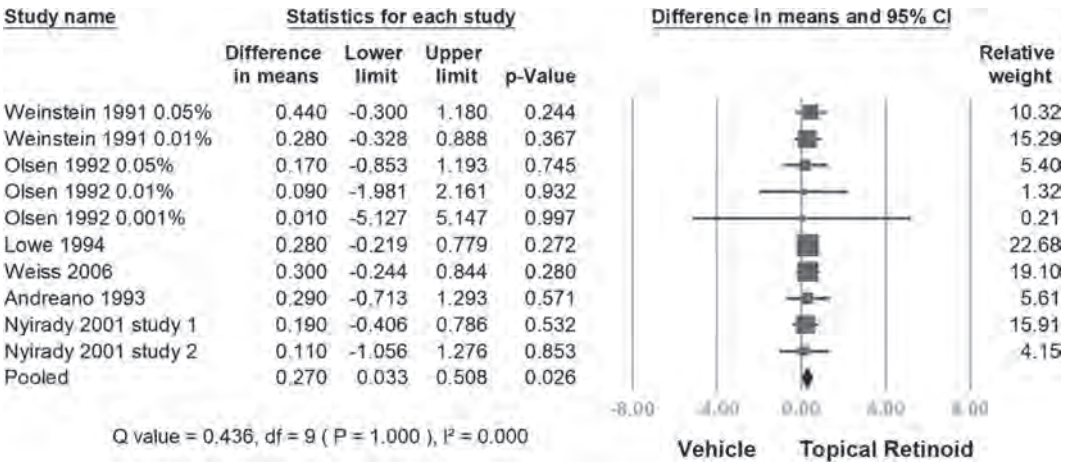


Figure S5. Forest plot of patient self-assessment of overall improvement of photodamaged skin from six relative trials. The statistically significant result revealed that patients favored the treatment effect of tretinoin over placebo. CI: confidence interval.

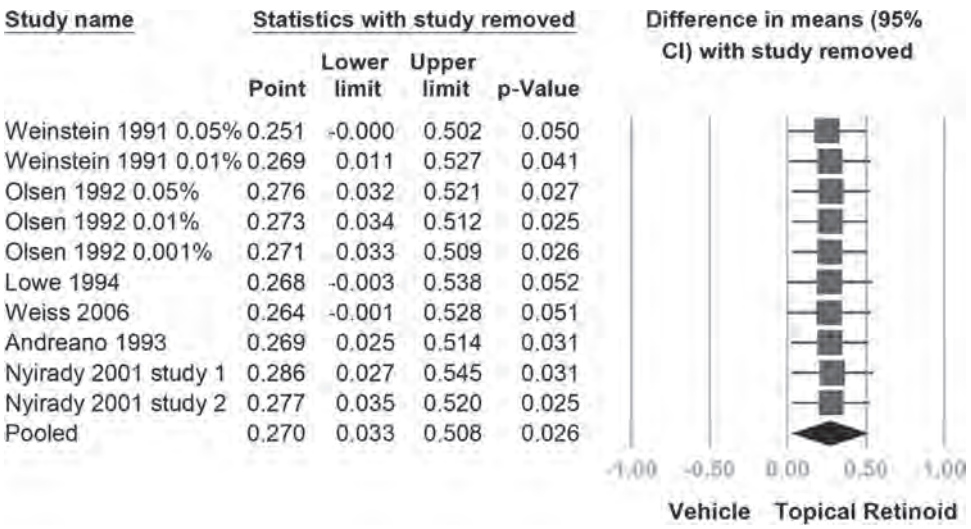


Figure S6. Sensitivity analysis of patient self-assessment of overall improvement of photodamaged skin using the one-study-removal method. The results indicated maintenance of significant improvement in overall photodamaged skin even after removing any one of the included trials. CI: confidence interval.

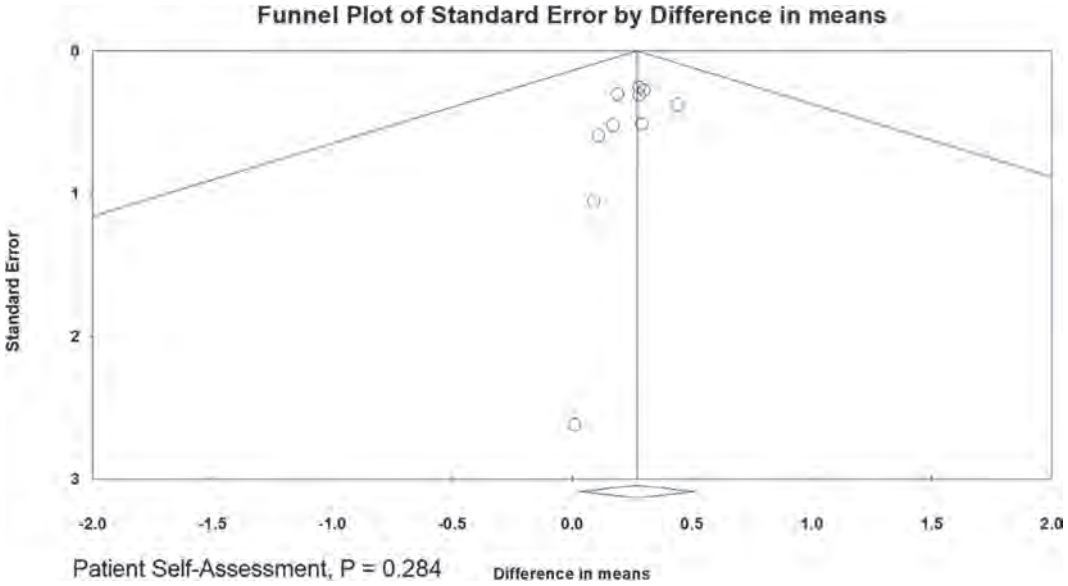


Figure S7. Funnel plot of six out of eight trials that were included in the analysis of patient self-assessment. Egger's test revealed a p-value of 0.284, indicating no notable publication bias.

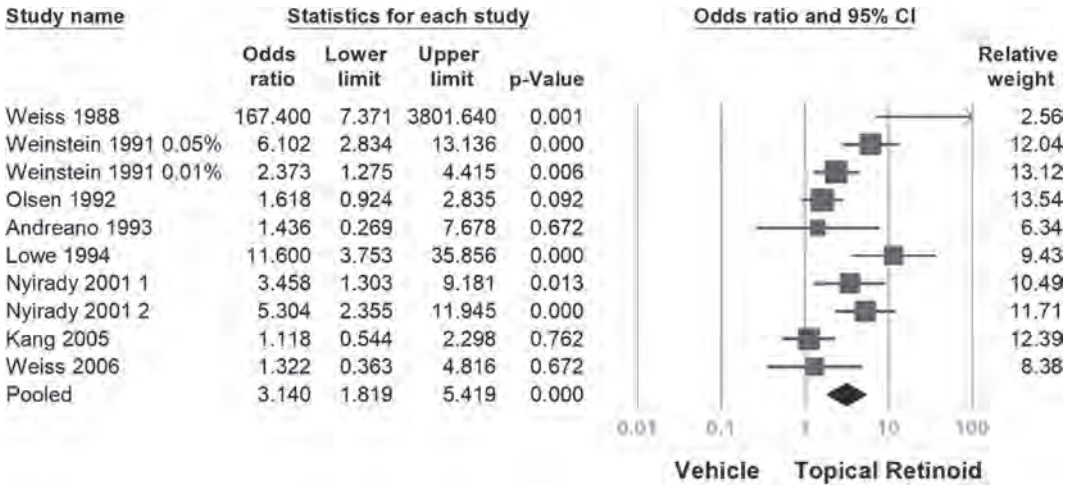


Figure S8. Forest plot of adverse events rate related to treatment: 492 out of 822 patients in the active treatment group with tretinoin experienced skin irritation. CI: confidence interval.

Table S1. Keywords and Search Results in Different Databases.

Database	Keyword	Filter	Date	Results
PubMed	((topical retinoid) OR (retinoic acid) OR (all-trans-retinoic-acid)) AND ((photoaging) OR (photodamaged)) AND ((improvement) AND (wrinkle))	Randomized Controlled Trial	16 January 2024	67
Embase	((topical retinoid) OR (retinoic acid) OR (all-trans-retinoic-acid)) AND ((photoaging) OR (photodamaged)) AND ((improvement) AND (wrinkle))	Randomized Controlled Trial	16 January 2024	26
Cochrane CENTRAL	((topical retinoid) OR (retinoic acid) OR (all-trans-retinoic-acid)) AND ((photoaging) OR (photodamaged)) AND ((improvement) AND (wrinkle))	Title Abstract Keyword	16 January 2024	35

Table S2. Excluded Studies and Reasons for Exclusion.

Citations	Reasons
Phillips TJ, Gottlieb AB, Leyden JJ, Lowe NJ, Lew-Kaya DA, Sefton J, Walker PS, Gibson JR; Tazarotene Cream Photodamage Clinical Study Group. Efficacy of 0.1% tazarotene cream for the treatment of photodamage: a 12-month multicenter, randomized trial. Arch Dermatol. 2002 Nov;138(11):1486-93. doi: 10.1001/archderm.138.11.1486. PMID: 12437455.	Different regimen (other topical retinoid; tazarotene)
Kang S, Leyden JJ, Lowe NJ, Ortonne JP, Phillips TJ, Weinstein GD, Bhawan J, Lew-Kaya DA, Matsumoto RM, Sefton J, Walker PS, Gibson JR. Tazarotene cream for the treatment of facial photodamage: a multicenter, investigator-masked, randomized, vehicle-controlled, parallel comparison of 0.01%, 0.025%, 0.05%, and 0.1% tazarotene creams with 0.05% tretinoin emollient cream applied once daily for 24 weeks. Arch Dermatol. 2001 Dec;137(12):1597-604. doi: 10.1001/archderm.137.12.1597. PMID: 11735710.	Different regimen (other topical retinoid; tazarotene)
Armstrong RB, Lesiewicz J, Harvey G, Lee LF, Spoehr KT, Zultak M. Clinical panel assessment of photodamaged skin treated with isotretinoin using photographs. Arch Dermatol. 1992 Mar;128(3):352-6. PMID: 1550367.	Different regimen (other topical retinoid; isotretinoin)
Bagatin E, Parada MO, Miot HA, Hassun KM, Michalany N, Talarico S. A randomized and controlled trial about the use of oral isotretinoin for photoaging. Int J Dermatol. 2010 Feb;49(2):207-14. doi: 10.1111/j.1365-4632.2009.04310.x. PMID: 20465648.	Different regimen (oral isotretinoin)
Griffiths CE, Russman AN, Majmudar G, Singer RS, Hamilton TA, Voorhees JJ. Restoration of collagen formation in photodamaged human skin by tretinoin (retinoic acid). N Engl J Med. 1993 Aug 19;329(8):530-5. doi: 10.1056/NEJM199308193290803. PMID: 8336752.	Different outcome (assessed collagen formation as primary outcome)
Gupta MA, Schork NJ, Ellis CN. Psychosocial correlates of the treatment of photodamaged skin with topical retinoic acid: a prospective controlled study. J Am Acad Dermatol. 1994 Jun;30(6):969-72. doi: 10.1016/s0190-9622(94)70119-9. PMID: 8188889.	Different outcome (assessed psychosocial aspect of treatment)
Bhawan J, Olsen E, Lufrano L, Thorne EG, Schwab B, Gilchrest BA. Histologic evaluation of the long term effects of tretinoin on photodamaged skin. J Dermatol Sci. 1996 Mar;11(3):177-82. doi: 10.1016/0923-1811(95)00432-7. PMID: 8785167.	Different outcome (assessed histological parameter)
Bhawan J, Gonzalez-Serva A, Nehal K, Labadie R, Lufrano L, Thorne EG, Gilchrest BA. Effects of tretinoin on photodamaged skin. A histologic study. Arch Dermatol. 1991 May;127(5):666-72. Erratum in: Arch Dermatol 1991 Sep;127(9):1382. PMID: 2024984.	Different outcome (assessed histological parameter)

Table S2. Excluded Studies and Reasons for Exclusion. *(continued)*

Citations	Reasons
Rafal ES, Griffiths CE, Ditre CM, Finkel LJ, Hamilton TA, Ellis CN, Voorhees JJ. Topical tretinoin (retinoic acid) treatment for liver spots associated with photodamage. N Engl J Med. 1992 Feb 6;326(6):368-74. doi: 10.1056/NEJM199202063260603. PMID: 1729619.	Different outcome (assessed liver spots)
Ho ET, Trookman NS, Sperber BR, Rizer RL, Spindler R, Sonti S, Gotz V, Mehta R. A randomized, double-blind, controlled comparative trial of the anti-aging properties of non-prescription tri-retinol 1.1% vs. prescription tretinoin 0.025%. J Drugs Dermatol. 2012 Jan;11(1):64-9. PMID: 22206079.	Not a vehicle-controlled trial
Bagatin E, Gonçalves HS, Sato M, Almeida LMC, Miot HA. Comparable efficacy of adapalene 0.3% gel and tretinoin 0.05% cream as treatment for cutaneous photoaging. Eur J Dermatol. 2018 Jun 1;28(3):343-350. doi: 10.1684/ejd.2018.3320. PMID: 30105991.	Not a vehicle-controlled trial
Chien AL, Kim DJ, Cheng N, Shin J, Leung SG, Nelson AM, Zang J, Suh H, Rainer B, Wallis L, Okoye GA, Loss M, Kang S. Biomarkers of Tretinoin Precursors and Tretinoin Efficacy in Patients With Moderate to Severe Facial Photodamage: A Randomized Clinical Trial. JAMA Dermatol. 2022 Aug 1;158(8):879-886. doi: 10.1001/jamadermatol.2022.1891. PMID: 35675051; PMCID: PMC9178500.	Not a vehicle-controlled trial
Bagatin E, Guadanhim LR, Enokihara MM, Sanudo A, Talarico S, Miot HA, Gibson L. Low-dose oral isotretinoin versus topical retinoic acid for photoaging: a randomized, comparative study. Int J Dermatol. 2014 Jan;53(1):114-22. doi: 10.1111/ijd.12191. Epub 2013 Oct 29. PMID: 24168514.	Not a vehicle-controlled trial
Kligman DE, Draelos ZD. Combination Superficial Peels With Salicylic Acid and Post-Peel Retinoids. J Drugs Dermatol. 2016 Apr;15(4):442-50. PMID: 27050699.	Not a vehicle-controlled trial
Miura T, Takada A, Ooe M. Tretinoin cyclodextrin complex (RA/CyD) causes less irritation with an equal antiwrinkle effect compared with conventional tretinoin: clinical and histologic studies of photoaged skin. Aesthetic Plast Surg. 2012 Aug;36(4):971-81. doi: 10.1007/s00266-012-9903-4. Epub 2012 Apr 27. PMID: 22538278.	Not a vehicle-controlled trial
Sumita JM, Miot HA, Soares JLM, Raminelli ACP, Pereira SM, Ogawa MM, Picosse FR, Guadanhim LRS, Enokihara MMSS, Leonardi GR, Bagatin E. Tretinoin (0.05% cream vs. 5% peel) for photoaging and field cancerization of the forearms: randomized, evaluator-blinded, clinical trial. J Eur Acad Dermatol Venereol. 2018 Oct;32(10):1819-1826. doi: 10.1111/jdv.15020. Epub 2018 May 27. PMID: 29704456.	Not a vehicle-controlled trial
Leyden JJ, Grove GL, Grove MJ, Thorne EG, Lufrano L. Treatment of photodamaged facial skin with topical tretinoin. J Am Acad Dermatol. 1989 Sep;21(3 Pt 2):638-44. doi: 10.1016/s0190-9622(89)70231-0. PMID: 2674225.	Different outcome scale (lack data on wrinkle improvement percentages)
Olsen EA, Katz HI, Levine N, Nigra TP, Pochi PE, Savin RC, Shupack J, Weinstein GD, Lufrano L, Jou HC. Sustained improvement in photodamaged skin with reduced tretinoin emollient cream treatment regimen: effect of once-weekly and three-times-weekly applications. J Am Acad Dermatol. 1997 Aug;37(2 Pt 1):227-30. doi: 10.1016/s0190-9622(97)80129-6. PMID: 9270508.	Different outcome scale (lack data on wrinkle improvement percentages)
Samuel M, Brooke RC, Hollis S, Griffiths CE. Interventions for photodamaged skin. Cochrane Database Syst Rev. 2005 Jan 25;(1):CD001782. doi: 10.1002/14651858.CD001782.pub2. Update in: Cochrane Database Syst Rev. 2015;6:CD001782. PMID: 15674885.	Not a randomized trial

Table S3. Clinical Improvement and Patient Assessment of all Studies Included in Meta-Analysis.

	Fine Wrinkles Clinical Improvement Rates (Patient number/Total patient)			Coarse Wrinkles Clinical Improvement Rates (Patient number/Total patient)			Overall self-assessment of global response (% of subjects)		
Study	Grades of Clinical Improvement (% for Quantification)	Tretinoin-treated	Vehicle-treated	Grades of Clinical Improvement (% for Quantification)	Tretinoin-treated	Vehicle-treated	Grades of Clinical Improvement (% for Quantification)	Tretinoin-treated	Vehicle-treated
Weiss et al, 1988	Tretinoin 0.1% Much improved Improved Slightly improved No change or worse	0/15 1/15 13/15 1/15	0/0 0/0 0/0 15/15	Much improved Improved Slightly improved No change or worse	0/0 0/0 6/15 9/15	0/0 0/0 0/0 15/15	ND[ɣ]	ND	ND
Weinstein et al, 1991	Tretinoin 0.05% Tretinoin 0.01%	60/85[ǂ] 51/84[ǂ]	31/82[ǂ]	ND[ɣ]	ND	ND	(Tretinoin doses) Overall improvement (includes much improved and somewhat improved)	0.05%; 0.01% 87; 71	43
Olsen et al, 1992	Tretinoin 0.05% Tretinoin 0.01% Tretinoin 0.01% ND[ɣ]	43/76[ǂ] 29/73[ǂ] 20/75[ǂ]	27/72[ǂ]	ND[ɣ]	ND	ND	(Tretinoin doses) Improved • Much improved • Somewhat improved	0.05%; 0.01%; 0.001% 78; 70; 60 14; 10; 9 63; 60; 51	61 7 54
Andreano et al, 1993	Tretinoin 0.01% Much improved Improved Slightly Improved No improvement/worse	0/17 3/17 10/17 4/17	0/17 0/17 3/17 14/17	Much improved Improved Slightly Improved No improvement/worse	0/17 1/17 6/17 10/17	1/17 0/17 0/17 16/17	ND[ɣ]	76	47
Lowe et al, 1994	Tretinoin 0.05% ND[ɣ]	45/62	26/63	ND[ɣ]	32/62	22/63	ND[ɣ]	60	32
Nyirady et al, 2001	Tretinoin 0.02% ND[ɣ]	Study1: 50/77[ǂ] Study2: 46/82[ǂ]	Study1: 30/83[ǂ] Study2: 34/86[ǂ]	ND[ɣ]	Study1: 33/77[ǂ] Study2: 31/82[ǂ]	Study1: 20/83[ǂ] Study2: 18/86[ǂ]	Improved • Much improved • Somewhat improved	Study1; Study2 83; 83 25; 29 58; 54	Study 1; Study 2 64; 72 7; 24 57; 48
Kang et al, 2005	Tretinoin 0.05% ND[ɣ]	76/101[ǂ]	56/103[ǂ]	ND[ɣ]	44/101[ǂ]	38/103[ǂ]	ND[ɣ]	ND	ND
Weiss et al, 2006	Tretinoin 0.1% ND[ɣ]	16/18[ǂ]	5/22[ǂ]	ND[ɣ]	3/18[ǂ]	1/22[ǂ]	ND[ɣ]	65	35

ND, no data. [ɣ]Results of clinical improvement without adequate definition. [ǂ]Patient numbers are from estimated calculation from provided data.

Table S4. Summary of the Topical Retinoid Interventions Administered in the Study Treatment Arms of the Retrieved Trials.

First author & year	Photoaging severity at baseline	Duration	Topical retinoid product / manufacturer	Daily topical retinoid frequency (per-protocol N)	Control (per-protocol N)	Wrinkle improvement measurement	AE associated with topical retinoid treatment
Weiss 1988	mild to moderate	16 weeks	Tretinoin 0.1% cream (Retin-A, Ortho Pharmaceutical Corp, Raritan, NJ)	Once nightly (15)	Matching vehicle (15)	0-4 points scale converted to improvement scores[1]	Most common AE was dermatitis experienced by 92% of patients using tretinoin and no AE seen in vehicle group
Weinstein 1991	mild or moderate	24 weeks	Tretinoin 0.05% or 0.01% emollient cream (Renova)	Once daily (169)	Matching vehicle (82)	0-9 point scale converted to percentage of subjects' improvement	Most common AE were peeling and dryness and were highest in Tretinoin 0.05% (64%) compared with vehicle (25%)
Olsen 1992	mild or moderate	24 weeks	Tretinoin 0.05% Tretinoin 0.01% Tretinoin 0.001% emollient cream (Renova)	Once every evening (76)	Comparable vehicle (72)	10 point scale converted to percentage of subjects' improvement	Most common AE was dryness and was highest in Tretinoin 0.05% (65%) compared with vehicle (33%)
Andreano 1993	mild or moderate	48 weeks (24 weeks[2])	Tretinoin 0.01% emollient cream (RW Johnson Pharmaceutical Research Institute, Raritan, NJ)	Daily (17)	Matching vehicle (17)	0-9 points scale converted to improvement scores[1]	AE rate was similar between the tretinoin (82%) and the vehicle (76%) group. Most common AE were dryness, peeling, and acne.
Lowe 1994	mild-to-moderate	24 weeks	Tretinoin 0.05% (Janssen-Cilag (Australia) Pty Ltd)	Once nightly (62)	Matching vehicle (63)	0-6 points scale converted to percentage of subjects' improvement	49% of the tretinoin treatment group experienced AE compared to 35% in the vehicle group. Most common AE was irritation.

Table S4. Summary of the Topical Retinoid Interventions Administered in the Study Treatment Arms of the Retrieved Trials. *(continued)*

First author & year	Photoaging severity at baseline	Duration	Topical retinoid product / manufacturer	Daily topical retinoid frequency (per-protocol N)	Control (per-protocol N)	Wrinkle improvement measurement	AE associated with topical retinoid treatment
Nyirady 2001	moderate-to-severe	24 weeks	Tretinoin 0.02% cream	Once nightly (Study 1: 77 Study 2: 82)	Matching vehicle (Study 1: 83 Study 2: 86)	0-9 point scale converted to percentage of subjects' improvement	Most common AE was irritation occurred in 20% (study 1) and 38% (study 2) of the treatment group.
Kang 2005	moderate-to-severe	2 years (24 months[2])	Tretinoin 0.05% emollient cream	Once nightly (101)	Matching vehicle (103)	10 point scale converted to percentage of subjects' improvement	AE rate was similar between the tretinoin (83%) and the vehicle (82%) group. Most common AE were irritation and upper respiratory tract infection
Weiss 2006	moderate-to-severe	6 months double-blinded period[2]	Tretinoin 0.1% Microsphere gel	Once nightly (22)	Matching vehicle (23)	10 point scale converted to percentage of subjects' improvement	AE rate was similar between the tretinoin (32%) and the vehicle (30%) group. Most common AE was infection

AE, adverse effect. [1] Improvement scores were calculated into percentage by combining all the patients with "slightly improved", "improved", and "much improved" groups and divided by the total participants. [2] Primary outcome of wrinkle improvement was extracted by this end-point of the trial.

Table S5 Detailed Quality Assessment of the Included Studies using the Cochrane Risk of Bias Tool (Version 2)

First Author	Randomization process	Intervention adherence	Missing outcome data	Outcome measurement	Selective reporting	Overall RoB
Weiss 1988	L	L	L	L	L	L
Weinstein 1991	L	L	L	L	S[1]	S
Olsen 1992	L	L	L	L	S[2]	S
Andreano 1993	L	L	L	L	L	L
Lowe 1994	L	L	L	L	L	L
Nyirady 2001	L	L	L	L	L	L
Kang 2005	L	L	L	L	L	L
Weiss 2006	L	L	L	L	L	L

H, high risk of bias; L, low risk of bias; RoB, risk of bias; S, some risk of bias. [1]This study did not provide data on tretinoin's treatment effect on coarse wrinkling. [2]This study only provided p-values of one of the three concentrations of tretinoin being tested.

Dermatology Practical & Conceptual

Training Primary Care Practitioners In Dermoscopy Diagnostic Algorithms Enhances Diagnostic Accuracy and Triage of Suspected Skin Cancer: Scoping Review Evidence

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Key words: Primary care, Skin cancer, Melanoma, Dermoscopy, Diagnostic algorithm

Citation: Ladet A, Lawton S, Boffa MJ. Training Primary Care Practitioners In Dermoscopy Diagnostic Algorithms Enhances Diagnostic Accuracy and Triage of Suspected Skin Cancer: Scoping Review Evidence. *Dermatol Pract Concept*. 2025;15(4):5208. DOI: https://doi.org/10.5826/dpc.1504a5208

Accepted: March 17, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: In many Western countries, access to a dermatologist can be difficult, while the incidence of skin cancer has risen steadily over the past 50 years.

Objective: We reviewed the published literature to determine whether training primary care practitioners (PCPs) in dermoscopy through brief interventions based on diagnostic algorithms could improve patient care by improving their diagnostic accuracy of suspect lesions.

Methods: A scoping review of the literature was conducted, focusing on studies published in the period 2003–2023 that assessed the ability of low-experienced PCPs to triage suspicious dermatological lesions using dermoscopic diagnostic algorithms. Regarding outcomes, we focused on quantitative variables relevant to screening practice in general practice, including sensitivity, specificity, referrals to specialists, and unnecessary lesion excisions.

Results: Of the 926 studies initially identified, 13 were eventually selected: 10 cross-sectional observational studies and three randomized controlled trials. The studies were carried out in North America (N=6), Western Europe (N=4), and Australia (N=3). There was heterogeneity in the training interventions and the criteria used to assess diagnostic accuracy of PCPs after training; however, all studies showed an improvement in this parameter. The preferred algorithms for training PCPs were the 3-point checklist, the 7-point checklist, and the Triage Amalgamated Dermoscopy Algorithm.

Conclusion: This review demonstrates the value of training PCPs in dermoscopic diagnostic algorithms through short courses to improve triage of suspicious lesions. However, it is still necessary to define a territorial organization, a precise working framework and limits for PCPs who take on this role.

Introduction

Many Western countries are facing a shortage of healthcare professionals, including in the field of dermatology. In Europe, the ageing physician population and lack of replacements is straining healthcare systems [1]. North America has not been spared either, with a predicted shortage of primary and secondary care physicians by 2033 in the USA [2] and a chronic shortage of physicians in rural areas in Canada [3]. In many Western countries with publicly-funded healthcare systems, the waiting time to see a dermatologist is long, increasing pressure on PCPs to acquire new skills to fill the gap [4–7]. Furthermore, skin cancer incidence is increasing, particularly in developed countries with ageing populations. The prognosis for melanoma, which is the most serious of these cancers, depends on the Breslow thickness and can therefore be improved by early detection and appropriate management [8, 9].

Dermoscopy has become an established tool in dermatology that facilitates diagnosis, particularly of pigmented skin lesions. It is widely used in practice throughout the world. In Europe, the most recent observational studies show a usage rate among dermatologists of between 94.6% and 99% [10-12]. A very recent questionnaire-based study conducted in Greece showed that dermoscopy is used in more than 80% of clinical situations [13]. Dermoscopy could also be useful in primary care for identifying suspicious lesions and prioritizing their management while reducing unnecessary excisions and referrals. Teledermoscopy could further improve triage accuracy. However, dermoscopy is only beneficial when performed by trained operators [14-16]. Algorithms can be used to train non-experts in dermoscopic screening, providing acceptable diagnostic sensitivity and specificity [17]. Various algorithms, such as the ABCD rule, Menzies method, 3-point and 7-point checklists, CASH algorithm, BLINCK, and TADA (Table 1) have, to varying degrees, been validated for use by dermoscopy operators [18-24]. Strengthening training of PCPs in dermatology and promoting dermoscopy practice could help address the skin cancer burden; however, it is important to assess whether training PCPs in dermoscopic algorithms improves their diagnostic accuracy. Additionally, identifying scientifically robust and suitable dermoscopic algorithms for PCP training is necessary.

Method

A scoping review was conducted following the PRISMA extension reference checklist focusing on the analysis of dermatological lesions suspicious for cancer using dermoscopy algorithms [25]. The selected algorithms were the 3-point and 7-point checklists, Menzies method, ABCD rule, CASH, BLINCK, and TADA [18-24] (Table 1). The review specifically looked at primary care settings and practitioners with little dermoscopy experience. Studies involving specialists, hospitals, other algorithms, or benign lesions were excluded.

Searches were conducted in the following databases: MEDLINE, EMBASE, PASCAL, Cochrane Library, National Institute for Health Research Dissemination Centre, Campbell Library of Systematic Reviews, and the HealthSTAR database for grey literature.

The use of the PICO method, categorizing subjects into Population, Intervention, Control, and Outcome, was employed in the research strategy. The selection of keywords considered synonyms, alternative formulations, acronyms, and spelling variations [26].

The search was limited to the period 2003–2023, and only articles in English, French, Italian, Spanish, or German were reviewed. Most studies available were observational and of low evidence. Therefore, we included all studies up to level 3b of the Oxford Centre for Evidence-Based Medicine classification [27].

Regarding outcomes, we focused on quantitative variables relevant to screening practice in general practice, including sensitivity, specificity, referrals to specialists, and unnecessary excisions. To assess strengths and weaknesses, we used a generic method for evaluating articles, which included eight evaluation criteria, using critical appraisal tools proposed by the Oxford Centre for Evidence-Based Medicine [28]. Finally, we used an interpretative method to analyze and summarize the results obtained. The lack of consistent data in publications made it challenging to use quantitative methods for analysis.

Results

Selection of Studies and Data Collected

The seven selected databases were searched between March and July 2023, identifying 926 studies potentially relevant to the research topic. The selection process was carried out in successive stages, reducing the working sample to 39 studies, of which 12 fully meeting the pre-defined criteria were retained. One additional study emerged after repeating the same selection process on the 912 references cited in the last 39 studies assessed. In the end, 13 studies were selected (Figure 1); of these, 10 were observational studies and three were controlled trials (Table 2). The studies were conducted between 2005 and 2021 in North America (N=6), Western Europe (N=4), and Australia (N=3) [23, 29-40]. Of the sample of studies collected by our method, only the 13 selected fully met our inclusion and exclusion criteria. We only selected studies that aimed to evaluate the diagnostic accuracy of lesions suspected of being cancerous by inexperienced PCPs who had received a short training course and used dermoscopy by means of algorithms.

Table 1. Overview of Algorithms Utilized in the Included Studies.

Full name	Abbreviation	Description
3-point checklist	None	Using this algorithm, the operator looks for 7 signs of malignancy in the pigmented lesion. Two points are given for each of the three major criteria: atypical pigment network, blue-white veil and atypical vascular pattern and one point for each of the four minor criteria: irregular streaks, blotches or globules and regression structures. A score of 3 or more identifies a melanoma with a sensitivity of 95% and a specificity of 75%..
7-point checklist	None	Using this algorithm, the operator looks for 7 signs of malignancy in the pigmented lesion: atypical pigment network, blue-white veil, atypical vascular pattern, streaks, blotches, globules, all irregularly distributed and regression structures. It is a weighted scoring system. The signs are divided into 2 categories: major signs and minor signs, which are assigned a score of 2 or 1 respectively. A score of 3 or more identifies a melanoma with a sensitivity of 95% and a specificity of 75%.
Menzies method	None	The principle of this algorithm is that to be suspicious for melanoma, the lesion must not have a symmetrical pattern or a single colour, and it must have at least one feature that is considered a warning sign: blue-white veil, pseudopods, scar-like depigmentation, multiple brown dots, radial streaming, peripheral black globules, peppering and multiple colours. The colours considered by this algorithm are black, light and dark brown, red, blue and grey.
ABCD rule	None	A scoring tool with parameters such as asymmetry in 2 axes (0-2 points), border in 8 sectors (0-8 points), number of colours (1-6 points) and number of dermoscopic structures (1-5 points). The score for each parameter is then weighted by a coefficient and the values are added together to give the final score. Scores below 4.75 indicate a benign lesion, scores above 5.45 indicate a melanoma and intermediate scores indicate at least the need for lesion monitoring.
Colour, Architecture, Symmetry, and Homogeneity	CASH	This algorithm is similar to the ABCD rule but also considers architecture. It evaluates colour (blue, red, black, dark brown, tan or white), architecture, symmetry and homogeneity. The architecture is assessed by the operator's overall impression of whether it is ordered or not. Each criterion is scored on a scale from 2 to 17. A score of 8 or more indicates melanoma with a sensitivity of 98% and a specificity of 68%.
Benign, Lonely, Irregular, Nervous, Change and Known	BLINCK	The BLINCK algorithm is a simplified method designed for PCPs. The checklist mixes macroscopic clinical and dermoscopic items. The first clinical step is to determine whether the lesion is benign in which case the process is stopped. The other steps are used to produce a score. A score of 2 or more indicates the need for referral or biopsy.
Triage Amalgamated Dermoscopy Algorithm	TADA	The TADA is designed for PCPs with little experience of dermoscopy. Its aim is not to make a diagnosis, but simply to triage between lesions for which the patient should be reassured and those for which they should be referred to a specialist or biopsied. It dispenses with the first stage of differentiation between melanocytic and non-melanocytic lesions using the 2-step algorithm. In this sense, it makes it possible to include NMSCs in the lesions to be referred or biopsied. It consists of 3 steps. The first aims to eliminate 3 types of commonly encountered benign lesions. The second looks for disorganised patterns and the third looks for clues associated with malignant lesions. The sensitivity of this algorithm for all types of cancer is 94.6% and the specificity is 72.5%.

The population of PCPs in the studies was heterogeneous: 11 studies observed a population that was 100% primary care, while two observed a mixed population. Three studies included nurses, and one included students. Seven studies observed practitioners with little experience of dermatology and dermoscopy, while the other six studies observed populations with varying levels of experience. The number of participants in the individual studies varied (range 4–293; mean 76, median 61). Three studies that observed performance in real clinical situations included only practitioners with a sufficient volume of skin cancer screening activity.

The number of studies utilizing the various dermoscopy algorithms were as follows: TADA – five; 3-point checklist – three; 7-point checklist – three; Menzies method – three; ABCD rule – two; BLINCK – one. Of these studies, one compared BLINCK, the 3-point checklist, and the Menzies method, while another compared the 7-point checklist, the ABCD rule, pattern analysis, and the Menzies method.

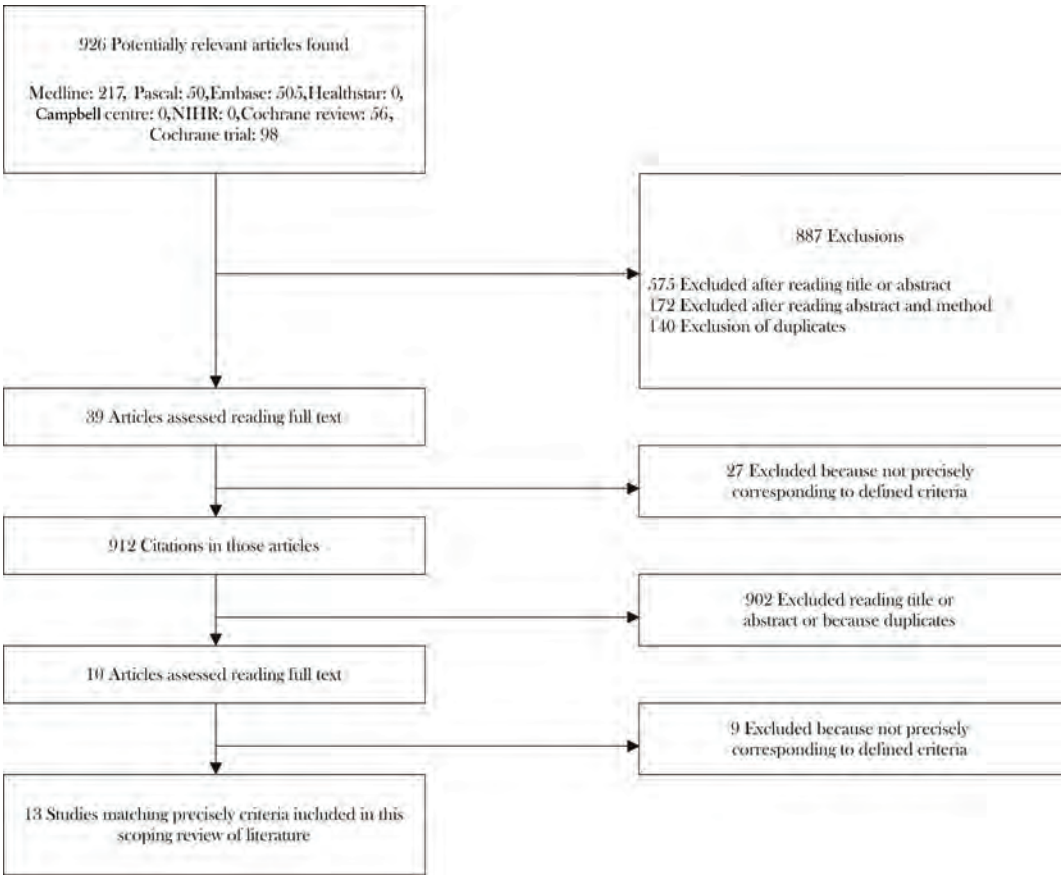


Figure 1. Flowchart of study selection.

The learning interventions varied. In nine studies, participants received face-to-face training, and in three studies they received training using various computer media, CD-ROM, web or smartphone, or books; one study did not clearly indicate the teaching method. Three studies utilized mixed types of training. The duration of face-to-face training ranged from one to 10 hours (mean three hours 40 minutes, median two hours 40 minutes). All included an introduction to dermatological oncology and dermoscopy before focusing on the chosen algorithm.

Only five studies assessed lesions in clinical practice by PCPs. Four of them assessed lesions in real-life conditions by the practitioner. A minimum of 235 and a maximum of 2,548 lesions were assessed (mean 899, median 406). The reference comparators varied, including pathology, expert opinion, teledermoscopy, or absence of evolution over time. The last study evaluated the impact of a dermoscopy diagnostic algorithm training on referral numbers. The study durations ranged from six to 17 months (mean 10.5 months, median eight months). In the other eight studies, the clinician assessed the lesions using high-resolution photographs, with clinical information in four of them. The photographs provided covered all types of skin cancer, except one study, which included only pigmented lesions, and the malignant lesions were only early-stage melanomas. The number of images analyzed ranged from 30 to 200, (mean 74, median 55).

Outcomes

Four cross-sectional studies found that PCPs without experience in dermatological oncology or dermoscopy showed significantly improved diagnostic accuracy (range 18–54%) for skin cancer screening from dermoscopic images after receiving training in skin cancer basics and TADA. The PCPs had increased sensitivity and stable or increased specificity in their diagnoses. One comparable study which, however, used the 7-point checklist, found the same outcome apart from a significant decrease in performance for benign lesions. Another similar study compared the performance of different practitioner subpopulations and showed no difference except that dermatologists had better specificity. The sensitivity and specificity values for PCPs (93.7% and 72.1%, respectively) were consistent with those reported in previous studies.

Two studies compared the effect of teaching different algorithms on diagnostic accuracy. In both studies, assessment was based on high-resolution photographs selected by experts. One study evaluated the difference between the BLINCK, 3-point checklist and Menzies method, and the purely clinical method. The use of BLINCK showed a

Table 2. Profile of Selected Studies.

Article	Type	Population	Algorithm	Intervention	Lesions	Comparison	Outcome
Seiverling et al. 2021 USA	Observation study, Cross-sectional	• 100% PCP • Low experience • 96 participants	TADA	• 120 min In-Person Generalities • 60 min Web Algorithm	• Images • No clinical information • All types of tumours • 30 images	Before vs after	• Significant increase of accuracy for benign and malignant lesions
Cyr et al. 2021 USA	Observation study, Cross-sectional	• 100% PCP • Very low experience • 32% Students • 12% Nurses • 31 participants	TADA	• 90 min in-person workshop	• Images • No clinical information • All types of tumours • 60 images	Before vs after	• Significant improvement in test results regardless of subpopulation
Sawyers et al. 2020 Canada	Observation study, Cross-sectional	• 100% PCP • 31 participants • Special interest in screening diabetes, BP, osteoporosis • No experience in dermatology	TADA	• In-Person slides short presentation	• Images • Clinical information • All types of tumours • 100 images	• Before vs after • TADA 1st step only is assessed	• Significant improvement in test results • Women did better than men • Significant increase in specificity (-33% of unnecessary excision or referrals) • Significant increase in sensibility for all malignancies
Seiverling et al. 2019 USA	Observation study, Cross-sectional	• 100% PCP • 59 participants • 8 Nurses • Special interest in dermatology • Low experience in dermoscopy	TADA	• 1h about TADA + aspect of benign lesions	• Images • No clinical information • All types of tumours • 60 images	Before vs after	• Significant improvement in test results regardless of sub-population • Significant increase in sensibility • Stability of specificity for all lesions but significant increase of specificity for 3 types of benign lesions (dermatofibroma, seborrheic keratosis, angioma)
Robinson et al. 2018 USA	RCT	• 100% PCP • Sufficient volume of patients • 89 participants	3-point checklist	• 3 sessions: 20 min, 1h, 1h • Smartphone • Nothing about NMSC	• Observed in clinical practice • Referrals assessment • 6 months	Referrals assessment 3 months before vs 3 months after	• Significant reduction of number of referrals for benign lesions for trained participants • Significant increase of number of melanoma referrals for trained participants • No effect on NMSC referrals
Secker et al. 2017 Netherlands	Observation study, Cross-sectional	• 100% PCP • Low experience • 293 participants	7-point checklist	• 1 day In-Person workshop • Book provided	• Images • Clinical information • All types of tumours • 40 images	Before vs after	• Significant increase of accuracy for all lesions except naevi after training • Significant improve of therapeutic strategy for all lesions including all malignant lesions after training except for naevi
Rogers et al. 2016 USA	Observation study, Cross-sectional	• Mixed • 34.2% PCP • 42.3% No training • 23.3% No experience • 120 participants	TADA	• 1 day in-person workshop	• Images • Clinical information • All types of tumours • 50 images	• Dermatologists vs PCP • Experienced vs non experienced	• Sensitivity 94.8% • Specificity 72.3% • No significant differences between sub-populations excepting specificity of dermatologists

Table 2 continues

Table 2. Profile of Selected Studies. *(continued)*

Article	Type	Population	Algorithm	Intervention	Lesions	Comparison	Outcome
Koelink et al. 2014 Netherlands	RCT	• 100% PCP • 53 participants	7-point checklist	• 4h general training for all • 6h extra course about dermoscopy for one arm	• Observed in clinical practice • Secondary assessment by 2 experts via teledermatology • Tertiary assessment if excision or face-to-face consultation with dermatologist needed • 400 patients 437 lesions • 17 months	Naked eye vs dermoscopy	• OR of correct diagnosis with dermoscopy compared with naked eye: 151 • Same OR for melanomas only: 552 • RR: 125 (probability of correct diagnosis is 25% higher with dermoscopy)
Bourne et al. 2012 Australia	Observation study, Cross-sectional	• 100% PCP • 4 participants only including 1 nurse • Variable experience	• BLINCK • 3-point checklist • Menzies method	• Only BLINCK is taught • Method of teaching is not known	• Images • Clinical information provided only after assessment using 3pCheck then Menzies • All types of tumours but selection of lesions • 50 images	Method vs method including naked-eye assessment	• No differences between clinicians • BLINCK showed a significant higher sensibility than other method • Menzies method and clinical assessment showed a significant higher specificity
Menzies et al. 2009 Australia	Observation study, Cross-sectional	• 100% PCP • Low experience • Sufficient volume of patients • 63 participants	Menzies method	• Textbook and CD-Rom provided • 2h in-person workshop	• Observed in clinical practice • Secondary assessment by pathology or expert or no change for benign lesions • Suspicious pigmented lesions only • 374 lesions • 8 months	• Naked eye vs dermoscopy • Naked eye vs Dermoscopy + SDDI	• Benign pigmented lesion/melanoma ratio significant decrease from 95/1 to 37/1 with dermoscopy alone and to 33/1 with dermoscopy + SDDI • Non significant improvement of sensitivity and specificity for melanoma diagnosis between naked-eye examination and dermoscopy alone • Significant improvement in confidence of diagnosis (naked eye vs dermoscopy) • Significant improvement of sensitivity with dermoscopy + SDDI Specificity unchanged • Melanoma's mean thickness is not significantly different after waiting 3 months for SDDI second picture

Grimaldi et al. 2009 Italy	Observation study, Cross-sectional	• 100% PCP • 13 participants	ABCD rule	• Web-training	• Observed in clinical practice • Secondary assessment by experts using teledermoscopy • 197 patients 235 lesions • 5 months	• Naked-eye vs dermoscopy • Naked-eye + dermoscopy vs teledermoscopy	• Significant change in OR • Clinical vs Dermoscopy 035 • Clinical vs Teledermoscopy 018 • Dermoscopy vs Teledermoscopy 052
Argenziano et al. 2006 Italy and Spain	RCT	• 100% PCP • Sufficient volume of patients • 73 participants	3-point checklist	• In-Person • 2h, clinical ABCD rule • 2h, algorithm	• Observed in clinical practice • Secondary assessment by 2 experts then excision if needed • 2522 patients 2548 lesions • 16 months	• Naked eye vs dermoscopy • PCP vs expert	• Improvement of PPV, NPV and sensitivity • Stability of specificity • Good accuracy for NMSC even if the algorithm is not designed for
Dolianitis et al. 2005 Australia	Observation study, Cross-sectional	• Mixed • 57.4% PCP • Mainly with experience • 61 participants	• 7-point checklist • ABCD Rule • Pattern Analysis • Menzies method	• CD-Rom provided	• Images • No clinical information • Pigmented lesions only • Early stage melanoma only • 200 images	Algorithm vs algorithm	• Best sensitivity and accuracy for Menzies method • Best specificity for clinical examination • Heterogeneous results depending on lesion

significant improvement in sensitivity, while the Menzies method or the pure clinical method retained the best specificity. The methodology of the intervention was poorly described. The population was small (four participants), and the photographs showed all types of lesions. The other study compared the diagnostic accuracy of the 7-point checklist, ABCD rule, pattern analysis, and Menzies method. Only 57.4% of the study population were PCPs, with varying levels of experience. Only pigmented lesions were evaluated. The cancers were all early-stage melanomas. The results were very heterogeneous, depending on the type of lesion. The Menzies method showed the best sensitivity and diagnostic accuracy. The best specificity was obtained by examining macroscopic images only.

Five studies assessed the diagnostic accuracy of PCPs in a real-life situation; two were cross-sectional studies, which evaluated dermoscopy versus naked eye examination using the Menzies method or the ABCD rule algorithms. The former study focused on suspicious pigmented lesions, showing a significant reduction in referrals for these lesions by using dermoscopy, further improved by the combined use of Sequential Digital Dermoscopic Imaging (SDDI). However, sensitivity and specificity for melanoma diagnosis were not improved. The combination with SDDI only significantly improved sensitivity for melanoma detection. The use of dermoscopy in this study also improved clinicians' diagnostic confidence. The latter study looked more broadly at diagnosis of all lesion types and showed a significant improvement in the odds ratio in favor of dermoscopy, further improved by the use of teledermoscopy. The other three studies were RCTs investigating the diagnostic skills of PCPs trained in the 3-point checklist or 7-point checklist algorithms for any type of lesion. The first one showed a significant improvement in the odds ratio in favor of a correct diagnosis with dermoscopy. This increase is particularly relevant for diagnosing melanoma. The second showed a significant improvement in sensitivity, negative predictive value, and positive predictive value, while specificity remained stable. Diagnostic accuracy for non-melanoma skin cancers (NMSCs) increased, although the 3-point checklist algorithm was not designed for this purpose. The third study focused on the number of referrals three months before and three months after training, showing a significant reduction in benign lesion referral and a significant increase in melanoma referrals for trained participants, with no effect on NMSC referrals.

Discussion

Introducing Dermoscopy in Primary Practice

There are currently too few trials of melanoma screening to be able to say with certainty that implementing a large-scale screening program in the general population would be effective [41]. However, there is a strong presumption in favor of involving health professionals in melanoma screening to promote early diagnosis and thus reduce associated mortality [42]. A study in France found that training a portion of PCPs in melanoma management significantly reduced the proportion of late diagnoses (Breslow thickness >3 mm) in their practice [43].

From our review it is clear that short training courses for PCPs on skin tumors and diagnostic dermoscopy can lead to improved diagnostic performance, earlier detection of skin cancer, and reduction in unnecessary excisions and referrals. It is therefore reasonable to recommend implementing educational measures and encourage the use of dermoscopy in primary care, especially given the ageing population, increasing skin cancer incidence, and strained healthcare systems.

Teaching Format

By studying published findings concerning the training of PCPs in dermatology, we consider that the positive results in our review are linked to the common characteristics of the teaching utilized. Indeed, it appears that short, interactive, practical dermoscopy training courses utilizing algorithms are effective in increasing awareness of dermatological oncology among PCPs. Furthermore, the available evidence suggests that the best format is interactive teaching, available online, designed by expert dermatologists in close collaboration with PCPs, and covering the practical management of the lesions observed. Other types of teaching have had more mixed results [17, 44-49].

Durability of Training Interventions

This question remains, as few studies have been conducted for longer than six months. One study suggested that refresher courses are necessary to maintain the benefits of training. However, one Dutch study showed that the effects of dermato-oncology training did not fade over nine months without any refresher training [38, 50, 51]. Nevertheless, we know that humans' ability to perform complex tasks deteriorates over time and that refresher training is one way to counteract this phenomenon [52, 53]. In the more specific field of dermoscopy in PCPs, a recent study confirms this deterioration after a short period (one year) [54]. We therefore suggest that a continuing education program, preferably in a short online format, is a reasonable option for maintaining the benefits of training, particularly for PCPs who perform dermoscopy on a regular basis.

Reproducibility in Real Life of Studies Using Images Only

It is reasonable to ask whether assessing diagnostic accuracy on photographs is a coherent approach. The recent development of teledermoscopy, although requiring further

validation, appears promising [15,55]. The good results of clinical practice studies after similar interventions also support the results of studies that have evaluated PCPs using images alone. It is known that dermoscopy supports clinical examination but does not replace it and that clinical examination has better specificity than dermoscopy [17]. All proposed interventions included a teaching component on dermatological oncology in general, with workshops including a simulation component. This mixed teaching format thus seems to be the one to replicate to maximize the chances of adapting the training to future practice.

Best Algorithm

Three algorithms, namely, the 3-point checklist, 7-point checklist, and TADA, were highlighted for teaching purposes in the 13 selected studies. These algorithms were frequently used and consistently showed positive results in improving diagnostic accuracy. The 3-point and 7-point checklists were used in trials with robust designs, while TADA was evaluated in observational studies. All three algorithms demonstrated diagnostic performance, even when used by relatively inexperienced practitioners. TADA was specifically designed for PCPs and seems well-suited for triaging suspicious skin lesions [34]. However, large-scale studies under real conditions are still needed. Our review accepted all algorithms in its inclusion criteria. We chose to highlight the 3-point checklist because in this review it was associated with studies with the highest level of evidence. In addition, we find it easy to use and teach, which is important to encourage PCPs to use dermoscopy. Furthermore, we believe that TADA occupies a special place because it is specifically designed for use by PCPs by avoiding the preliminary phase of detection of melanocytic lesions by the 2-step algorithm. Its purpose is not so much to make an accurate diagnosis but rather to triage lesions and is relevant to all types of skin cancer.

Future Role for PCPs

The adoption of dermoscopy by PCPs and their role in managing skin cancer is still limited. As most of the studies in this review focused on physicians with an interest in dermatology, the results may not be fully representative of the wider community. In Australia, where skin cancer is a major public health concern [56], dermatology has a special GPwSI (General Practitioner with a Special Interest) status, with PCPs who have an interest in skin cancer taking the lead in skin cancer screening locally and acting as a link between primary and secondary care [57].

This status also exists in the UK with the GPwER (General Practitioner with an Extended Role) [58]. However, even among such motivated practitioners, there may be barriers to accessing training [51]. Surveys show that dermoscopy use among PCPs without a specific interest in dermatology varies worldwide but is generally limited [59-60]. It therefore seems that, although the assessment of suspicious lesions by PCPs using clinical and dermoscopic tools has proved its worth, there is still a long way to go before this practice becomes widespread. Factors influencing dermoscopy use by PCPs were identified in a recent qualitative study conducted in the UK, which showed that easy access to training and support in teaching dermoscopy build confidence in PCPs and may be the main game changer [61]. However, the cost of purchasing a dermoscope can be a barrier [38]. This suggests that a small group of motivated PCPs should be trained and provided with the necessary tools, while maintaining a link with continuing education and expert support. On the other hand, despite its clear potential, the role of PCPs in diagnosing cutaneous tumors has limitations compared to experts [34-36], and it is important to define the boundaries and framework for their practice. Furthermore, it would appear logical that PCPs involved in skin cancer screening should be able to communicate directly with experts for advice when necessary.

Scope for Future Research

Research on the triage of skin lesions by PCPs to address the skin cancer burden is incomplete. Future research required includes evaluating the TADA algorithm under real clinical conditions, exploring the role of nurses and other non-physician healthcare professionals in triage, assessing the cost-effectiveness of SDDI devices, investigating alternative training methods for PCPs, and considering the organization of PCPs with extended roles. Qualitative studies on the impact of these changes on workload and patient care are also needed. Furthermore, the role of teledermoscopy, which has recently developed with the advance of computer systems, can be considered. The benefits of this practice on the diagnostic accuracy of online consultations have been demonstrated, although standardization efforts will be needed in the future to limit the heterogeneity of practice. When used by a trained PCP, teledermoscopy can introduce a second level of triage to minimize unnecessary face-to-face consultations [15,55,62]. Finally, the use of artificial intelligence algorithms to triage suspicious lesions is even more recent and has shown promising results in the diagnosis of skin cancer. AI can assist in tasks that involve comparing patterns over time. However, at its current stage of development, AI cannot completely replace the clinician's diagnostic approach [63-66].

Strengths and Limitations

This study was based on a well-designed methodology to minimize bias. The principal investigator's perspective as a PCP adds relevance to the qualitative analysis. The study includes a sufficient amount of diverse material to meet the objectives and provide recommendations for professional

practice. However, we acknowledge several limitations, including the inability to use cross-methods due to a single investigator. Furthermore, the choice of search algorithm and language limitations could have introduced selection bias. The decision to focus on the last 20 years, made to highlight recent teaching techniques and modern technology, led to the exclusion of one study even if this did not contradict the review's conclusions. Furthermore, the relative heterogeneity of the populations of PCPs in our review may suggest an additional weakness; however, as dermoscopy is rarely taught to PCPs and primary care trainees, it is reasonable to assume that all participants in fact started from the same low level of dermoscopy expertise prior to training [67-70].

Conclusions

The increasing incidence of skin cancer and the shortage of doctors have led to a need for PCPs to participate in skin cancer screening using dermoscopy. However, there are barriers to doing so, including limited access to training and equipment. One proposed solution is a coordinated practice model where PCPs with an interest in dermatology take the lead at a practice and/or territory level. Additionally, nurses and other non-physician healthcare professionals could also be involved in carrying out screening. Teledermoscopy and AI lesion analysis techniques could be further options. Research is needed to establish coherent models with clearly defined roles and effective communication between different levels of care providers.

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Dermatology Practical & Conceptual

Psoriasis and Alopecia: Unveiling the Links

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Key message: Psoriasis and alopecia are related through several pathways, which can be classified as follows: psoriatic alopecia; drug-induced alopecia, especially from TNF-α inhibitors; concomitant psoriasis and alopecia areata.

Key words: Psoriasis, Alopecia, Alopecia areata, Lichen planopilaris, Hair loss

Citation: Pourani MR, Khajeamiri Y, Abdollahimajd F, Zargari O. Psoriasis and Alopecia: Unveiling the Links. *Dermatol Pract Concept.* 2025;15(4):5283. DOI: https://doi.org/10.5826/dpc.1504a5283

Accepted: March 18, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Psoriasis is a chronic inflammatory disease that may lead to scalp involvement, with a significant impact on patients' quality of life. Although most patients with scalp psoriasis do not experience alopecia, alopecia in the context of psoriasis is a multifaceted issue on which studies are limited.

Objectives: The purpose of this review was to investigate different types of alopecia in psoriasis and the potential mechanisms.

Methods: A thorough literature review was performed, focusing on the relationship between psoriasis and alopecia areata (AA), drug-induced alopecia, and psoriatic alopecia.

Results: Psoriasis and alopecia are related through several pathways. Regarding psoriatic alopecia, in most cases of psoriasis patients with scalp involvement, hair loss is attributed to telogen effluvium. In late-stage lesions, destruction of the hair follicle, perifollicular fibrosis, and free bare hair shafts in the dermis are revealed. However, hair loss in psoriasis is almost always non-scarring and reversible. In drug-induced alopecia, both conventional systemic treatments and biologics may cause hair loss in psoriatic patients. Specific side effects have been reported with TNF-α inhibitors and IL-17 blockers. TNF-α inhibitors may cause several types of alopecia: i) TNF-α inhibitor-associated psoriatic

alopecia, ii) TNF-α inhibitor-associated AA, and iii) TNF-α inhibitor-associated lichen planopilaris. In concomitant psoriasis and alopecia areata, there is strong and convincing evidence that patients with psoriasis are at increased risk of developing AA, suggesting a complex interplay of autoimmune mechanisms.

Conclusion: Understanding the types and causes of alopecia in patients with psoriasis is crucial to proper management, thus highlighting the need for more research.

Introduction

Psoriasis is one of the most common inflammatory cutaneous diseases, affecting around 2% of the population. Scalp is a common site of involvement in psoriasis, with a frequency of 50–80%. Classic scalp psoriasis typically presents as well-defined erythematous lesions which are covered with silvery scales; in severe cases, the entire of the scalp may be involved [1, 2].

While the majority of patients with scalp psoriasis do not experience alopecia, hair loss is one of their main concerns and can occur due to different causes. The relationship between psoriasis and alopecia has not been fully investigated. Alopecia may be related to the psoriasis itself, the treatment modalities, or to related autoimmune conditions. In this review, we aimed to investigate the association between psoriasis and alopecia and to discuss the possible causes of hair loss in patients with psoriasis.

Psoriasis and alopecia are related in different ways, which can be classified as: i) psoriatic alopecia; ii) drug-induced alopecia; iii) concomitant psoriasis and AA.

Psoriatic Alopecia

The true frequency of hair loss directly related to psoriasis is unknown and appears to be uncommon [3]. Alopecia and other hair abnormalities in patients with psoriasis were first reported about 50 years ago; however, psoriatic alopecia is still a little-known condition [3, 4]. In psoriasis patients with scalp involvement, hair loss is a common complaint, but telogen effluvium is believed to be the cause in most cases due to the inflammatory process and trauma from scratching itchy lesions [4, 5]. Histological findings of psoriatic alopecia have shown features of psoriasis in the interfollicular epithelium, with perifollicular inflammation and atrophy or loss of sebaceous glands [3, 5, 6]. Also, in late-stage lesions, destruction of the hair follicle, perifollicular fibrosis, and free bare hair shafts in the dermis are revealed [7, 8] (Figure 1).

The main cause of hair loss in psoriasis is telogen effluvium (TE), which can be both localized or generalized. The localized telogen effluvium is more common in psoriasis. In fact, in involved areas of the scalp, there is a higher proportion of telogen and catagen hairs, which is responsible for a localized telogen effluvium in some patients [6]. Also, generalized TE is a well-known consequence of severe forms of psoriasis, including erythrodermic psoriasis and generalized pustular psoriasis [6]. As mentioned, hair loss in psoriasis is almost always non-scarring and reversible. However, there are several reports of scarring alopecia in psoriatic patients such as the first case of "destructive alopecia" described by Shuster in 1972 [9].

One of the largest case series of alopecia among psoriatic patients was reported by Runne and Kroneisen-Wiersma in 1992. They described 47 patients with acute and chronic hair loss in patients with scalp psoriasis, in which five patients had clinical and histopathological features of scarring alopecia [5]. The severity and duration of scalp involvement in psoriasis is correlated with the risk of scarring alopecia [10]. Remarkably, familial cases of scarring alopecia in psoriatic patients have also been reported [11].

Drug-Induced Alopecia

Both conventional and biological therapies may lead to hair loss in psoriatic patients. Hair loss is a well-known adverse effect of some drugs, including methotrexate and systemic retinoids. Over the past decades, biologics have revolutionized the treatments of psoriasis. Although hair loss due to biologics seems to be less common in comparison with conventional treatments, it is not very rare. Indeed, alopecia secondary to biologics has been reported with both TNF-α antagonists and IL-17 blockers [12, 13]. TNF-α inhibitor may cause different types of alopecia: i) TNF-α inhibitor-associated psoriatic alopecia (TiAPA), ii) TNF-α inhibitor-associated AA (TiAAA), and iii) TNF-α inhibitor-associated LP (TiALP).

TNF-α Inhibitor-Associated Psoriatic Alopecia (TiAPA)

The overall success rate of TNF-α inhibitors (TNFi) in many individuals is remarkable, but some side effects such as increased risk of infection and paradoxical induction of psoriasiform skin lesions have been increasingly reported over the past few years [14]. TiAPA has been reported in several studies. In a review done by Baniel et al., they described six new cases of scarring alopecia following treatment with

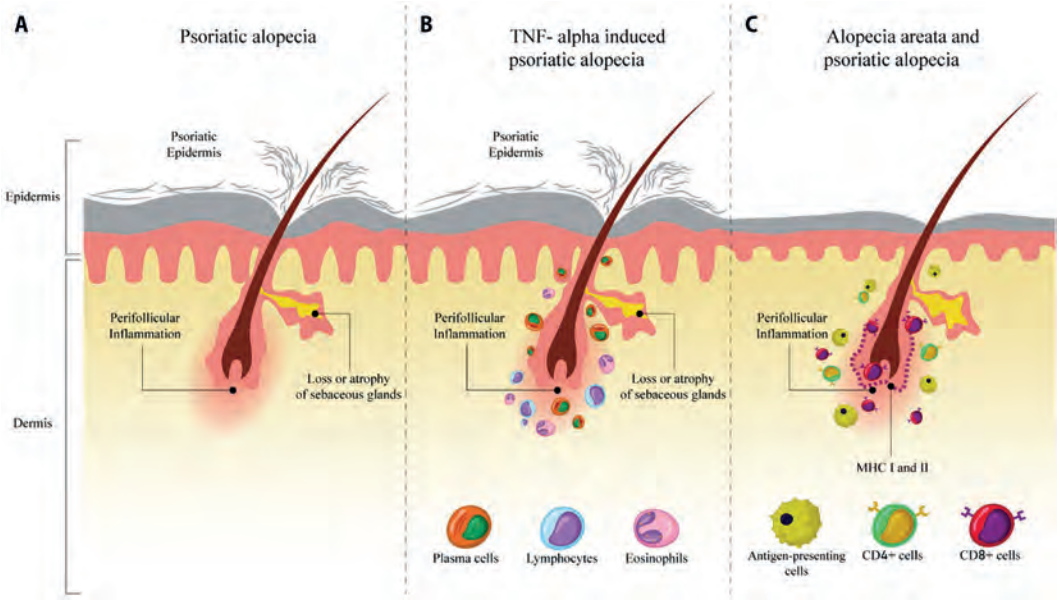


Figure 1. (A) Psoriatic alopecia. Histological findings are features of psoriasis in the interfollicular epithelium, with perifollicular inflammation and atrophy or loss of sebaceous glands. (B) Psoriatic alopecia induced by TNF-α inhibitors, atrophy of sebaceous lobules, and a brisk superficial and deep perifollicular infiltrate consisting of peribulbar lymphocytes, prominent plasma cells, and variable eosinophils; (C) Alopecia areata and psoriatic alopecia, perifollicular infiltrations of APCs, CD4+ and CD8+ T cells. APCs, antigen-presenting cells.

TNF-α blockers [15]. The authors suggest a prompt histological evaluation of alopecia in psoriatic patients and discontinuing the TNFi therapy in the presence of scarring [15]. The proposed clinical diagnostic criteria for TiAPA include recent initiation of TNFi therapy, no previous history of psoriasis, flare-up of psoriasis after initiation of TNFi therapy, alopecic plaques on the scalp, and erythematous, scaly plaques with or without pustular lesions on the scalp and other parts of the body [16, 17].

Histologically, psoriatic alopecia induced by TNF-α inhibitors has two distinctive features: atrophy of sebaceous lobules, which is a potentially reversible characteristic and conspicuous feature of TiAPA, and a brisk superficial and deep perifollicular infiltrate consisting of peribulbar lymphocytes, prominent plasma cells, and variable eosinophils [12] (Figure 1).

Although there is no guideline for the treatment of TiAPA, most cases sufficiently respond to topical steroids [16]. In general, several therapeutic options, including discontinuation of TNFi therapy, switching to a different TNFi, and medication dose adjustment, can be considered depending on the disease severity, underlying disease, and risk-benefit ratio of therapy modification [16-18].

TNF-α Inhibitor-Associated AA (TiAAA)

Alopecia areata (AA) is a non-scarring pattern of hair loss with well-circumscribed patchy areas that frequently appear on the scalp. Although AA can occur as a coincidence in patients receiving TNF-α inhibitors, it seems that there is a causal effect in at least some patients [19, 20]. The exact incidence of AA during anti-TNF-α therapy is unknown because there are no prospective controlled studies. Furthermore, the exact diagnosis of the cause of AA is debatable because AA may occur as an autoimmune manifestation in predisposed patients with chronic inflammation or as a side effect of TNF-α inhibitors. The cases of AA following treatment with TNF-α inhibitors has been reported with all of the TNF-α blockers. In a recent systematic review, the most common etiology of drug-induced AA was TNF-α inhibitors (47%), including adalimumab (18.6%), infliximab (14.7%), etanercept (11.7%), and golimumab (1.9%) [21]. The possible mechanism of TiAAA is that by increasing plasmacytoid dendritic cell production of interferon-α, the expression of the ligands CXCL9, CXCL10, and CXCL11 leading to AA will increase [18-20].

In a multicenter study, of the 29 cases with AA, 11, 11, and seven patients had psoriasis, inflammatory rheumatism, and inflammatory bowel disease, respectively. Moreover, the most common clinical presentation of cases was patchy AA affecting the scalp or beard (79% of patients). In addition to AA, vitiligo, psoriasiform eruptions, or Hashimoto's thyroiditis were observed in 24% of patients [19]. Clinical presentations of alopecia areata during anti-TNF-α therapy can vary widely, from mild limited patches to diffuse alopecia areata. Meanwhile, the onset of AA can range from one to 42 months after the initiation of TNF-α inhibitors [22].

To date, no valid clinical trial has been conducted to investigate the optimal treatment options for alopecia areata

occurring during anti-TNF-α therapy. Most patients achieved complete hair regrowth after discontinuing anti-TNF-α therapy, while some patients continued on TNF-α inhibitor therapy and still experienced some hair regrowth [19]. There are currently no accepted guidelines that indicate whether a TNF-α inhibitor should be discontinued or not in these patients, and this should be evaluated on a case-by-case basis.

TNF-α Inhibitor-Associated LP (TiALP)

Lichenoid drug reactions are a well-established adverse reaction to TNF-α inhibitors, while the reported cases of TNF-α inhibitor-induced lichen planopilaris are rare [23]. One of the first case of lichen planopilaris (LPP) secondary to anti-TNF-α therapy was reported by Garcovich in 2008 [24]. Moreover, Asarch et al. presented two cases of LP-like eruptions after infliximab and adalimumab therapy for psoriasis [23]. Since then, several similar cases with different TNF-α blockers have been reported. Some studies suggest that TNF-α inhibitors can stimulate a wide range of inflammatory diseases, including cutaneous and mucosal LP. The exact mechanism for the induction of inflammatory skin disease such as LPP during TNF-α inhibitor therapy is unknown. IFN-α increases following inhibition of TNF-α, leading to the activation of T cells and dendritic cells. It is suggested that dendritic cells, T cells, and other related factors such as T-cell mediated pathways and inflammatory cytokines, including IFN-α, play a crucial role in the occurrence of LP [25].

The onset of lichenoid reactions can vary, from a few weeks to months after the start of the responsible agent, although most cases are reported in the first two months of treatment [23]. The decision on discontinuation of TNF-α blocking agents depends on the condition of the patient.

Concomitant Psoriasis and AA

Several studies have shown that there is a greater risk of developing a variety of autoimmune diseases in psoriatic patients [26, 27]. Considering psoriasis as an autoimmune disease, several biochemical pathways may overlap with altered pathways associated with other autoimmune diseases such as Crohn's disease, type 1 diabetes, and rheumatoid arthritis [27]. The frequency of immune-related conditions is higher among patients with psoriasis than in the general population, and many inflammatory autoimmune diseases are the result of a disruption of multiple cytokine pathways [27]. Moreover, psoriasis may be associated with other immune-related conditions such as systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease, including Crohn's disease, celiac disease, autoimmune thyroid disease, vitiligo, Sjögren's syndrome, and alopecia areata [28,29]. There is strong and convincing evidence that patients with psoriasis have a higher risk of developing AA [30]. However, as mentioned above, many reports of AA were in psoriatic patients undergoing systemic treatments [19]. In a retrospective study by Wu, patients with psoriasis were at a 2.5 times higher risk of developing alopecia areata [26]. In a recent meta-analysis, the pooled prevalence and odds ratio of alopecia areata among psoriatic patients were 0.5% and 2.71, respectively. Furthermore, the pooled prevalence and odds ratio of psoriasis among patients with alopecia areata were 2.5% and 3.52, respectively [31]. Interestingly, there is a bidirectional association between psoriasis and alopecia areata [31]. Furthermore, the prevalence of psoriasis incidents in AA patients was 1.8%, with an odds ratio (OR) of 1.79 [32]. Additionally, the association between psoriasis and AA was significantly increased, with OR 2.4; however, psoriatic arthritis was not associated with AA [26].

In addition, an interesting case of the Renbök phenomenon or inverse Köbner phenomenon was reported in a female with a history of long-lasting AA who presented with new psoriasis lesions. In AA areas with psoriasis, complete regrowth of hairs was observed [33]. Furthermore, another case of the Renbök phenomenon was reported in a female with presentation of both AA and psoriasis, with a regression of psoriatic scalp lesion following the appearance of AA lesion in the same area. Also, normal regrowth of hairs was noticed in an alopecic area with new lesions of psoriasis [34].

The complex cytokine milieu plays an important role in the flare-up of psoriasis and AA. The correlation between these two diseases is plausible as psoriasis is related to a class of factors such as Th17 and Th1 pathway cytokines, including interferon-λ, interleukin (IL)-12, and IL-2, which are also important in the pathogenesis of AA [35, 36] (Figure 1). Furthermore, AA worsening after successful treatment of psoriasis in patients with concomitant AA has been reported [37].

Thus, treatment regimens for these patients are complex as they involve preventing the worsening of one inflammatory condition while treating another [38]. In addition, according to the findings of a nationwide population-based study conducted by Chu et al., the age at onset of AA provides clues for the diagnosis of specific autoimmune diseases and can be used for timely diagnosis and treatment [37].

Conclusion

Hair loss in psoriatic patients can be related to various causes. Most patients with psoriatic alopecia experience complete regrowth of scalp hair after successful treatment, although there are a few reports of scarring alopecia secondary to psoriasis. TNF-α inhibitors can induce psoriatic alopecia (TiAPA), alopecia areata (TiAAA), and lichen planopilaris (TiALP). All dermatologists should know the possible complications following the administration of TNF inhibitors. Understanding the type and cause of alopecia in patients with psoriasis is essential to the proper management

of this condition. Given the limited information in this area, more studies are needed to understand the association between psoriasis and alopecia.

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Dermatology Practical & Conceptual

Skin-Immune-Neuro-Gastro-Endocrine (SINGE) System: Lighting the Fire on Atopic Dermatitis Research

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Key words: Atopic dermatitis, Neuroimmunology, Gut-skin axis, Itch-scratch cycle, Neuroendocrine microbiome

Citation: Paz M, Lio P. Skin-Immune-Neuro-Gastro-Endocrine (SINGE) System: Lighting the Fire on Atopic Dermatitis Research. *Dermatol Pract Concept*. 2025;15(4):5329. DOI: https://doi.org/10.5826/dpc.1504a5329

Accepted: April 1, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: Dr. Peter Lio reports research grants/funding from AbbVie, AOBiome, and Regeneron/Sanofi, Genzyme, is on the speaker's bureau for AbbVie, Eli Lilly, Galderma, Hyphens, Incyte, LEO Pharma, L'Oreal, MyOR Diagnostics, ParentMD, Pfizer, and Regeneron/Sanofi Genzyme, and reports consulting/advisory boards for AbbVie, Almirall, Amyris, AOBiome, Arbonne, ASLAN Pharmaceuticals, Burt's Bees, Castle Biosciences, Codex Labs, Concerto Biosciences (stock options), Dermavant, Eli Lilly, Exeltis, Galderma, IntraDerm, Johnson & Johnson, LEO Pharma, L'Oreal, Menlo Therapeutics, Micreos, Pfizer, Pierre-Fabre, Regeneron/Sanofi Genzyme, Theraplex, and Unilever. In addition, Dr. Lio has a patent pending for a Theraplex product with royalties paid and is a Board member and Scientific Advisory Committee Member of the National Eczema Association. Meshi Paz reports no conflicts of interest.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by pruritic, dry, eczematous lesions. Traditionally regarded primarily as a cutaneous disorder influenced by genetic and environmental factors, AD is increasingly recognized as a multisystem condition involving immune, microbial, and neuroendocrine interactions.

Objectives: This review proposes the Skin-Immune-Neuro-Gastro-Endocrine (SINGE) network as a comprehensive framework to explore the interconnected pathophysiology of AD. The aim is to highlight how changes across various systems contribute to disease development, presentation, and treatment.

Methods: A comprehensive review of current literature was performed, examining the roles of skin barrier dysfunction, immune signaling, neuroendocrine pathways, and gut microbial dysbiosis. These domains were integrated into a unified model that describes bidirectional interactions and their clinical implications.

Results: The SINGE model reveals that epidermal barrier disruption activates a cascade of immune responses. Microbial dysbiosis, in concert with the gut-skin axis, further exacerbates AD symptoms, highlighting how alterations in one organ affect the other. Neuroinflammation further contributes

to AD symptoms by perpetuating the itch-scratch cycle. Neuroendocrine factors amplify the inflammatory dysregulation, particularly through endocrine involvement involving cortisol signaling in the hypothalamic-pituitary-adrenal (HPA) axis and the paradoxical inflammatory effects on the skin barrier. Together, these intertwined pathways perpetuate the chronic inflammation and skin barrier dysfunction in AD.

Conclusion: By examining these elements as an intricate, intertwined system, the SINGE network reframes AD as a multisystem condition. This apprach not only shifts the understanding of the disease, but also serves as a foundation for exploration of targeted therapies.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that presents as pruritic, dry, eczematous skin that is prevalent among 10%–30% of children and 2%-10% of adults [1,2][1]. The etiology of AD is complex, involving a combination of environmental triggers and a genetic predisposition [2]. The most notable genetic mutation has been seen involving filaggrin (*FLG*), which encodes an epidermal protein that maintains skin integrity and moisture [2]. The characteristic skin barrier dysfunction and immune dysregulation seen in AD often accompanies other IgE-associated diseases like asthma and allergic rhinitis, together known as the atopic triad [1,3,4]. Recognizing this heterogeneity is crucial to advancing precision medicine approaches in AD. The psychosocial comorbidities associated with this disease and the increased risk of multisystem involvement emphasizes the extent and burden of AD. [5].

The multisystem impact of AD is intricately linked to both the neuro-immuno-cutaneous-endocrine (NICE) network and the gut-skin axis, offering insight into the complex pathophysiology of the disease. Neuropeptides like calcitonin gene-related peptide (CGRP), substance P, and vasoactive intestinal peptide (VIP) promote inflammation via cutaneous nerves. Neuroendocrine mediators, including glucocorticoids, are produced in response to stress and activate the hypothalamic-pituitary-adrenal (HPA) axis and subsequent hormonal cascades [6]. Furthermore, overactivation of the Th2 immune response increases levels of IL-4 and IL-13 during disease flares (Figure 1) [7].

Additionally, gut dysbiosis, increased intestinal permeability, and changes in microbial metabolic byproducts exacerbate systemic inflammation, intensifying the hallmark itch-scratch cycle through neural and immune systems [8]. Collectively, these interconnected systems contribute to the multifaceted nature of AD pathology [9].

In addition to its systemic impact, AD is a highly heterogeneous disease, exhibiting variability in clinical presentation, pathophysiology, and treatment response. While inflammation in AD is primarily driven by the Th2 mechanism, recent studies have found Th1, Th17, and Th22 pathways implicated in some populations as well [10,11]. Moreover, the classification of intrinsic and extrinsic AD phenotypes further highlights the disease variability, with the two phenotypes differing in their IgE levels, epidermal barrier dysfunction, and immune activation pathophysiology [11,12]. Appreciating the heterogeneity of AD is essential to advancing individualized and comprehensive treatment approaches.

Objective

This paper proposes the Skin-Immune-Neuro-Gastro-Endocrine (SINGE) network as a framework to investigate the multisystem contributions of AD. By encapsulating the intricate connections between the systems, this study aimed to explore biomarkers and pathways involved in the disease pathogenesis in hopes of laying the foundation for future targeted treatments and ultimately enhancing patient care (Figure 2).

SINGE versus NICE systems

While the two systems have great overlap, they propose distinct approaches to understanding cutaneous disorders. The NICE network primarily highlights the bidirectional crosstalk between the skin, immune system, nervous system, and endocrine pathways. It emphasizes how stress-induced neuroendocrine signaling exacerbates immune-mediated cutaneous inflammation. Although the NICE system takes stress responses into account, it does not explicitly integrate the crucial role of the gastrointestinal (GI) system, which has emerged as a key contributor to systemic immune and inflammatory pathways.

The SINGE network builds upon the NICE framework by integrating the GI contributions to systemic inflammation and immune responses in AD. This addition accounts for the roles of the gut microbiome and the epithelial barrier dysfunction, both skin and intestinal, that contribute neuroendocrine signaling and immune responses [27,28]. As such, the SINGE system lays the foundation for a more comprehensive framework for understanding AD.

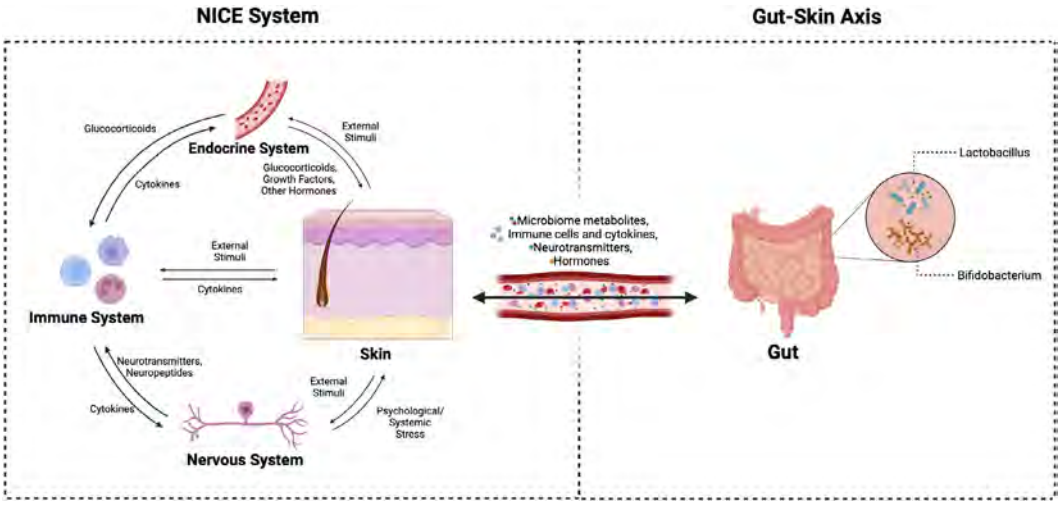


Figure 1. The NICE System and Gut-Skin Axis. The NICE system (left) illustrates the multisystem crosstalk affecting skin health. The gut-skin axis (right) depicts the bidirectional communication between the two organs, suggesting that the dysfunction of one organ can influence the other. Expanding on these concepts, the SINGE network synthesizes both frameworks to provide a more comprehensive understanding of AD pathogenesis.

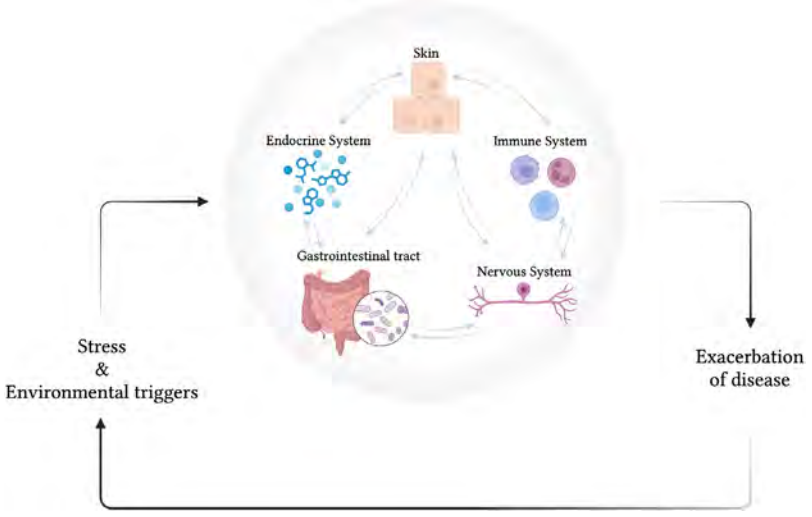


Figure 2. The Skin-Immune-Neuro-Gastro-Endocrine (SINGE) Network in atopic dermatitis (AD). The SINGE network illustrates the multisystem interactions involved in AD. Each system, interconnected by bidirectional communication, contributes to the cycle of disease progression in response to internal and external triggers.

Immune Involvement in AD

The epithelia serve as the first line of defense in the immune system through their physical barrier function. Keratinocytes in the epidermis play a key role in maintaining barrier integrity through tight junctions and FLG production [10]. Additionally, these cells engage the immune system by generating cytokines, signaling through major histocompatibility complex (MHC) class I and II proteins and producing antimicrobial peptides like cathelicidins and defensins. Toll-like receptors (TLRs) on keratinocytes interact with pathogen-associated molecular patterns (PAMPs) to detect harmful microbes, facilitating immune surveillance and maintaining a healthy skin microbiome [10,11]. Other cells, such as Langerhans cells and dendritic cells, recognize and present antigens to lymphocytes. T and B lymphocytes, macrophages, mast cells, and eosinophils also function in the skin to amplify the immune response [11,12]. Collectively known as the skin-associated lymphoid tissue (SALT), this network of cells bridges the innate and adaptive immune responses [11].

In AD, skin barrier dysfunction lays the foundation for disease progression. The epithelial barrier hypothesis suggests that initial disturbances, whether from *FLG* dysfunction or external triggers, allow allergens and pathogens to penetrate the skin surface, leading to chronic inflammation due to an overactive Th2 pathway seen in AD [13,14]. This

inflammatory response results in increased activity of cytokines like IL-4, IL-5, and IL-13, which further impair the skin barrier by inducing keratinocyte apoptosis and disrupting essential barrier proteins [1,12,14]. The resulting transepidermal water loss and susceptibility to pathogen infiltration exacerbates AD symptoms like dry skin and pruritus [14,15] (Figure 3).

While the acute phase of AD is mediated by Th2 overactivity, the chronic state of this disease demonstrates a shift to more Th1/Th22 signaling [1,15]. Th1 engagement leads to increased circulating proinflammatory cytokines like IL-1, while Th22 excitement stimulates skin remodeling and thickening. Together, this chronic immune activation causes epidermal thickening and hyperplasia [1,16].

Central to the manifestations of chronic AD is the itch-scratch cycle, where immune-mediated inflammation induces pruritus, leading to scratching that worsens skin barrier integrity and exacerbates AD symptoms [17]. The immune response communicates with cutaneous nerves through cytokines like IL-4, IL-13, and IL-31 [18,19]. IL-31, in particular, is known as the "itch cytokine" for its pivotal role in enhancing the sensitivity of these nerves, intensifying chronic itch sensation through neuroimmune pathways [8,19] (Figure 4).

The disrupted skin barrier in AD also predisposes to microbial colonization, notably *Staphylococcus aureus*, which worsens the disease severity and leads to a microbial dysbiosis. This imbalance heightens the Th2 immune response and increases the risk of infection, underscoring the intricate relationship between microbial colonization and immune dysregulation in AD [20,21].

Neuro/Nervous Involvement in AD

Neuroinflammation further facilitates AD pathogenesis by exacerbating both disease severity and symptom progression. As previously noted, immune mediators stimulate cutaneous sensory nerves, intensifying the itch-scratch cycle [8,22,23]. Individuals with AD have alterations of these nerves, including differences in density, abnormal morphology, and electrophysiologic properties, which may strengthen signaling to the brain and prompt a scratching response [8,24,25].

Neuropeptides play a crucial role in neurogenic inflammation. In response to a trigger, these vasoactive peptides attract inflammatory mediators like mast cells [26]. Neuropeptides also stimulate keratinocyte proliferation, leading to and epidermal thickening, which are key aspects of eczematous lesions [23].

Substance P (SP), markedly overexpressed in those with AD, drives itch perception by provoking mast cell degranulation [23,26]. Interestingly, SP is also produced by keratinocytes, suggesting its utility as a potential target for future therapies [23]. By activating immune responses and maintaining bidirectional interactions with the skin, SP serves as a critical connector between various systems.

Another significant pro-inflammatory neuropeptide involved in AD pathogenesis is calcitonin gene-related peptide (CGRP). Elevated in response to AD exacerbations, CGRP affects both central pruritus and peripheral neuroinflammation [8]. It activates immune responses by activating dendritic cells and Th2 cells as well as inducing epidermal changes through keratinocyte proliferation [8,17]. Further, pathogens like *S. aureus* directly stimulate local CGRP release, thus impairing bacterial clearance by modulating the immune response [17].

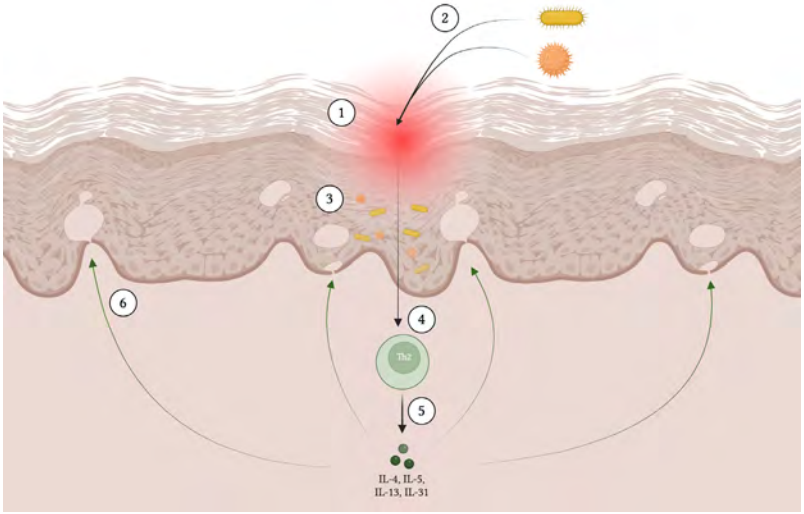


Figure 3. Pathophysiology of atopic dermatitis (AD). In AD, the skin barrier dysfunction (1) allows allergens, irritants, and pathogens (2) to penetrate into the skin (3), activating an exaggerated Th2 immune response (4). The subsequent cytokine release, including IL-4, IL-5, IL-13, and IL-31 (5), further weakens the skin barrier integrity, leading to water loss and worsening symptoms (6).



Figure 4. The itch-scratch cycle. The itch-scratch cycle perpetuates skin damage and inflammation, driving the pruritus seen in atopic dermatitis. The itch sensation triggers a scratching response, which worsens inflammation and epidermal barrier damage, further fueling the cycle.

Gastrointestinal Involvement in AD

The gut-skin axis further highlights the multisystem reach of AD, with gut microbiota serving a crucial role in the cross-talk between these organs. Similar to the skin microbiome, the gastrointestinal tract houses a multitude of microorganisms and thus contributes to the development of the immune system [27]. When disrupted, the gut microbiome demonstrates a reduced microbial diversity, a decrease in beneficial bacteria like *Bifidobacterium* and *Lactobacillus*, and an increase in harmful species like *Clostridium difficile* and *Escherichia coli*. These changes contribute to increased gut permeability, allowing inflammatory agents to enter the systemic circulation and exacerbate skin inflammation [27,28].

Microbial metabolites play a central role in the gut-skin axis, influencing immune responses, neuroendocrine-induced inflammation, and skin barrier integrity [27]. Short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate alter the circulating levels of neuroendocrine and immunological mediators [28,29]. For example, butyrate promotes T cell function and enhances epithelial barrier integrity, altogether mitigating inflammation [27]. Microbial dysbiosis, on the other hand, can activate immune responses through dysbiosis-associated metabolites including lipopolysaccharides, which trigger pro-inflammatory cytokines and exacerbate AD [30]. Gut dysbiosis is also linked to altered neuroendocrine signaling by modulating serotonin and GABA levels, which both further regulate AD symptoms. The gut-skin connection offers potential as a therapeutic target by leveraging the microbiotic and metabolic contributions. Diet modifications, probiotics, and postbiotics are being explored for their ability to reduce AD burden on affected individuals [28].

Given the extensive contributions by the gut-skin axis, it is imperative to incorporate the GI system into understanding dermatological diseases, especially systemic conditions like AD. Thus, the addition of this organ system into the SINGE framework strengthens knowledge of the disease.

Endocrine Involvement in AD

The endocrine system contributes to the pathophysiology of AD, primarily through the hypothalamic-pituitary-adrenal (HPA) axis. In response to stress, this axis activates a cascade of hormonal responses involving corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), leading to increased cortisol production. While it is an essential anti-inflammatory hormone, in AD, cortisol paradoxically contributes to the characteristic inflammation by impairing keratinocyte proliferation and barrier integrity due to dysfunctional signaling within the epidermis [30,31].

Additionally, the skin has developed a local HPA axis, which functions similarly to the central system. By producing CRH, ACTH, and cortisol independently, this peripheral axis enables a rapid response to stress, crucial for the skin's role in defense against external stressors [32].

In the context of AD, the regulatory function of both the central and local HPA axis is disrupted, exacerbating the vicious cycle of the disease. Chronic stress from physical discomfort, psychological challenges, and environmental triggers further impairs the HPA axis function [33-35]. This leads to dysfunctional cortisol signaling, which fails to suppress systemic inflammation and contributes to the barrier disruption [32,36]. The resulting compromised barrier perpetuates the underlying AD pathophysiology, underscoring the complexity of this disease.

Conclusion

The pathophysiology of AD reveals its multifactorial nature and is best understood through the SINGE network, which includes elements such as skin barrier dysfunction, immune dysregulation, neuropeptide involvement, gut microbiota contributions, and the endocrine stress axes. While each component uniquely contributes to the disease, examining them as a whole highlights their interdependent and synergistic impact, providing a more comprehensive understanding of AD and informing therapeutic targets.

Current therapies for AD typically target individual elements of the SINGE network. Preventative measures include trigger avoidance, moisturizer use, and gentle bathing [2,37,38]. Other common treatments include topical corticosteroids, phosphodiesterase inhibitors, and calcineurin inhibitors for flares as well as ultraviolet phototherapy and systemic immunomodulators for severe presentations [2,38]. Systemic treatment for AD includes biologic agents such as dupilumab, which inhibits both IL-4 and IL-13, and tralokinumab, which targets IL-13. Oral Janus kinase (JAK) inhibitors have also recently been approved for treatment of AD. Although these therapies significantly improve symptoms, their variable response rates and potential immune-related risks, including susceptibility to infections, present challenges for both patients and clinicians [39,40].

Given the multifactorial nature of AD, a more integrative approach to treatment should be explored to comprehensively address the disease. Emerging treatments offer promising therapeutic approaches by leveraging the interconnected SINGE network components. For instance, research on gut microbiome modulation with probiotics, postbiotics, and dietary interventions has suggested potential in such agents at restoring immune balance and enhancing barrier integrity in AD [28,40]. Additionally, agents targeting neuropeptides, such as SP and CGRP antagonists, are being explored as possible approaches to inhibit itch and neurogenic inflammation [40-42]. Given the role of the HPA axis in AD exacerbations, treatment aimed at modulating the dysregulated endogenous cortisol production rather than simply supplementing with exogenous corticosteroids may help address stress-induced flares [31,32]. Along a similar logic, psychosocial therapies could also mitigate the disease burden alongside medical treatment [33,35]. Considering the heterogeneity of AD, with diverse clinical presentations and immune profiles, future research should explore targeted, individualized therapies that account for this variability by leveraging the multiple systems of the SINGE network to better develop integrative therapies. This interconnected, holistic approach to studying AD paves the way for innovation that could improve patient outcomes and quality of life.

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Dermatology Practical & Conceptual

Clinical Efficacy and Safety of Intralesional Bevacizumab in Dermatology: Insights from a Systematic Review

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Key words: Bevacizumab, Avastin, Anti-VEGF, Intralesional, Dermatology

Citation: Rastegarnasab F, Tavousi N, Pourmahdi-Boroujeni M, Afshar K, Behfar S, Abtahi-Naeini B. Clinical Efficacy and Safety of Intralesional Bevacizumab in Dermatology: Insights from a Systematic Review. *Dermatol Pract Concept.* 2025;15(4):5430. DOI: https://doi.org/10.5826/dpc.1504a5430

Accepted: May 27, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Bevacizumab is a humanized monoclonal antibody specifically targeting the vascular endothelial growth factor (VEGF). In addition to cancer and ophthalmology, bevacizumab has other off-label uses. Among these, the treatment of hereditary hemorrhagic telangiectasia and hemangioma can be mentioned.

Objectives: Although there are reports of successful treatments by bevacizumab, there is no systematic review on the topical use of this medication in dermatology. Therefore, this study aimed to investigate this topic.

Methods: A systematic search on topical bevacizumab was done with MeSh-based keywords on online databases of PubMed, Scopus, and Web of Science in December 2022. The records were evaluated, and the eligible articles were selected.

Results: We reviewed related studies, and the disease name, treatment protocol (injection dosage and intervals), outcomes, and complications were summarized for conclusions.

Conclusions: In this study, we systematically reviewed related papers and summarized the use of bevacizumab in dermatology in four categories, including hereditary hemorrhagic telangiectasia, vascular malformation, vascular proliferation, and others (lichen planus, and basal cell carcinoma).

Introduction

Bevacizumab, an anti-VEGF-A medication, is a humanized monoclonal antibody specifically targeting the vascular endothelial growth factor (VEGF). Bevacizumab binds to VEGF-A and inhibits VEGF-A from connecting to its receptor. This process stops vascular endothelial growth, endothelial cell proliferation, and angiogenesis [1-3].

Neovascularization and angiogenesis are involved in the pathogenesis of several conditions, such as inflammatory and malignant processes. Theoretically, anti-VEGF medication can improve these conditions by inhibiting angiogenesis [4]. Bevacizumab prevents the growth of blood vessels that supply nutrients and oxygen to tumors, which results in slowing down their growth and spread [2,5].

In 2004, the US Food and Drug Administration (FDA) approved the use of bevacizumab (Avastin) for the treatment of metastatic colorectal cancer, and in 2009, for glioblastoma; since then, it has been authorized for use in many other types of cancer, including non-squamous cell lung carcinoma, prostate cancer, metastatic breast cancer, and metastatic renal cell carcinoma [2,6]. It is also one of the first choices for inhibiting angiogenesis approved by the FDA [2].

Avastin is widely used in ophthalmology to treat neovascular glaucoma, retinal vein occlusion, and diabetic retinopathy and as an intravitreal injection to treat macular edema [7-9]. It has also been increasingly used in the treatment of retinopathy of prematurity, alone or in combination with standard laser therapy [10,11].

In addition to the field of cancer and ophthalmology, bevacizumab has some off-label applications in the treatment of mucocutaneous conditions [12], including hereditary hemorrhagic telangiectasia (HHT) [13,14] and hemangioma [15].

Although there are several reports of successful treatments with bevacizumab in dermatological conditions, there is no systematic review about the use of this medication in dermatology.

Objectives

In this study, we systematically reviewed related papers and summarized the use of bevacizumab in dermatology in four categories, including HHT, vascular malformation, vascular proliferation, and others (lichen planus, and basal cell carcinoma).

Methods

In this study, online databases were searched systematically in December 2022. Keywords including "anti-vascular endothelial growth factor", "anti-VEGF", "bevacizumab", "Avastin", "derma*", "skin", "cutaneous", "intralesional", and "topical" were selected according to the MeSh terms.

All keywords were searched in PubMed, Scopus, and Web of Science with the following query: ((anti-vascular endothelial growth factor[Title/Abstract]) OR (anti-VEGF [Title/Abstract]) OR (bevacizumab[Title/Abstract]) OR (avastin[Title/Abstract])) AND ((derma*[Title/Abstract]) OR (skin[Title/Abstract]) OR (cutaneous[Title/Abstract]) OR (intralesional[Title/Abstract]) OR (topical[Title/Abstract])). All articles consisting of these keywords were included. Duplicated articles were removed by EndNote version 20 software.

First, titles of articles were screened, and any irrelevant record such as cancer or ophthalmological use was excluded. Also, reviews of any type were excluded. In the next step, the abstracts were screened, and reviews, experimental studies, and intravenous injections were omitted. In the final step, efforts aimed to screen the full texts of articles based on the same criteria.

Then the remaining full texts were evaluated, and the data were excluded. Finally, the disease name, treatment protocol (injection dosage and intervals), outcomes, and complications were summarized for conclusions.

Results

After conducting the systematic search, 3014 articles were found and inserted into EndNote software. By removing the duplicated records, 1229 articles remained, and 1199 articles were excluded due to their irrelevant title or abstract. The full text of 30 articles was screened and 14 of them were selected. An Explorer search was also conducted, and seven new article was added. Figure 1 shows the PRISMA flow diagram of the current review.

This study discusses the use of bevacizumab in dermatology in four categories: HHT, vascular malformation, vascular proliferation, and others (lichen planus (LP), and basal cell carcinoma (BCC)) (Table 1).

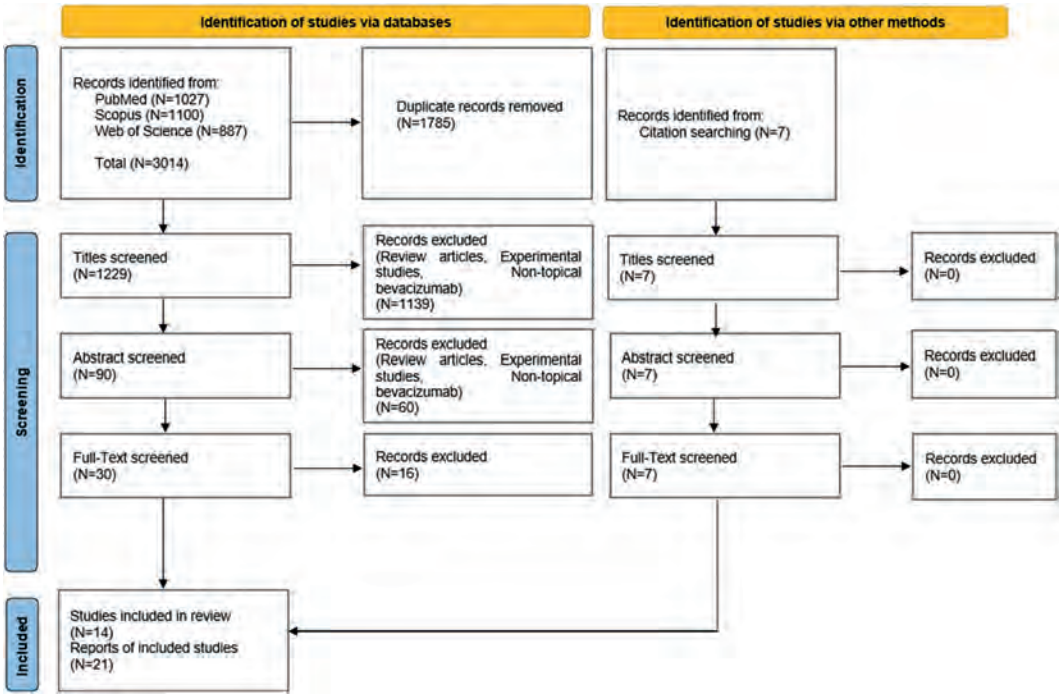


Figure 1. The PRISMA flow diagram of the study.

Hereditary Hemorrhagic Telangiectasia (HHT)

The use of bevacizumab for HHT, also known as Osler-Weber-Rendu syndrome, has been reported in 14 studies. Affected patients with HHT often develop arteriovenous malformations and mucocutaneous telangiectasias, including nasal mucosa with a susceptibility to bleeding [16]. Due to the elevated levels of serum and mucosal VEGF and transforming growth factor-β (TGF- β) in the affected patients, bevacizumab, as an anti-VEGF, inhibits angiogenesis and can help improve recurrent epistaxis [16]. Epistaxis severity is judged by epistaxis severity score (ESS), which was assessed pre- and post-treatment in most of the studies [17]. A proper evaluation of pre-treatment ESS is required to choose the best treatment protocol [18]. Intranasal spray, 50–100 mg, can treat mild symptoms, while a 100 mg submucosal injection is indicated for moderate-to-severe cases [16].

A randomized clinical trial (RCT) concluded that a single dose nasal spray had no clinical effect and that there should be repeated doses to reach sufficient epistaxis improvement [19]. Another RCT revealed that 4 mg topical bevacizumab per day for seven days had no clinical effect and concluded that the dosage may be inadequate [14]. This study aimed to compare the effect of bevacizumab, estriol, tranexamic acid, and placebo, and there was no difference between these groups [14]. A retrospective study was done on 32 patients with HHT receiving 25–100 mg bevacizumab, administered topically, submucosally, or both. Patients were interviewed about their post-treatment epistaxis severity and revealed a significant improvement [13]. Also, a prospective study was done on six patients receiving 10 treatment courses of 50 mg topical bevacizumab; an effective symptomatic treatment for patients with pre-treatment ESS<7 was found [14].

Bevacizumab can be injected intralesionally (IL) or intravenously (IV). In comparison to IV injection of bevacizumab, IL injection is a much better choice because of less systemic adverse effects; it is also more available and the more cost-effective. The intranasal submucosal injection is frequently administered to the lateral nasal wall, middle/inferior turbinate, nasal floor, and bony septum [16]. Nasal cartilaginous septum should not be injected with and without laser surgery due to the possibility of septal perforation [20,21]. A study introduced a 4-injection site technique as a new treatment option: the sphenopalatine area, the upper part of the bony septum, the upper part of the lateral nasal wall, and the anterior floor of the nose. These sites are near the entrance points of vessels, which may result in better control [22]. An RCT compared the effect of a 100 mg single-dose submucosal injection of bevacizumab with placebo in reducing HHT-related epistaxis. Reducing epistaxis was much greater in the bevacizumab group [23].

A 5-year-old female was reported with epistaxis since birth. Many treatment methods had been used, with no clinical improvement, including moisturizing therapy, aminocaproic acid, tranexamic acid, and cauterization. Finally, she was treated successfully with two injections of intranasal bevacizumab [24]. There are limited complications reported for intranasal therapy, including septal perforation [20,21], subfebrile body temperature [24], nasal symptoms, headache, abdominal pain [14], elevated blood pressure, body tingling [23], ageusia, and anosmia [18].

Table 1. Overview of Literature Included in this Systematic Review.

No.	First Author / Year	Study Design	Sample Size	Age	Disease	Bevacizumab Protocol	Outcome	Complications
1	Simonds et al. / 2009	Retrospective	10	58.3±8.2	HHT	100 mg submucosal injection	Effective	Septal perforation (N=4)
2	Davidson et al. / 2010	Case report	1	45	HHT	100 mg submucosal injection in addition to 2 courses of topical application	Effective	N/A
3	Chen et al. / 2011	Retrospective	58	54.99±11.8	HHT	50-100 mg topical (nasal spray) (N=18), 25-100 mg submucosal injection (N=26), Both (N=8)	Effective	Septal perforation (N=5)
4	Rohrmeier et al. / 2011	Retrospective	11	65 (46–77)	HHT	<7.5 mg submucosal injection	Effective	No complication
5	Karnezis et al. / 2011	Retrospective	32	53.8±13.2	HHT	50-100 mg topical (nasal spray) (N= 17), 100 mg submucosal injection (N=10), Both (N=5)	Effective	N/A
6	Karnezis et al. / 2012	Prospective	19	60 (40-80)	HHT	100 mg submucosal injection. In addition, 6 patients received 100 mg topical (nasal spray) for 8 times.	Effective	No complication
7	Steeples et al. / 2012	Case Letter	1	31	Hemangioma	2.5 mg/0.1 ml monthly intralesional injections, 4 times	Effective	No complication
8	Brinkerhoff et al. / 2012	Case report	1	55	HHT	100 mg topical (nasal spray), every 8-9 weeks	Effective	No complication
9	Dheyauldeen et al. / 2012	Prospective	8	56.5±12.7	HHT	100 mg submucosal injection	Effective	N/A
10	Guldmann et al. / 2012	Prospective	6	56.3	HHT	50 mg topical (nasal spray)	Effective	Headache, ageusia, and anosmia
11	Gaitanis et al. / 2013	Case series	7	70 (50-88)	BCC	25 mg intralesional injection, 1-3 times	Effective	Pain during injection (N=6), Flu-like symptoms (N=2), Reversible leukopenia (N=1)

No.	First Author / Year	Study Design	Sample Size	Age	Disease	Bevacizumab Protocol	Outcome	Complications
12	Kalinina et al. / 2014	Case report	1	5	HHT	10 mg/ml submucosal injection, 2 times every 3 weeks	Effective	Subfebrile body temperature up to 37.5°C
13	Riss et al. / 2014	RCT	9	59 (41-71)	HHT	100 mg submucosal injection	Effective	Elevated blood pressure (N=1), Rhinitis (N=1), Itching at the nose tip (N=1), Body tingling (N=1)
14	Dupuis-Girod / 2014	RCT	30	57 (39-75)	HHT	12.5, 25, 50, 75, or 100 mg topical (nasal spray), single episode	No clinical effect	No complication
15	Ablanedo-Terrazas et al. / 2015	RCT	7	35 (29–39)	Mucosal KS	0.2 mL (5 mg)/cm2 intralesional injection, 3 times every 2 weeks	No clinical effect	Mild pain and tenderness at the injection site (N=1), Fever (N=1)
16	Whitehead et al. / 2016	RCT	29	48 (42-53)	HHT	4 mg/day topical (nasal spray), for a week	No clinical effect	Nasal symptoms (N=11), Headache (N=10), Abdominal pain (N=5)
17	Mahmoud et al. / 2016	RCT	20	43±1.3	OLP	2.5 mg/0.5 ml intralesional injection	Effective	No complication
18	Hwang et al. / 2017	Case report	1	10	Lymphangioma	2.5-10 mg intralesional injection, 5 times monthly and then 4 times every 3 months	Effective	No complication
19	Kinzinger et al. / 2018	Case report	1	67	Sinonasal hemangioma	50 mg intralesional injection	Effective	N/A
20	Sabry et al. / 2019	RCT	15	3-9 months	Hemangioma	25 mg/ml (2mg/cm2) intralesional injection, 6 times monthly	Effective	No complication
21	Bowers et al. / 2020	Case report	1	61	HHT	100 mg Submucosal injection	Effective	No complication

Abbreviations: RCT: Randomized Controlled Trial, HHT: Hereditary Hemorrhagic Telangiectasia, BCC: Basal Cell Carcinoma, KS: Kaposi Sarcoma, OLP: Oral Lichen Planus, N/A: Not Available.

Persistent bleeding may occur even for a few weeks after submucosal injection because of the pre-existing telangiectasia. Therefore, combination therapies can help to improve these symptoms. Cauterization [16], potassium titanyl phosphate (KTP) laser [13,17,20,21], neodymium-doped yttrium aluminum garnet (Nd: YAG) laser [25], and topical bevacizumab [16,26] are used as adjuvant therapies accompanied by submucosal injection. Another case was a 55-year-old female dealing with HHT, breast cancer, and chemotherapy-induced anemia and increased epistaxis. Episodes of intravenous bevacizumab were initially used, then 100 mg topical therapy (nasal spray) every 8–9 weeks was used as an effective maintenance control for epistaxis and anemia [1].

In addition to nasal mucosa, HHT can present with other mucosal involvements, including the tongue. A study reported a case involving recurrent bleeding of tongue telangiectasia successfully treated with dual therapy of KTP laser and 100 mg submucosal bevacizumab injection, without any complication [13]. The patient had had two episodes of KTP laser previously but without any improvement.

Vascular Malformation

Lymphangioma

Lymphangioma is a benign tumor that can be treated by sclerotherapy or surgical intervention. Non-surgical treatments such as IL steroid or bleomycin may also be useful [25].

A 10-year-old female was reported with a hemorrhagic, swollen lesion on her tongue. She was initially treated with 40 mg/ml triamcinolone acetonide injection and 1 mg/ml bleomycin. The lesion shrank but did not disappear [25]. After adding 25 mg/ml IL bevacizumab to the previous medication, every three months for a year, the lesion completely regressed. No side effect or recurrence was observed after three years of follow-up. Therefore, bevacizumab can be used as a potential adjuvant treatment for extensive lymphangioma [27].

Vascular Proliferation

Recurrent Sinonasal Hemangioma

Sinonasal hemangioma usually originates from the nasal septum or lateral wall. It is a benign tumor that presents with epistaxis and nasal obstruction. Surgical intervention is the choice treatment [28]. These procedures may lead to aesthetic and functional complications such as excessive tearing, diminished sensation, scarring, deformities, and blockage of nasal passages [29].

A 67-year-old male with nasal hemangioma complained of recurrent epistaxis and nasal obstruction even after surgery. He was successfully treated with a single injection of 50 mg bevacizumab into the lesion and nasal septal mucosa. Ten months later, the lesion had improved, and at the 6-year follow-up, the patient was asymptomatic, with no recurrence or complication observed [28]. Therefore, IL bevacizumab may be an effective noninvasive option for treating sinonasal hemangioma.

Infantile Hemangioma

Infantile hemangioma (IH) is the most common vascular tumor in infants. VEGF overexpression may be responsible during the initial proliferative stage of IH [30]. An RCT was conducted on children aged 3–9 months with IH to compare the effectiveness of IL bevacizumab with triamcinolone acetonide. The children in each group were treated with 25 mg/mL of IL bevacizumab and 2 mg/2 cm^2 of triamcinolone acetonide monthly for six months. After three months, lesions were successfully healed, with no recurrence or side effect. This study concluded that IL bevacizumab and triamcinolone acetonide both could be safe and effective for infantile hemangioma. However, triamcinolone acetonide was more effective in this study [15].

Capillary Hemangioma in Pregnancy

Capillary hemangioma is a proliferative lesion with an overexpression of angiogenic growth factors such as VEGF. Pregnancy is associated with an increased risk of tumoral lesions, including vascular proliferative lesions. Hormonal factors may contribute to these complications [31]. In a case study, a female with hemangioma during her third trimester lasting until six months post-partum resisted invasive treatments. A 4 mg IL triamcinolone acetonide was administered, with no improvement. Finally, IL bevacizumab was initiated at a dose of 1.25 mg in 0.05 mL, leading to a significant improvement. Additional monthly injections with a dose of 2.5 mg in 0.1 mL were given four times, resulting in complete regression, without any complication or recurrence [31].

Kaposi Sarcoma

Therapeutic options for Kaposi sarcoma (KS) include chemotherapy and radiation therapy along with antiretroviral agents and immunomodulators [32]. An RCT was conducted on 14 human immunodeficiency virus (HIV)-infected individuals with mucosal KS. The disease involved the upper airway regions (oral cavity, pharyngeal, and laryngeal areas). The participants were divided into two groups: one received IL bevacizumab in addition to antiretroviral therapy (ART), while the control group received ART alone [32]. The intervention group received three injections every two weeks, each with a dose of 0.2 mL (5 mg/cm^2). IL bevacizumab resulted in side effects, including pain and tenderness at the injection site, which were relieved with a single dose of acetaminophen 1000 mg. In addition, one patient experienced a fever of 39° C three days after the injection,

leading to hospitalization [32]. In the end, the study revealed that the combination of IL bevacizumab and ART did not show any significant effect on mucosal KS involving the upper respiratory tract in HIV-infected patients [32].

Others

Lichen Planus

Oral lichen planus (OLP) is a chronic inflammatory disease affecting mucocutaneous regions. The standard approach suggests treatment with topical corticosteroids. However, due to the strong correlation between OLP and angiogenesis, anti-angiogenic drugs could emerge as an alternate option for patients who cannot use conventional therapy or who have shown inadequate response [33]. An RCT was conducted on 40 patients with atrophic/erosive lesions of OLP. Twenty patients were randomly selected to receive 2.5 mg IL bevacizumab, and other participants were instructed to use triamcinolone acetonide on the buccal mucosa. The patients underwent seven follow-up sessions, for a total duration of three months [33]. Tissue biopsy revealed that bevacizumab effectively reduced levels of IL-8 and stopped the activity of pro-inflammatory cells and cytokines, which inhibited VEGF and angiogenesis. A week after IL bevacizumab injection, the size of lesions and pain intensity improved, without complication. Therefore, IL bevacizumab may be an effective and a safe treatment for atrophic/erosive LP [33].

Basal Cell Carcinoma

The goal for the treatment of basal cell carcinoma (BCC) is to achieve complete tumor removal. This can be accomplished through conventional surgical excision, Mohs micrographic surgery, cryosurgery, electrodesiccation and curettage, topical application of imiquimod or fluorouracil, photodynamic therapy, or radiation therapy [34]. In a case series, seven patients with extensive local BCC were initially treated with immunocryosurgery alone, which was ineffective. IL bevacizumab was then used as an adjuvant treatment [35]. The treatment protocol was 12.5 mg of topical imiquimod 5% every night, 1 g of tazarotene 0.1% daily, and two cycles of cryosurgery every two weeks. As an adjuvant medication, three sessions of 25 mg IL bevacizumab were immediately used after cryosurgery [35]. The tumor shrank successfully after two bevacizumab injections. Pain during injection, flu-like symptoms, and reversible leukopenia were the only reported complications. Therefore, bevacizumab may be an effective and minimally invasive therapeutic option for BCC [35].

Conclusion

Intralesional bevacizumab has some off-label applications in dermatology beyond its previous advantages for the treatment of cancer and ophthalmological conditions. These dermatological applications can be summarized based on previous reports into four categories: hereditary hemorrhagic telangiectasia, vascular malformation, vascular proliferation, and others (lichen planus and basal cell carcinoma).

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Dermatology Practical & Conceptual

Photodynamic Therapy with 5-Aminolevulinic Acid for Cosmetic-Induced Acne Fulminans: Case Report and Literature Review

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Key words: Acne Fulminans, Photodynamic Therapy, 5-Aminolevulinic Acid, Supramolecular Salicylic Acid, Cosmetic-Induced Reactions

Citation: An R, Liu R, Gu H. Photodynamic Therapy with 5-Aminolevulinic Acid for Cosmetic-Induced Acne Fulminans: Case Report and Literature Review. *Dermatol Pract Concept*. 2025;15(4):6693. DOI: https://doi.org/10.5826/dpc.1504a6693

Accepted: August 26, 2025; **Published:** October 2025

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Funding: This work was supported by the Beijing Medical Award Foundation, 7th Round of the "Rui-Ying" Scientific Research Fund.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Acne fulminans (AF) is a rare, explosive variant of inflammatory acne marked by rapidly progressing nodulocystic lesions, hemorrhagic crusts, and systemic symptoms. Standard therapy combines oral corticosteroids with isotretinoin, but teratogenic risk and systemic adverse effects may limit acceptance among females of reproductive age [1,2]. We report a non-systemic regimen—5-aminolevulinic acid photodynamic therapy (ALA-PDT) plus supramolecular salicylic acid (SSA)—for AF occurring after use of a non-compliant cosmetic product, with positive patch-test reactivity to the product.

Case Presentation

A 25-year-old female with a history of acne developed intense facial burning and erythema shortly after using a non-compliant "whitening and anti-acne" cosmetic. Within three days she had extensive inflammatory papules, pustules, hemorrhagic nodules, and purulent crusts on both cheeks and the jawline, with fatigue, fever (38.5° C), and elevated inflammatory markers (WBC, CRP, ESR), consistent with acne fulminans. She declined systemic steroids and isotretinoin because of concerns about adverse effects and teratogenicity. Standardized closed patch testing with the patient's product (neat and 1:10 in petrolatum; 48-h occlusion) yielded positive (++) reactions at 48/72 h, while petrolatum and blank controls were negative. VISIA® imaging showed diffuse inflammatory erythema with telangiectatic dilation in the same regions, and dermoscopy at the test site revealed diffuse background erythema with scattered dotted and short linear vessels (Figures 1A–E).

Because she declined systemic therapy, we initiated weekly ALA-PDT plus 30% supramolecular salicylic acid (SSA) for four sessions. Each visit included gentle cleansing, a 3-minute application of 30% SSA (controlled-release) to affected areas, removal with a mild cleanser, application of

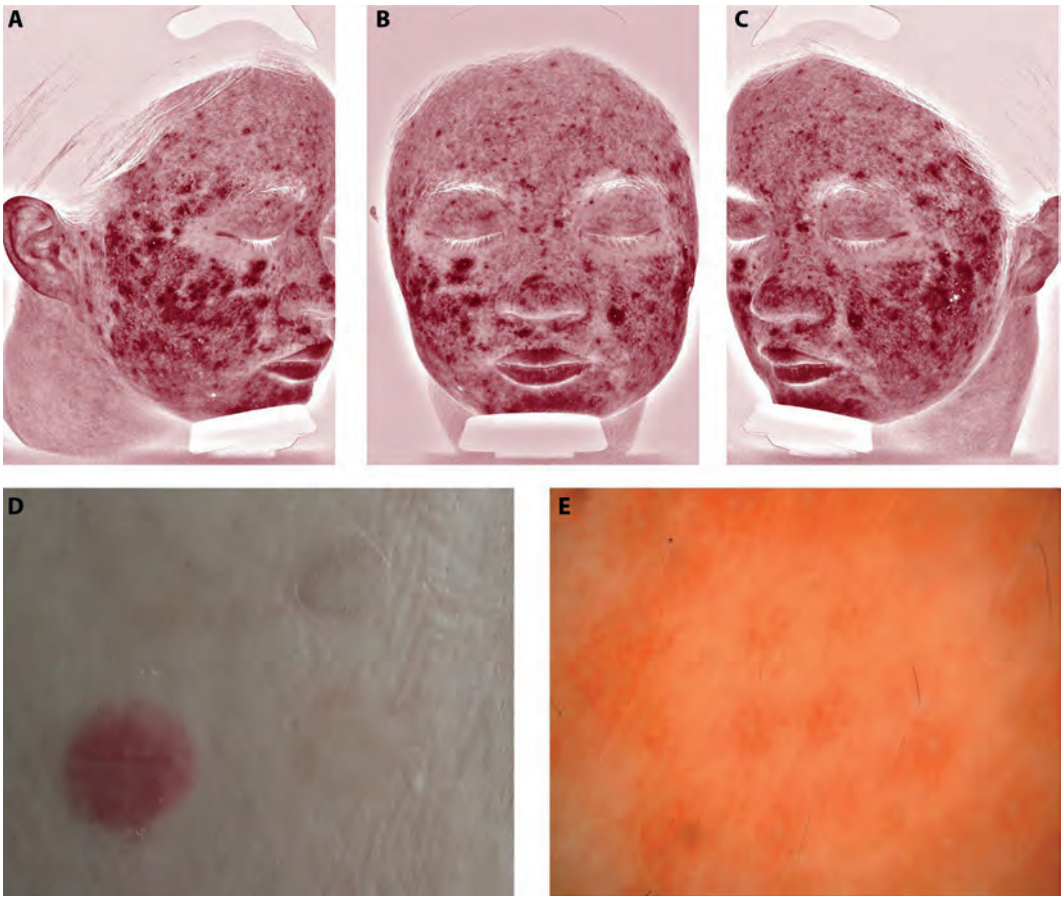


Figure 1. (A–C) VISIA® skin analysis of the cheek demonstrates pronounced, diffuse inflammatory erythema with noticeable capillary/telangiectatic dilation in the same area. (D) At 72 h after standardized closed patch testing with the patient's non-compliant cosmetic product, the left cheek test site showed erythema, infiltration/induration, papules, and small vesicles with marked pruritus, whereas the contralateral right cheek control (petrolatum vehicle) showed no reaction. (E) Dermoscopy of the test site revealed diffuse background erythema with scattered dotted and short linear vessels.

5% ALA cream under sterile gauze occlusion for 30 minutes, and illumination with 635 nm LED at 50 mW/cm² to a total fluence of 150 J/cm². After one session, most hemorrhagic/purulent crusts and suppurative nodulocystic lesions had subsided. By the fourth session, inflammatory papules had improved by approximately 80%, with marked reductions in pain, erythema, and swelling; only mild atrophic scarring persisted. No notable adverse event occurred, and no recurrence was observed on follow-up (Figures 2A–F).

Conclusion

This case highlights AF—occurring after exposure to a non-compliant cosmetic product with positive patch-test reactivity—successfully managed without systemic agents using ALA-PDT plus SSA. Published evidence on ALA-PDT for AF remains scarce but includes two case-level reports describing rapid clinical improvement and good tolerability, despite heterogeneous parameters and use as mono- or adjunct therapy [4,6] (Table 1). Mechanistically, ALA-PDT promotes intrafollicular protoporphyrin IX accumulation and reactive oxygen species formation, reducing Cutibacterium acnes, modulating inflammation, and attenuating sebaceous activity [3,4], while SSA provides keratolysis and additional anti-inflammatory effects that relieve follicular occlusion and may aid barrier recovery [5]. For reproductive-age patients who decline or cannot tolerate systemic therapy, this topical/physical combination may offer rapid disease control with favorable tolerability. Larger series are warranted to confirm efficacy, refine parameters (photosensitizer concentration, occlusion time, fluence, session number), and define its role within stepwise AF management alongside careful identification and avoidance of potential external triggers.



Figure 2. (A–C). The cheeks exhibit extensive hemorrhagic and purulent crusts covering coalescent suppurative nodulocystic lesions. (D–F) After a single session of photodynamic therapy combined with supramolecular salicylic acid, most hemorrhagic and purulent crusts as well as purulent nodulocystic lesions had subsided. (G–I) Following four sessions, the majority of inflammatory papules resolved, with no recurrence observed during follow-up.

Table 1. 5-ALA Photodynamic Therapy in Acne Fulminans: Summary of Published Cases and the Present Case.

Author (Year)	Age/Sex	PDT Parameters	Adjunct Therapy	Outcome (Follow-up)
Hao & Wang, 2020, China	23 M	20 % ALA, 3 h occlusion; red-light LED (wavelength NR); 2 sessions	Oral isotretinoin 0.5 mg/kg/d	Complete remission after 2 sessions; no relapse at 6 months
Picone et al., 2022, Italy	18 M	ALA conc. NR, 3 h; red-light LED 630 nm; 3 weekly sessions	None reported	Complete clearance; scar remodeling at 2 months

Patient Consent: The authors have obtained the consent of the patient for clinical images.

Data Availability: Data will be made available on request.

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Dermatology Practical & Conceptual

Dermoscopic Features and Diagnostic Criteria of Galli-Galli Disease: A Clinical Update

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Key words: Galli-Galli disease, reticulate pigmentary disorders, pigmentary skin disordes, dermoscopy

Citation: Piana S, Zendri E. Dermoscopic Features and Diagnostic Criteria of Galli-Galli Disease: A Clinical Update. *Dermatol Pract Concept*. 2025;15(4):4640. DOI: https://doi.org/10.5826/dpc.1504a4640

Accepted: September 26, 2024; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Galli-Galli disease (GGD) is a very rare acantholytic disease belonging to the reticulate pigmentary disorders, a group of cutaneous diseases mainly inherited as autosomal dominant [1]. Sporadic cases of GGD have been described [2]. The clinical resemblance with Dowling-Degos disease (DDD) and the presence of the same gene mutations in DDD [3] prompts considering GGD and DDD as two distinct phenotypes of the same pathological entity.

In GGD mutations in genes *KRT5*, *POFUT1*, *POGLUT1*, or *PSENEN*, affecting melanosome transfer and melanocyte and keratinocyte differentiation, may account for the polymorphous phenotype. While *KRT5* mutation is responsible for classic and generalized DDD and "classic" GGD, mutations in *POGLUT1* are described in the generalized "atypical" GGD phenotype, in which the characteristic flexural lesions are absent and persistent macules are distributed mainly on trunk and extremities [4].

Case Presentation

Case 1. A healthy 41-year-old Caucasian female presented with a 2-year history of a slightly pruritic rash affecting the trunk. Physical examination revealed thin flat non-folliculotropic papules, some of which scaly, admixed with mottled lentigo-like macules (Figure 1A). The flexural areas and the face were spared. Dermoscopy of papular lesions showed a yellowish-to-brown-tan star-like or polygonal central area surrounded with a whitish halo on a faint erythematous background with fine linear-curved vessels at the periphery (Figure 1B). Macular lesions, on the other hand, showed a pseudo-reticular pattern with well demarcated borders (Figure 1C). At histological

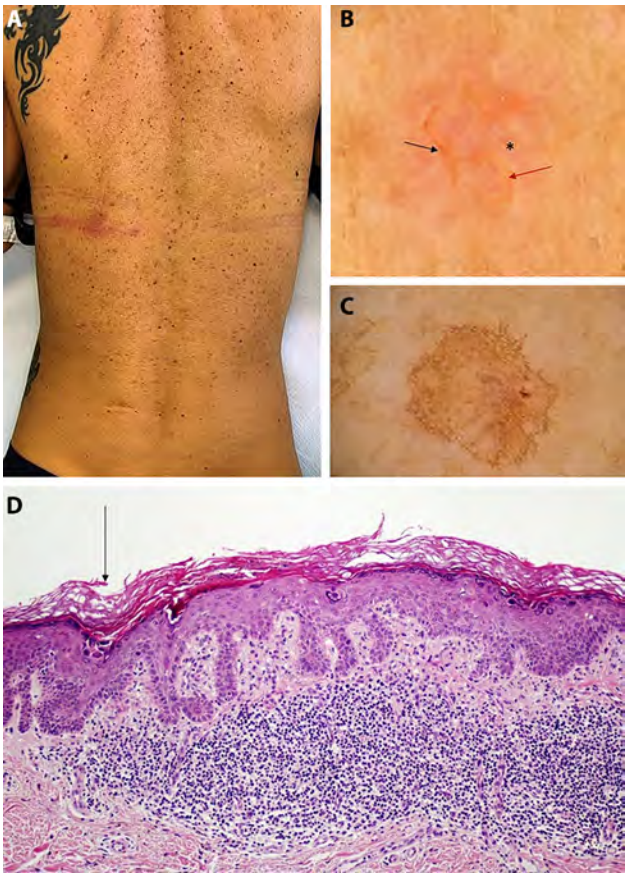


Figure 1. (A) Papular and macular lesions on the trunk in a 41-year-old female. (B) Dermoscopy of a Galli-Galli disease (GGD) papule with a polygonal yellowish center (black arrow), a whitish halo (red arrow), and fine linear and curved vessels at the periphery (asterisk). (C) Dermoscopy of a macule with pseudo-reticular pattern and clear-cut borders. (D) Histology of a GGD papular lesion showing subtle focal acantholysis in the stratum spinosum and granulosum (arrow) with rare dyskeratotic keratinocytes (H&E, original magnification ×100).

examination of a papule, elongation of the rete ridges, hyperparakeratosis, and deceptively focal acantholysis in the stratum spinosum and granulosum with occasional dyskeratinocytes were present (Figure 1D). The dermis showed a moderate lymphocytic infiltrate. Based on the clinical findings and on the histopathological features, the patient was diagnosed with GGD.

Case 2. A 50-year-old female presented with a 10-year history of crops of asymptomatic fine erythematous-brownish papular lesions limited to the lower limbs associated with round lentigo-like macules (Figure 2A). Dermoscopic findings of the papular and the macular lesions were similar to those described in Case 1, but in Case 2, macular lesions prevailed, and "hybrid" papulo-macular lesions were



Figure 2. (A) Papular and macular lesions of the limb of a 50-year-old female. (B) Dermoscopy of an almost involute papular lesion showing a star-like uniform pinkish center with scales fading to macules with a pseudo-network pattern (black arrow).

observed (Figure 2B). Histology of a papular lesion showed the same characteristic as observed in Case 1.

Conclusion

In GGD, an accurate histopathological examination is necessary to identify foci of acantholysis as this clue may be extremely subtle in the atypical, generalized variant, and it is mainly linked to the age of the lesion. Of note, as acantholysis is commonly observed in different dermatoses (Table 1), clinical-pathological correlation is always mandatory.

To our knowledge, dermoscopic features of GGD have been only reported by two groups [5,6], which also employed reflectance confocal microscopy and line-field optical coherence tomography, with a good correlation to histological features, suggesting a reliable non-invasive approach. Thus, the whitish central area and the lentigo-like pattern observed with dermoscopy likely correspond respectively to the hyper-parakeratosis and acanthosis and to the elongate rete ridges seen at histology.

The dermoscopic brownish star-like brown pattern with a thin peripheral halo and a pinkish background, along with the absence of follicular plugging and inclusion microcysts, are very characteristic of GGD. Moreover, we showed a possible dermoscopic continuum between the papular and the macular late phase.

Table 1. Papular Acantholytic/Dyskeratotic Disorders Clinically Mimicking GGD.

Disease	Diagnostic clues
Dowling-Degos disease (DDD)	Genetically inherited. Hyperpigmented macules in a reticulate distribution. Dermoscopy may show follicular plugging and milia within papular lesions.
Grover disease	Itchy papular and vesicular eruption on trunk and proximal extremities. Superficial indentations/micro fissures at dermoscopy.
Darier disease	Genetically inherited with variable expressivity. Warty itchy lesions on seborrheic areas of the trunk and face. Palmoplantar and nail manifestations.
BRAF-inhibitor-induced acantholytic dyskeratosis	Oncological patient under treatment.
Acantholytic dyskeratotic acanthoma (acantholytic dyskeratoma)	Solitary lesions. Superficial indentations/microfissures at dermoscopy.

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Dermatology Practical & Conceptual

Dermatoscopic Patterns in Keloid, Hypertrophic, and Atrophic Scars: Cross-Sectional Analysis and Clinical Correlation

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Key words: Dermatoscopy; Keloid, Hypertrophic scar, Vascular patterns; Scar maturation

Citation: Metsavah LdO, Espíndola GC, Fernandes EL, et al. Dermatoscopic Patterns in Keloid, Hypertrophic, and Atrophic Scars: Cross-Sectional Analysis and Clinical Correlation. *Dermatol Pract Concept*. 2025;15(4):5315. DOI: https://doi.org/10.5826/dpc.1504a5315

Accepted: February 20, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Keloids, hypertrophic scars, and atrophic scars represent distinct forms of abnormal wound healing. Differentiating between these entities is often based on clinical and histopathological criteria. Dermatoscopy has been suggested as a supportive tool in this differentiation, yet published data remain limited. While earlier studies proposed that dermatoscopy could assist in distinguishing scar subtypes, we aimed to clarify its role by analyzing a broad set of dermatoscopic images. Our findings demonstrate that dermatoscopy is more effective for evaluating scar activity and maturation than for classifying scar types.

Case Presentation

A dermatoscopic evaluation was conducted on 68 scars (38 keloids, 20 hypertrophic scars, and 10 atrophic scars) at a dermatology outpatient clinic using polarized digital dermatoscopy (Fotofinder©). Clinical and dermatoscopic

findings focused on vascular patterns, color, and the presence or absence of skin appendages.

In keloids (N=38), arborizing (branched) vessels were observed in 36.8% of cases, often associated with white or yellow structureless areas, indicating dense collagen nodules. Dotted vessels were less frequent. Mature keloids showed reduced vascularity, and in some cases, reappearance of trapped hair follicles, suggesting a transition to a regressive phase.

In hypertrophic scars (N=20), thin linear vessels were the most common vascular pattern (50%), along with pinkish or reddish areas and parallel white bands, likely corresponding to compact collagen bundles.

Atrophic scars (N=10), often following intralesional corticosteroid therapy, exhibited prominent arborizing vessels (70%) and dermal thinning. These scars lacked curved or dotted vessels, helping differentiate them from proliferative-phase scars.

Statistical analysis revealed that vascular patterns (arborizing, linear, dotted) were more strongly correlated with scar activity (e.g., inflammation, growth phase) than with scar subtype (Figure 1). Dermatoscopy also revealed the reappearance of pilosebaceous units during scar regression, serving as a useful marker of scar maturation (Figure 2).

Dermatoscopic findings are summarized in Table 1.

Conclusions

Dermatoscopy is not reliable for distinguishing between keloids and hypertrophic scars based solely on morphology. However, its true clinical utility lies in tracking scar dynamics, such as vascular patterns, color changes, and follicular visibility, which reflect scar activity and maturation phase rather than classification.

Keloids in active growth show arborizing vessels and yellow-white structureless areas, while reduced vascularity and reappearance of follicles indicate regression. Hypertrophic scars show linear vessels that diminish with maturation along with increased follicular visibility. In atrophic scars, prominent arborizing vessels are typically shown due to steroid-induced dermal thinning, although arborizing vessels, reminiscent of a distorted reticular vascular pattern, may be indicative of the emergence of the reticular vascular pattern of superficial plexus of normal skin in the maturation of a scar.

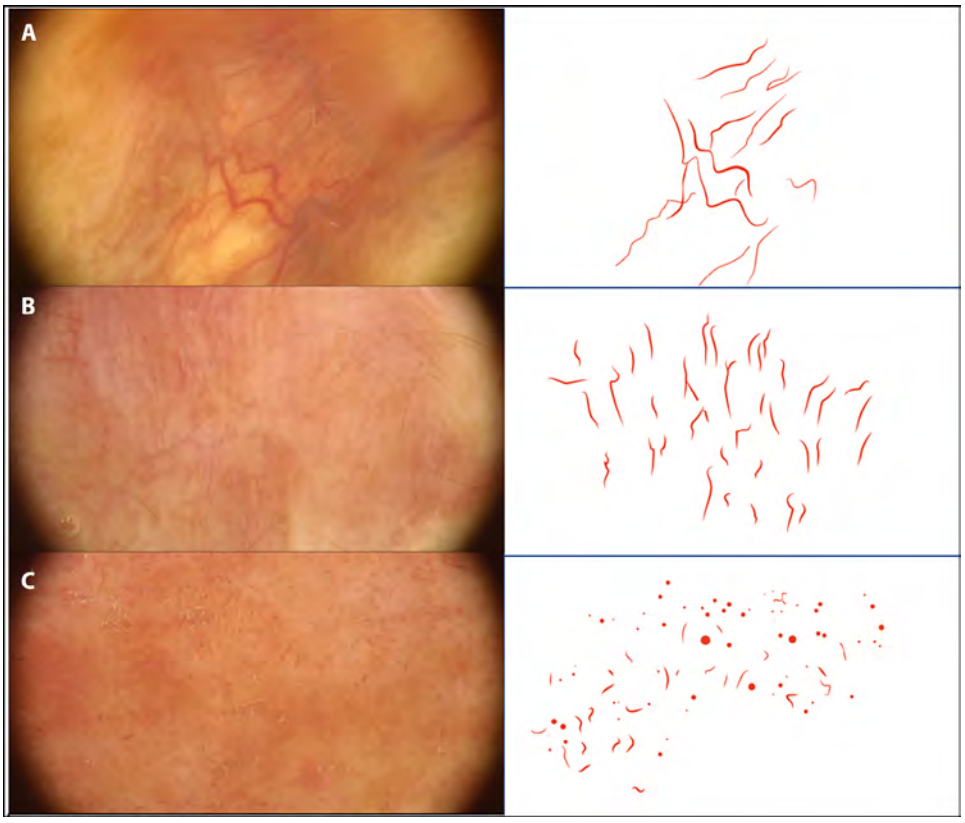


Figure 1. Dermatoscopic patterns of curved, crossing and arborizing (A), linear (B) and dotted (C) vessels. Branched vessels increased significantly across scar types (P=0.005), especially in atrophic lesions. Linear and curved vessels showed progressive trends by scar type.

Table 1. Dermatoscopic features of patients with atrophic, hypertrophic, and keloid Scars.

General Dermoscopic Findings			
Finding	Keloid Scars (N=38)	Hypertrophic Scars (N=20)	Atrophic Scars (N=9)
Erythematous areas	9 (23.7%)	3 (15.0%)	2 (22.2%)
Blood Vessels			
Vascular Pattern	Keloid Scars (N=38)	Hypertrophic Scars (N=20)	Atrophic Scars (N=9)
Arborizing (branched) vessels	14 (36.8%)	2 (10.0%)	6 (66.7%)
Linear vessels	11 (28.9%)	10 (50.0%)	1 (11.1%)
Dotted / comma-like (curved) vessels	6 (15.8%)	0 (0.0%)	1 (11.1%)

Abbreviations: N: number of lesions; values in parentheses represent percentages. Statistical analysis: Fisher's exact test showed a significant association between arboriform (branched) vessels and scar type (P=0.005). No statistically significant association was found for erythematous areas (P=0.69), linear vessels (P=0.10), or dotted/comma-like (curved) vessels (P=0.13).

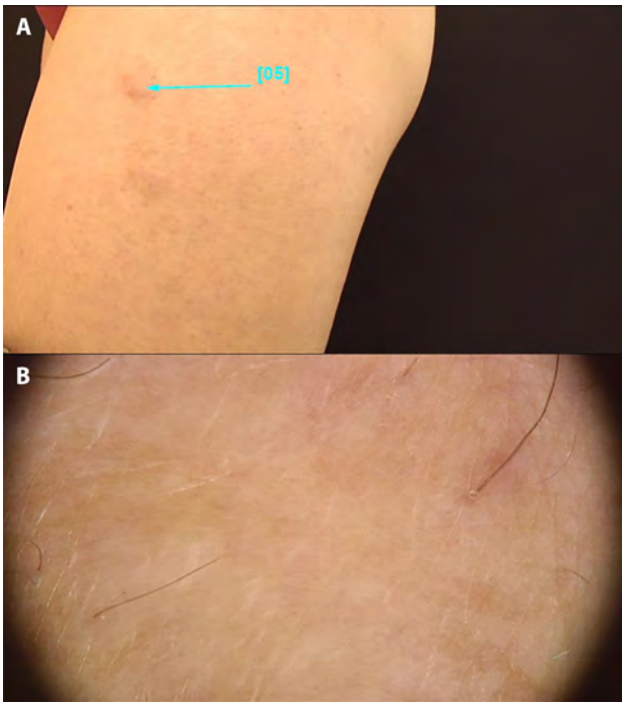


Figure 2. (A) Macroscopic image showing a treated scar on the left thigh. (B) Under dermoscopy, hair follicles are identified extruding from non-hypertrophic scar tissue. As scar thickness decreases, dermatoscopy reveals the return of previously trapped hair follicles. Preserving these structures during treatment may support repigmentation and enhance the scar's cosmetic appearance.

Dermatoscopy thus serves as a noninvasive, practical tool for monitoring scar progression and guiding treatment decisions, particularly timing and selection of adjunctive therapies like laser, cryotherapy, or energy-based devices.

Dermatoscopy enhances the clinical assessment of abnormal scars by identifying features linked to scar activity and evolution. Though it cannot differentiate scar types definitively, it provides valuable insights into scar maturation and treatment response, supporting personalized and optimized care.

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Dermatology Practical & Conceptual

Imiquimod-Induced Vitiligo: An HLA Case Investigated

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Key words: Imiquimod, HLA, Vitiligo

Citation: Klimi E. Imiquimod-Induced Vitiligo: An HLA Case Investigated. *Dermatol Pract Concept*. 2025;15(4):5797. DOI: https://doi.org/10.5826/dpc.1504a5797

Accepted: April 22, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Vitiligo is an autoimmune disease of the skin that manifests with well-circumscribed white patches due to epidermal melanocyte loss [1]. It may appear de novo, but it may also be associated with either thyroid dysfunction or atopy. It may also be the side effect of cancer treatment with immune checkpoint inhibitors. Development of vitiligo is linked with genetic predisposition. Herein we present a case of imiquimod-induced vitiligo that was HLA investigated.

Case Presentation

A 57-year-old male with unremarkable past medical and family history was prescribed three times weekly for four months the application of imiquimod, an interferon inducer that provokes a CD8+ cytotoxic reaction against keratinocytes infected with HPV virus, for the treatment of genital warts. At the beginning of the third month of application, the patient noticed erythema, severe irritation, and ulceration at the site of application. Despite these side effects, the patient completed the treatment, which led to the resolution of the lesions. One and a half months after the end of the treatment, the patient noticed depigmentation of the penis and scrotum without involvement of other areas (Figure 1). The clinical diagnosis was imiquimod-induced vitiligo. The patient persisted in questioning about the nature and the cause of the disease; this motivated an HLA examination. The HLA typing was performed for the HLA-A, -B, and -C antigens using the sequence specific oligonucleotide- polymerase chain reaction (PCR), and for the HLA-DR, DQ the sequence specific primer PCR-based assay. The patient proved positive for the HLA Class I A31, 68, HLA B 49,51, HLA C:0,715. HLA Class II HLA DRB1*11:01, HLADQB1*03,05. HLA-A31 has been associated with vitiligo development in Indian patients [2] and HLA DQB1*03 and DQB1*05 alleles have been associated with vitiligo in Chinese patients as well [3]. In addition, DRB1*11:01 has been associated with the development of thrombocytopenic purpura in Turkey [4]. Several case reports of imiquimod-induced vitiligo have been found in the literature, one of which reporting vitiligo in an one patient the wife of the affected couple and lichen planus



Figure 1. Vitiligo of the penis and scrotum.

in the husband, lichen planus being also a CD8* cytotoxic-mediated reaction suggesting a common immunopathogenic mechanism for both side effects [5]. An association between nivolumab-induced vitiligo, used for metastatic acral melanoma, and HLA Bw4, DRB107:01, and HLA A 02:179 was reported in a recent study in the literature [6].

Conclusion

Vitiligo is a rare side effect following treatment with imiquimod for genital warts. However, it provokes considerable discomfort and anxiety in the affected patients. Therefore, it should be included as a side effect of the medication in the leaflet of the drug. This case is reported to increase awareness about the possible occurrence of imiquimod-induced vitiligo in genetically predisposed individuals. HLA genetic test should be performed before initiation of treatment if suspicion of such genetic predisposition-stigmata of autoimmunity- already exists.

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Dermatology Practical & Conceptual

Trends in Gender Representation at US Dermatology Grand Rounds (2000-2025): A Cross-Sectional Study

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Key words: Grand rounds, Dermatology, Gender representation, Women speakers

Citation: Zhou MH, Li W, Chukwu F, Singal A, Lipner SR. Trends in Gender Representation at US Dermatology Grand Rounds (2000-2025): A Cross-Sectional Study. *Dermatol Pract Concept*. 2025;15(4):5653. DOI: https://doi.org/10.5826/dpc.1504a5653

Accepted: April 8, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Over the last two decades, female dermatology trainees have outnumbered male trainees. However, women are still underrepresented in academic leadership positions [1]. Grand rounds (GRs) are forums for showcasing research and clinical insights, playing an important role in career advancement. Gender disparities among GR speakers have been reported in cardiology and orthopedic surgery [2,3]. Therefore, we sought to evaluate gender representation of dermatology GR speakers in the United States to determine alignment with current dermatologist gender distribution.

Findings

Dermatology residency programs listed in the American Medical Association's FRIEDA directory were reviewed for publicly available GR records 1/2000-2/2025. Speaker demographics and lecture topics were collected from program websites. Publication number was determined by PubMed search prior to lecture date. Comparisons between speaker genders were performed using Chi-square or Fisher's exact test.

Overall, 1380 lectures were included in our analysis, with 826 (59.9%) delivered by male speakers and 554 (40.1%) by female speakers. The proportion of female speakers increased from 33.2% to 58.5% between 2016–2020 and 2021–2025, respectively ($P<0.001$). Male vs. female speakers more often held senior academic positions, including Chair (20.3% vs. 3.8%) or Professor (34.7% vs. 28.3%) (both $P<0.001$) and had greater publication numbers (59.3% vs. 37.7% above median, $P<0.001$). There was a greater proportion of female vs. male speakers in the West (25.8% vs. 17.9%) and Northeast (43.1% vs. 39.2%) but lower in the Southwest (9.8% vs. 21.7%) (all P<0.001) (Table 1).

Table 1. Speaker Characteristics for Male and Female Speakers.

Characteristic	Male Speakers	Female Speakers	P Value
No. of lectures	826 (59.9%)	554 (40.1%)	
Speaker academic rank			
• Assistant professor	193 (23.4%)	182 (32.9%)	<0.001
• Associate professor	112 (13.6%)	144 (26.0%)	
• Professor	287 (34.7%)	157 (28.3%)	
• Chair	168 (20.3%)	21 (3.8%)	
• Other	66 (8.0%)	50 (9.0%)	
Speaker field			
• General dermatology	647 (78.3%)	388 (70.0%)	<0.001
• Pediatric dermatology	17 (2.1%)	41 (7.4%)	
• Surgical dermatology	42 (5.1%)	40 (7.2%)	
• Dermatopathology	20 (2.4%)	13 (2.4%)	
• Medicine	40 (4.8%)	29 (5.2%)	
• Pediatrics	4 (0.5%)	4 (0.7%)	
• Other	56 (6.8%)	39 (7.0%)	
Speaker publications			
• < total median	336 (40.7%)	345 (62.4%)	<0.001
• ≥ total median	490 (59.3%)	209 (37.7%)	
Speaker region			
• Northeast	324 (39.2%)	239 (43.1%)	<0.001
• Southwest	179 (21.7%)	54 (9.8%)	
• West	148 (17.9%)	143 (25.8%)	
• Southeast	103 (12.5%)	64 (11.6%)	
• Midwest	64 (7.8%)	49 (8.8%)	
• International	8 (1.0%)	5 (0.9%)	
Lecture topics			
• Medical dermatology	159 (19.2%)	100 (18.1%)	<0.001
• Oncodermatology	76 (9.2%)	53 (9.6%)	
• Hail/nail disorders	9 (1.1%)	24 (4.3%)	
• Dermatopathology	121 (14.6%)	64 (11.6%)	
• Pediatric dermatology	10 (1.2%)	23 (4.2%)	
• Social	175 (21.2%)	85 (15.3%)	
• Patient cases	39 (4.7%)	11 (2.0%)	
• Other	237 (28.7%)	194 (35.0%)	
Lecture year			
• 2000-2005	2 (0.2%)	0 (0.0%)	<0.001
• 2006-2010	6 (0.7%)	2 (0.4%)	
• 2011-2015	67 (8.1%)	44 (7.9%)	
• 2016-2020	364 (44.1%)	184 (33.2%)	
• 2021-2025	387 (46.9%)	324 (58.5%)	

Female vs. male speakers more often lectured on pediatric dermatology (4.2% vs. 1.2%) and less often on quality improvement, innovation, and health systems (6.5% vs. 14.8%) (all $P<0.001$) (Figure 1). A greater proportion of female vs. male speakers were pediatric dermatologists (7.4% vs. 2.1%, $P<0.001$) (Table 1).

We showed an increase in representation of female dermatology GR speakers over the study period, with female vs. male speakers having lower academic rank and fewer publications. Similarly, in a cross-sectional study of 3806 cardiology GRs, female vs. male speakers less often held senior academic positions (37.9% vs. 45.3%, $P<0.001$) [3]. Furthermore, a review of dermatology journals reported that female editors comprised only 22% of editorial board positions [4].

We also identified a greater proportion of female vs. male speakers from the West and Northeast. Notably, a cross-sectional study including 11,911 dermatologists reported a tendency for female dermatologists to cluster in counties with more equal female to male earning ratios ($r=+0.11$, $P<0.001$), which may partially explain our findings [5]. In addition, a greater proportion of female vs. male speakers were pediatric dermatologists, and females spoke more frequently on pediatric dermatology, consistent with

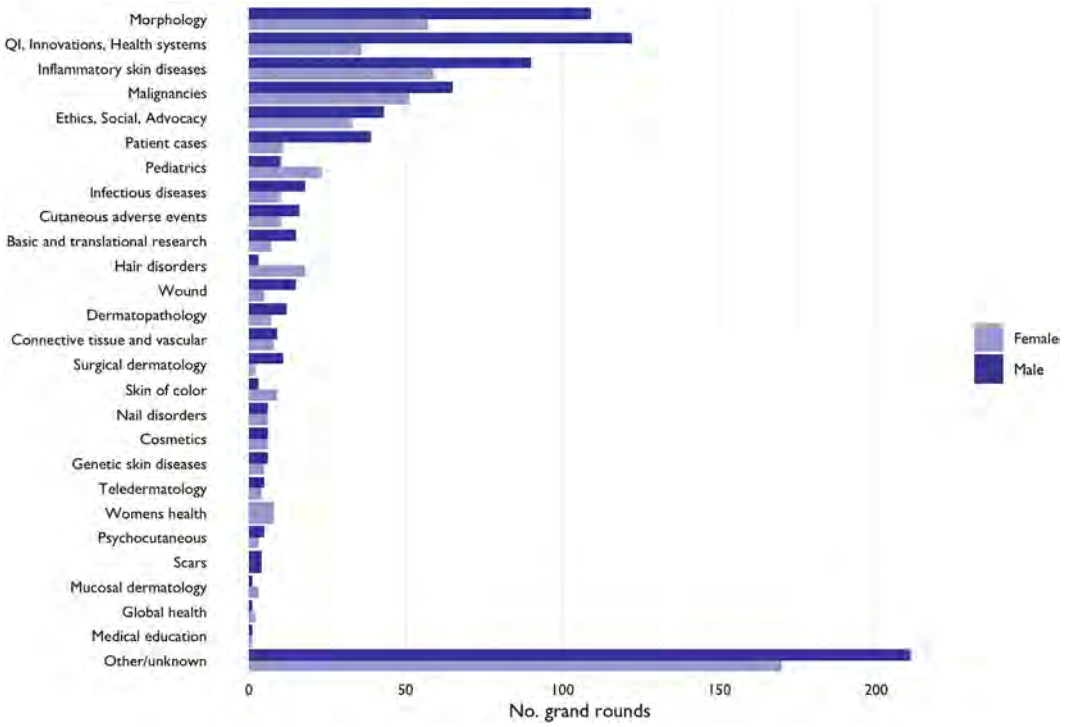


Figure 1. Dermatology Grand Rounds Stratified by Lecture Topic and Speaker Gender.

demographics that most pediatric dermatologists are female (76.8% in 2021) [6].

Limitations include incomplete access to public GR records and incomplete lecture topic data. Gender was determined by name and excluded nonbinary gender identities. We could not account for declined speaker invitations.

Conclusion

Gender diversity in GR speakers has improved over time, though there are persistent disparities by academic rank. As the number of female dermatology trainees increases, continued efforts are needed to increase speaking opportunities for women to advance in academic medicine.

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Dermatology Practical & Conceptual

Combination of Fractional CO_2 Laser and Imiquimod in Pigmented Basal Cell Carcinoma: Preliminary Clinical Observations

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Key words: Pigmented Basal Cell Carcinoma, Fractional CO_2 Laser, Imiquimod, Combination Therapy, Preliminary Clinical Outcomes

Citation: Ambrosio L, Di Lella G, Longo C, Pellacani G, Zalaudek I, Conforti C. Combination of Fractional CO2 Laser and Imiquimod in Pigmented Basal Cell Carcinoma: Preliminary Clinical Observations. *Dermatol Pract Concept*. 2025;15(4):5586. DOI: https://doi.org/10.5826/dpc.1504a5586

Accepted: March 15, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Basal cell carcinoma (BCC) is the most common cutaneous malignancy, with rising incidence rates. Typically presenting as a solitary or multiple lesions, surgical excision remains the gold standard treatment; however, non-surgical options are gaining traction, particularly for patients unable or unwilling to undergo surgery. Systemic immunotherapy, reserved for advanced BCC, often has limited use due to significant side effects. Among non-surgical treatments, imiquimod, a topical immunotherapeutic agent approved for superficial BCC, has demonstrated efficacy. Acting as an agonist of toll-like receptors 7 and 8, imiquimod stimulates innate immune cells, promoting adaptive immune responses through cytokine and chemokine production [1]. Physical modalities like cryotherapy are also approved for superficial BCC, but the use of conventional CO_2 lasers has been studied less, with few reports. Over the past decade, fractional CO_2 laser therapy has emerged as a novel technique to enhance topical drug absorption through laser-assisted drug delivery (LADD). This combination approach is particularly useful for deeper subtypes, such as pigmented and nodular BCC, where imiquimod's dermal penetration is insufficient. Beyond its facilitative role, laser therapy itself has demonstrated immunomodulatory properties, including local immune activation, tumor mass reduction, and the induction of resistance to tumor reinoculation [2]. Despite these advances, non-surgical therapies yield lower complete response rates than surgery, necessitating rigorous post-treatment monitoring. Dermoscopy is widely used for follow-up but

may present limitations, such as overlapping features with other lesions, and the presence of features like fine telangiectatic vessels or whitish areas may not definitively indicate tumor persistence [3]. Reflectance confocal microscopy (RCM), offering superior sensitivity and specificity, is more effective for detecting tumor persistence and recurrence in BCC and other non-melanoma skin cancers (NMSC) [4,5].

Case Presentation

We report the case of an 83-year-old female with a pigmented lesion on her left back diagnosed as pigmented BCC (pBCC) via dermoscopy and RCM. The patient refused surgery due to cosmetic concerns and accepted an off-label combination of fractional CO_2 laser and imiquimod cream. Dermoscopy revealed structureless gray-blue areas, arborizing vessels, and gray nests, while RCM identified basaloid islands in the deep dermis, peripheral clefting, palisading of nuclei, bright dendritic cells, and tortuous vessels (Figure 1). Fractional CO_2 laser was performed biweekly to create epidermal channels, facilitating imiquimod penetration into the dermis where BCC nests were located. Imiquimod was applied five days weekly for six weeks. At the 8-week follow-up, RCM revealed no residual BCC feature, demonstrating collagen fiber remodeling and the absence of basaloid islands. Excellent cosmetic results were achieved, with no scarring or discoloration. Follow-ups at 12, 24 weeks, and one year confirmed sustained remission, with no evidence of recurrence on RCM.

Conclusion

This case highlights the potential of laser immunotherapy as an effective, minimally invasive treatment for pBCC, offering robust clinical responses and excellent cosmetic outcomes [2]. Advanced imaging modalities like RCM are invaluable for monitoring, enabling early detection of recurrence. These findings underscore the need for further clinical

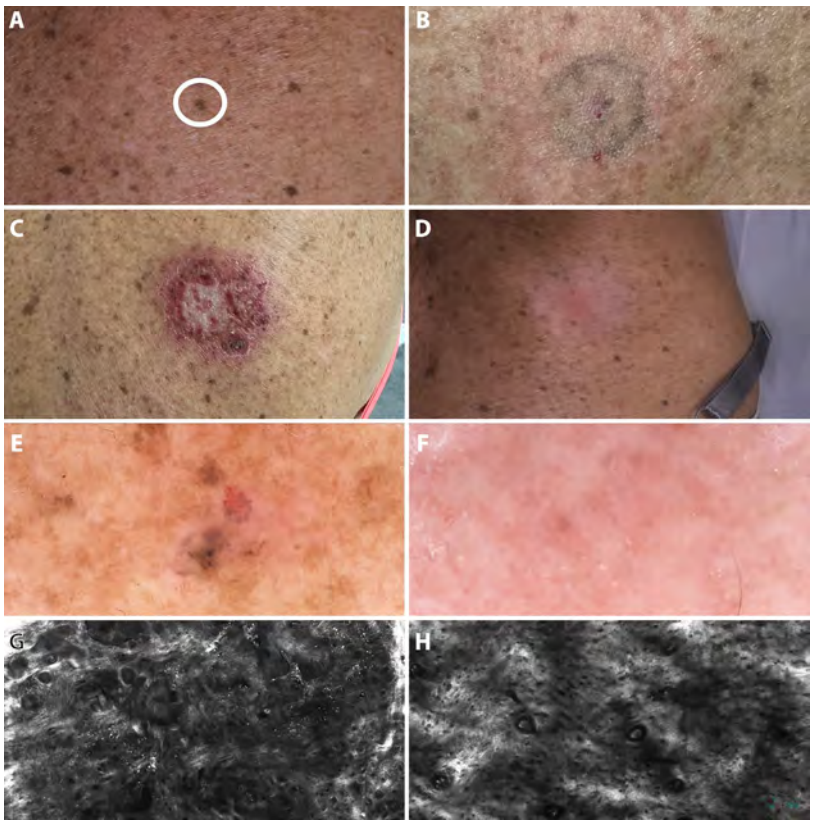


Figure 1. (A) Pigmented macular lesion on the right scapular region pre-treatment. (B) Right scapular area post-treatment with fractional CO2 laser. (C) Local inflammatory reaction in the right scapular area after imiquimod cream application. (D) Complete lesion resolution with minimal dyspigmentation 12 weeks after initiating laser-immunotherapy. (E) Pre-treatment dermoscopy showing a structureless area with gray-blue nests and arborizing telangiectatic vessels, consistent with BCC. (F) Dermoscopy at 12-week follow-up showing absence of BCC features. (G) Pre-treatment confocal microscopy (RCM) showing basaloid islands with peripheral clefting, palisading of nuclei, bright dendritic cells, and tortuous vessels. (H) RCM at 12-week follow-up showing significant collagen remodeling and absence of basaloid island.

trials to validate combined non-surgical therapies for BCC and NMSC, paving the way for personalized treatments that prioritize both efficacy and patient quality of life.

Ethical Approval: The study was a retrospective evaluation conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonization and Good Clinical Practice guidelines. Written informed consent was obtained from the patient to publish this paper.

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Dermatology Practical & Conceptual

Eruptive Clear Cell Acanthomas with Atypical Dermoscopic Features

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Key words: Clear Cell Acanthoma, Eruptive, Atypical Dermoscopic Features, Dermoscopy, Clinical Observations

Citation: Ambrosio L, Di Guardo A, Roberti V, Ascione A, Conforti C, Pellacani G. Eruptive Clear Cell Acanthomas With Atypical Dermoscopic Features. *Dermatol Pract Concept*. 2025;15(4):5595. DOI: https://doi.org/10.5826/dpc.1504a5595

Accepted: June 29, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Clear cell acanthoma (CCA) is a rare, benign epidermal tumor first described in 1962 by Degos et al. [1]. It is characterized by glycogen-containing epithelial cells and presents as dome-shaped, reddish papules or papule-nodules [2]. A rare eruptive form, with the presence of more than 30 lesions, has been described [3]. We report a case of eruptive clear cell acanthomas (ECCA) in a patient with a family history of multiple CCAs.

Case Presentation

A 67-year-old male presented to our dermatology clinic with multiple asymptomatic skin lesions of varying morphology with a gradual appearance over the preceding several years. His family history revealed that his brother had multiple CCAs excised years earlier. Clinical examination identified over 50 well-demarcated, bright red-to-brown papules and nodules, ranging from 2 to 10 mm, located primarily on the lower extremities and trunk. Some lesions exhibited a collarette of peripheral scaling. Dermoscopy of the suspected CCAs revealed dotted and globular vascular structures arranged in a "pearl necklace pattern," while others exhibited "wafer-like" crusty scales. Some lesions also exhibited non-specific features such as pink areas with irregularly distributed vessels (comma-shaped, linear irregular, or glomerular) accompanied by white-yellow scales (Figure 1). An incisional biopsy of three suspected lesions was performed. Histopathological examination revealed marked acanthosis composed of glycogen-rich clear cells (Figure 2). The papillary dermis displayed tortuous, ectatic vessels surrounded by a moderate lymphohistiocytic infiltrate. These findings, together with the patient's history and clinical presentation,

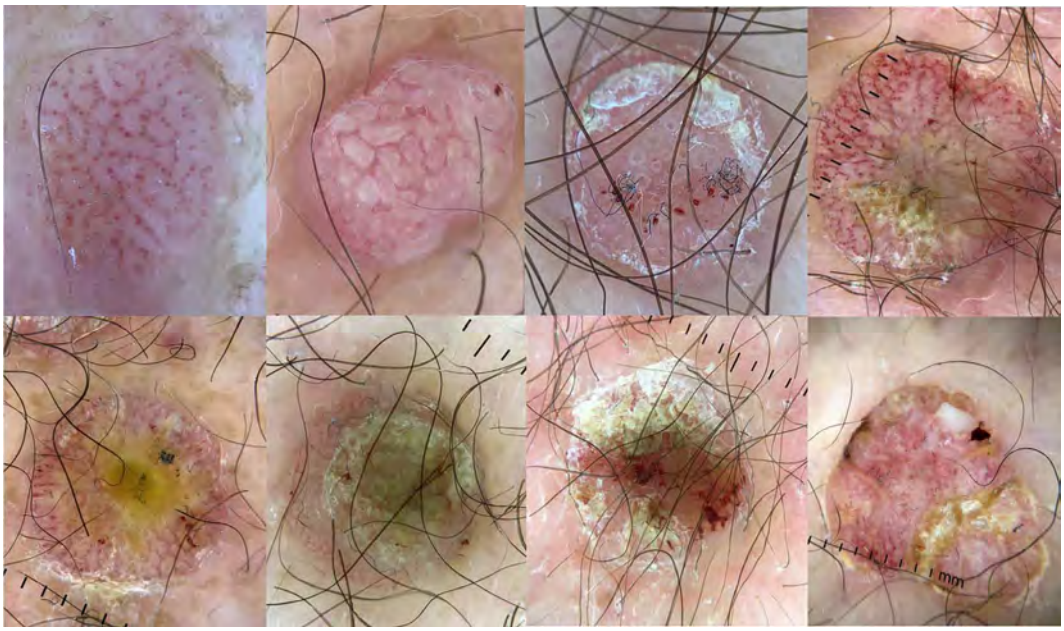


Figure 1. Dermoscopy on polarized mode of eight lesions suspected of being clear cell acanthomas. Some lesions exhibit the classic "pearl necklace" appearance, others display scaling and hyperkeratosis, while some show a pinkish coloration with dotted vessels.

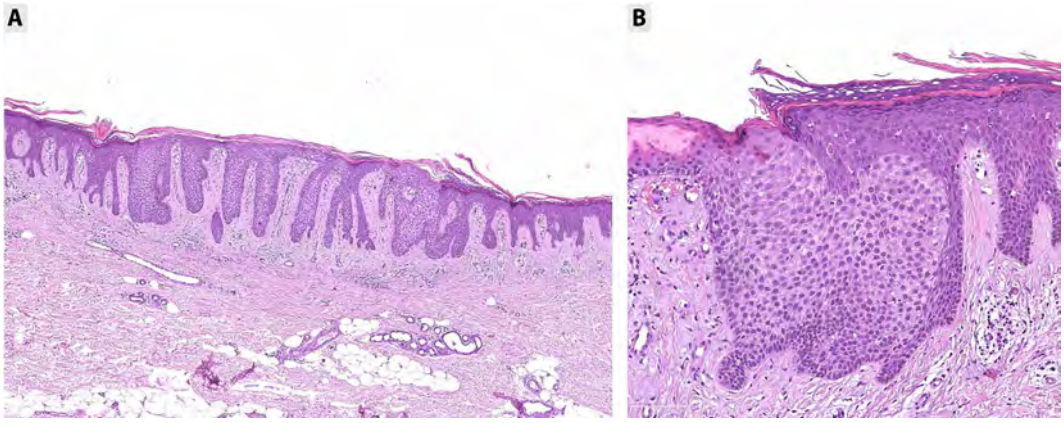


Figure 2. Histology shows the typical features of a clear cell acanthoma. The lesion is characterized by acanthosis, cells with clear cytoplasm, and by abrupt transition with the nearby normal epidermis. (A: H&E, original magnification 1.25x; B: H&E, original magnification 20x).

confirmed the diagnosis of ECCAs. Given the patient's extensive lesions and reluctance to undergo comprehensive treatment, only lesions with suspicious dermoscopic features were excised, and regular follow-up was arranged.

Conclusion

This case underscores the importance of dermoscopy in distinguishing CCAs from mimickers like basal cell carcinomas or squamous cell carcinomas. The characteristic "pearl necklace" vascular pattern and keratotic scales serve as helpful diagnostic clues, particularly in atypical or eruptive cases. Dermoscopy also aids in identifying lesions that warrant biopsy or excision, as in this case, where only lesions with suspicious dermoscopic features were surgically removed. Additionally, this report highlights a rare familial occurrence of ECCAs characterized by the appearance of multiple lesions in both the patient and his brother. Eruptive CCAs are an uncommon clinical variant, with more than 30 lesions often appearing progressively over time [4]. Additionally, this familial occurrence of ECCA raises questions about genetic predisposition or shared environmental triggers. While the exact pathogenesis of CCAs remains unclear, hypotheses include metabolic enzyme defects, localized inflammatory

responses, and epidermal glycogen accumulation [3-5]. Future research exploring genetic pathways and inflammatory markers may further clarify the mechanisms underlying familial and eruptive variants of CCA.

Ethical Approval: The study was a retrospective evaluation conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonization and Good Clinical Practice guidelines. Written informed consent was obtained from the patient to publish this paper.

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Dermatology Practical & Conceptual

Nevus Unius Lateris and Nevus Anemicus in a Patient With Neurofibromatosis Type 1: Noninvasive Imaging With Line-Field Confocal Optical Coherence Tomography and High-Resolution Video Dermoscopy

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Key words: Nevus Unius Lateris, Neurofibromatosis Type 1, LC-OCT, Nevus Anemicus, High-Resolution Video Dermoscopy

Citation: Falcinelli F, Calabrese L, Rubegni P, Tognetti L. Nevus Unius Lateris and Nevus Anemicus in a Patient With Neurofibromatosis Type 1: Noninvasive Imaging With Line-Field Confocal Optical Coherence Tomography and High-Resolution Video Dermoscopy. *Dermatol Pract Concept*. 2025;15(4):5633. DOI: https://doi.org/10.5826/dpc.1504a5633

Accepted: April 23, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Neurofibromatosis type 1 (NF1) is a multisystem autosomal dominant disorder that leads to abnormalities in the nervous and skeletal system; cutaneous hallmarks for diagnosis include café-au-lait macules, skinfold freckling, Lisch nodules, and dermal neurofibromas [1]. Nevus anemicus (NA) is a congenital vascular malformation appearing as a hypopigmented, pale, well-defined oval patch. Due to a focal increased sensitivity of blood vessels to catecholamines, NA does not become erythematous after scratching, heat, or cold, while reactive erythema appears in the surrounding skin [2]. NA is considered a specific diagnostic clue for NF1 [1,2]. Nevus unius lateris (NUL) is an extremely rare congenital hamartoma characterized by papillomatous, verrucous to velvety papules/plaques distributed in a linear blaschkoid pattern and affecting one half of the body, regarded as a systematized verrucous variant of epidermal nevus [3].

Case Presentation

A 13-year-old male presented due to the appearance in the preceding few of years of hypopigmented patches localized at the lumbar, sternal, and pectoral areas (Figure 1). He was diagnosed with neurofibromatosis type 1 (NF1) during childhood and skinfolds freckling and café-au-lait patches were present. Multiple verrucous brownish lesions arranged along the Blaschko lines, limited to the left half of the trunk,

were also visible. The lesions had increased in dimension and number over time in the previous 10 years and had been diagnosed as warts. The patient had cognitive retardation and learning disorders. The parents denied their consent to perform skin biopsies.



Figure 1. Patient's clinical appearance at presentation: many café-au-lait patches and macules were visible all over the trunk; hypopigmented patches are visible at lumbar (B, white circle), sternal, and pectoral areas (A, white squares), corresponding to nevus anemicus. Multiple verrucous brownish lesions arranged along the Blaschko lines and delimited bythe midline to the left half of the trunk corresponding to nevus unius lateris are also visible.

Noninvasive skin examination with line-field confocal optical coherence tomography (LC-OCT) and high-resolution videodermoscopy (HRVD) were performed on the verrucous lesions and on the hypopigmented patch, revealing hyperkeratosis and acanthosis in the former and normal epidermis with narrowed dermal vessels in the latter (Figure 2).

Conclusion

Based on clinical and imaging findings, a diagnosis of NUL-NA-NF1 association was posed.

HRVD (30x–100x magnification) and LC-OCT are two recently introduced new noninvasive imaging techniques which can provide high-resolution images of the skin on vertical and horizontal planes with cellular resolution, and they prove to be particularly helpful for doubtful lesions in the pediatric populations [4,5]. HRVD examination is rapid and offers more detailed information than standard dermoscopy (17x), both in contact and non-contact mode, and is very useful in the visualization of vascular structures [4]. LC-OCT takes both vertical/horizontal and 3D images in vivo in real time and to a depth of 500 µm and a FOV of 1.2 mm. The result is histological-like imaging of the explored skin area in gray-scale, like a "virtual biopsy" [4,5].

Dermoscopy of NA can highlight thinned blood vessels in the center, compensatory flare, and blending with the surrounding skin [4], while histology is usually normal [1,2].

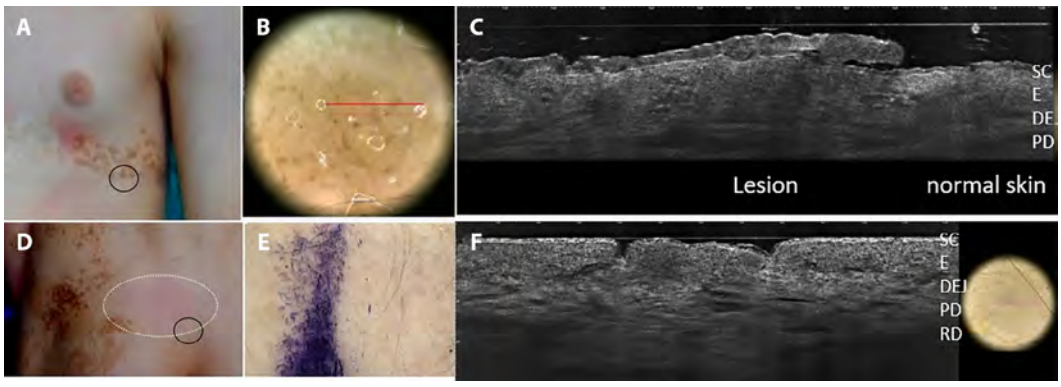


Figure 2. (A-C) Combined noninvasive imaging of nevus unius lateris performed at lesional margin on the submammary verrucous brownish lesions (A, black circle). (B) Polarized dermoscopy 20x highlights multiple brownish crusts and dots over a yellowish background. (C) corresponding vertical LC-OCT examination showed acanthosis with hyperkeratotic layer homogeneously distributed over the lesion surface. Dermal vessels appear as hyporeflective holes, normal in shape. (D-F) Combined noninvasive of lumbar nevus anemicus (white dotted circle) after moderate skin rubbing. (E) High-resolution video dermoscopy 30x and (F) polarized dermoscopy (20x) show both a pale hypopigmented skin appearance with signs of atrophy. (G) LC-OCT vertical examination taken at the lesional margin (D, black circle) identifies few thinned well-defined papillary vessels (v) and normal epidermis, with no sign of atrophy at the lesional site, while (F) normal-shaped vascular lacunae are seen in surrounding skin as hyporeflective dark holes. Abbreviations: SC, stratum corneum; E, epidermis; DEJ, dermal-epidermal junction; PD, papillary dermis; RD, reticular dermis; v, dermal vessels. Note: The red line inside the dermoscopic round frames corresponds to the exact point of LC-OCT examination (i.e., length of the LC-OCT frame).

Dermoscopic features of NUL include large brown circles on a brownish background; hyperkeratosis, acanthosis, and papillomatosis are detected by histopathology [3] as well as by LC-OCT [4,5], along with possible focal increase in basal melanin.

The combined HRVD and LC-OCT examination at multiple lesional sites oriented us toward the diagnostic suspicion of an NUL-NA-NF1 association. This high-resolution imaging also allowed us to respect the parents' wishes to avoid multiple skin biopsies with their consequent aesthetic impact and scarring in a fragile patient.

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Dermatology Practical & Conceptual

Line-Field Confocal Optical Coherence Tomography in Merkel Cell Carcinoma and Histopathological Correlation

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Key words: Merkel cell carcinoma, LC-OCT, Noninvasive diagnostic techniques, Skin cancer

Citation: Greco ME, Di Guardo A, Ascione A, Soda G, Pellacani G, Persechino F. Line-Field Confocal Optical Coherence Tomography in Merkel Cell Carcinoma and Histopathological Correlation. *Dermatol Pract Concept*. 2025;15(4):5647. DOI: https://doi.org/10.5826/dpc.1504a5647

Accepted: February 20, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Merkel cell carcinoma (MCC) is an uncommon and aggressive skin cancer that mainly affects the elderly. Clinically, MCC usually appears as a fast exophytic growing, often painful, cherry-red nodule that mostly affects sun-damaged areas, particularly the head and neck region [1]. Pathogenetic factors such as exposure to ultraviolet radiation may contribute to tumor development. MCC has also been associated with immunosuppression and the development of other tumors or virus [1]. Line-field confocal optical coherence tomography (LC-OCT) is a noninvasive diagnostic technique able to provide, through vertical and horizontal sections, real-time in vivo images of the epidermis and upper dermis, reaching nearly histological resolution. LC-OCT improves the technological properties of reflectance confocal microscopy (RCM) and of optical coherence tomography (OCT). LC-OCT has found widespread use in the noninvasive diagnosis of skin tumors and inflammatory dermatological conditions [2].

Case Presentation+ This correspondence describes Merkel cell carcinoma (MCC) in a 58-year-old male kidney-transplant recipient on maintenance immunosuppression. He was referred to our skin cancer unit for a rapidly enlarging, erythematous scalp nodule measuring 2.5 × 3.0 × 2.0 cm. (Figures 1A and B).

Usually, the diagnosis of MCC is based on clinical dermoscopic examination and excisional biopsy for histopathological examination. However, a thorough diagnosis may be difficult in early-stage disease and/or when clinical features are yet to be defined, potentially delaying appropriate therapeutic decisions. The present study aimed to be one of the first articles to

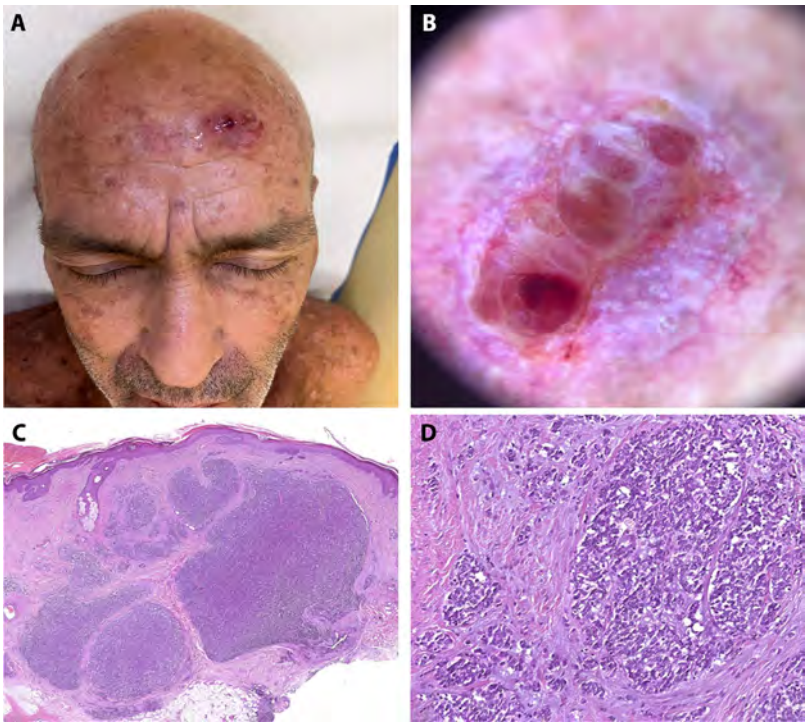


Figure 1. A. A) Clinical view reveals red nodule on the head. B) Dermoscopy image (magnification 10x) shows a reddish background with arborized vessels and a crystalline structure, central serous crust, surrounding whitish areas. C) Scanning magnification of the lesion shows a dermal, nodular, dense proliferation of basophilic cells. The lesion spares the epidermis and shows mostly expansile margins (hematoxylin and eosin, 2.5x magnification). D) At higher magnification, the lesion is composed of medium-sized monomorphic cells with scant cytoplasm and no nucleoli (hematoxylin and eosin, 20x magnification).

evaluate the new microinvasive investigation techniques in dermatology and to compare them with histological imaging with a view to the earliest possible diagnosis. Histologically, MCC is typically characterized as a monomorphous small round blue cell tumor with round or oval nuclei, finely dispersed chromatin, indistinct nucleoli, and scant cytoplasm (Figures 1C and D).

Immunohistochemistry is necessary for histopathological confirmation of MCC in order to distinguish it from other small cell neoplasms, including lymphoma, melanoma, and metastatic small-cell lung cancer. Molecular markers diagnostic for MCC include neuroendocrine markers (chromogranin A, synaptophysin, CD56), cytokeratin 20 (dot-like pattern), neurofilament, and MCPyV large T antigen (LT). Negative TTF1, S-100, and leukocyte common antigen (LCA) can be used to differentiate MCC from small-cell lung cancer, melanoma, and lymphoma, respectively [2]. LC-OCT images demonstrate hyporeflective nests of monomorphous neuroendocrine cells outlined by collagen septa, with occasional bright cells within the nests. These features, visible in both horizontal and vertical LC-OCT sections, closely match the histological structure of MCC. The epidermis appears regular, with a dermo-epidermal junction flattened by underlying dermal proliferation. MCC presents distinct alternations of white lines and dark spaces, differentiating it from other lesions, as shown in Figures 2A and B.

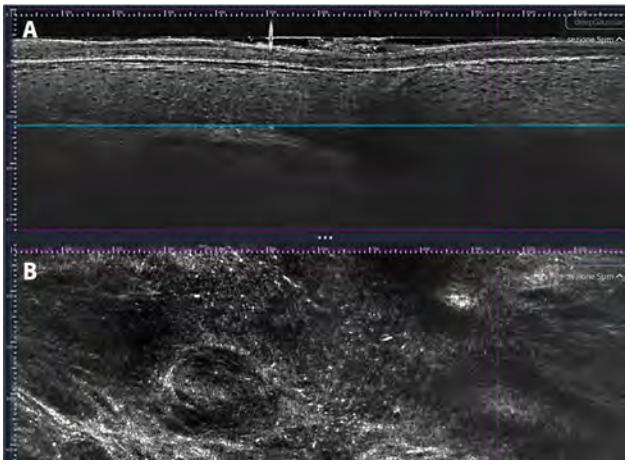


Figure 2. A) LC-OCT examination shows a preserved normal epidermis, dermal-epidermal junction slightly flattened but clearly visible. B) Detail of large central nest, increased cellularity, and collagen fiber septa.

Conclusion

On this basis, the aim of this study was to correlate LC-OCT with corresponding histopathological and dermoscopic clues. LC-OCT's ability to provide high cellular resolution, depth, and 3D views [3,4] makes it an effective tool for distinguishing

MCC from clinically similar skin cancers such as squamous cell carcinoma or basal cell carcinoma and amelanotic melanoma. In conclusion, LC-OCT proved to be a valuable noninvasive diagnostic tool capable of detecting key changes associated with MCC [5,6]. These findings suggest that it may complement traditional clinical diagnostic approaches. In addition, the ability to better characterize this disease could improve clinical management and therapeutic decision-making for patients with MCC. Further multicenter studies on this rare tumor are warranted to further explore LC-OCT specific morphology and the value of MCC features in clinical practice.

Ethics Statement: The patient provided consent for publication.

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Dermatology Practical & Conceptual

Langerhans Cell Histiocytosis and Mastocytosis: A Rare Association

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Key words: Langerhans cell histiocytosis, Mastocytosis, Rare association, Case report, Clinical features

Citation: Boisseau R, Scaramuzzino L, Bosphore G, Ly KH. Langerhans Cell Histiocytosis and Mastocytosis: A Rare Association. *Dermatol Pract Concept*. 2025;15(4):5660. DOI: https://doi.org/10.5826/dpc.1504a5660

Accepted: April 6, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Histiocytoses are rare disorders characterized by dysfunction or proliferation of mononuclear phagocytic system cells. These disorders can affect any organ, with the skeleton, skin, and pituitary gland most commonly involved [1]. Mastocytoses are marked by the accumulation of clonal mast cells in both the skin and internal organs, including the bone marrow, spleen, lymph nodes, liver, and gastrointestinal tract [2]. Therefore, histiocytoses and mastocytoses are distinct clonal diseases, with no documented overlap.

Case Presentation

A 25-year-old male patient presented to the emergency department (ED) in October 2023 with progressive right-sided facial swelling over two months, which had recently prevented him from opening his right eye (Figure 1). A computed tomography (CT) scan identified a 2-cm lytic lesion in the frontal bone (Figure 2). The patient remained in good health. Two days following his ED visit, the patient attended the Dermatology Department. Examination revealed pigmented macules on his limbs, abdomen, and lower back, which he reported having since childhood. Darier's sign was positive. A skin biopsy indicated cutaneous mastocytosis, and serum tryptase levels were 1.5 times above normal. Molecular analysis detected a KIT D816V mutation in both blood and skin samples. In December 2023, curettage of the frontal bone lesion revealed Langerhans cell histiocytosis (LCH), confirmed by immunohistochemistry and molecular testing for a *BRAF V600E* mutation. Pituitary function tests were normal. A chest CT scan showed multiple bilateral punched-out nodules in the upper lung lobes and scattered centrilobular micronodules, suggesting early pulmonary histiocytosis. By June 2024, post-surgical assessments showed resolved facial swelling. Magnetic resonance imaging (MRI) confirmed the stability of the right frontal bone lesion. A follow-up chest CT indicated resolution of the pulmonary nodules. All laboratory results were normal, except for elevated tryptase levels. The patient quit smoking and remained in excellent health. In November 2024, repeat MRI of the facial mass confirmed the stability of the frontal lesion. Based on these findings, treatment for both conditions was deemed unnecessary. A biannual follow-up plan was established.



Figure 1. Progressive right-sided facial swelling over two months.

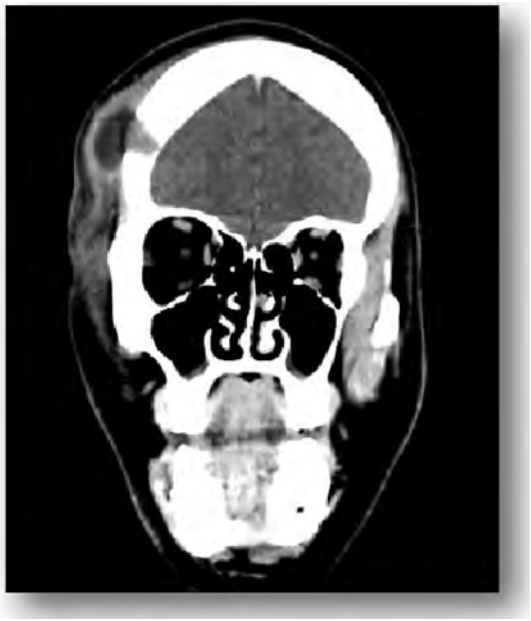


Figure 2. CT scan identifying a 2-cm lytic lesion in the frontal bone.

Conclusion

LCH exhibits a broad spectrum of severity. Treatment strategies are determined by the extent of disease, with localized single-system disease often managed through local therapy or observation, while multisystemic disease necessitates systemic treatment. This approach has led to improved 5-year survival rates of 90% in children and 70% in adults [3]. Typically beginning in early childhood, pediatric mastocytosis primarily affects the skin and regresses in ~75% of cases within six years [4]. However, the lesions can persist. Aggressive forms are symptomatic from the onset [4]. Histiocytoses and mastocytoses have occasionally been reported to co-occur [5]. However, the specific coexistence of mastocytosis and LCH is exceptional. The literature records only a single case involving a young child, who presented with LCH affecting the eye and skin at 15 days old, resolving within two months, followed by the emergence of two mastocytomas [5]. The coexistence of LCH and mastocytosis in adults remains virtually undocumented. Both diseases in our patient currently do not require treatment. However, as lesions persist, regular follow-up remains essential.

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Dermatology Practical & Conceptual

Betamethasone-Calcipotriol Foam: A Promising Treatment for Erythema Annulare Centrifugum With LC-OCT Monitoring

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Key words: Betamethasone-Calcipotriol, Erythema Annulare Centrifugum, LC-OCT

Citation: Giorgio CM, Licata G, Di Brizzi EV, Moscarella E, Argenziano G, Tancredi V. Betamethasone-Calcipotriol Foam: A Promising Treatment for Erythema Annulare Centrifugum With LC-OCT Monitoring. *Dermatol Pract Concept*. 2025;15(4):5695. DOI: https://doi.org/10.5826/dpc.1504a5695

Accepted: April 15, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Erythema annulare centrifugum (EAC) is a rare inflammatory skin disorder characterized by annular erythematous lesions that expand centrifugally with central clearing. Effective treatment is challenging, particularly when the cause is idiopathic or resistant to conventional therapies [1]. In this case series, we explored the use of calcipotriol-betamethasone foam in five patients with clinically and histologically confirmed EAC, employing line-field confocal optical coherence tomography (LC-OCT) to monitor treatment response. While corticosteroids are the standard of care for EAC, prolonged use risks side effects such as skin atrophy. The combination of calcipotriol and betamethasone addresses these concerns by combining anti-inflammatory and antiproliferative effects, with calcipotriol potentially counteracting steroid-induced atrophy. The foam formulation enhances patient adherence by facilitating ease of application and absorption [2]. Histologically, EAC is defined by a superficial perivascular lymphocytic infiltrate, variable degree of spongiosis, and dilated dermal vessels. LC-OCT offers a noninvasive method to visualize these features in vivo, providing valuable insights into disease activity and treatment outcomes.

Case Presentation

Five patients (three females and two males) aged between 30 and 55 years were treated with this drug combination. All patients presented with moderate-to-severe histologically confirmed EAC that had persisted from six months to four years and who were refractory to prior corticosteroid treatments. In fact, after initial improvement with two months of topical steroid daily, all cases showed rapid occurrence after steroid withdrawal. EAC was considered

idiopathic in all cases, with no clinical and biochemistry associated abnormality. The treatment protocol consisted of calcipotriol-betamethasone foam applied once daily for two months, followed by twice-weekly application for four additional months. Patients were clinically assessed at eight weeks and at six months. At eight weeks, three of the five patients achieved complete resolution of lesions (Figure 1), while the other two showed significant improvement. This clinical outcome was maintained after six months. At baseline, LC-OCT imaging of active lesion borders showed mild epidermal hyperplasia with spongiosis and dilated superficial dermal vessels surrounded by perivascular infiltrates (Figure 2A). LC-OCT findings corroborated the clinical outcomes, highlighting the resolution of pathological features in successfully treated cases (Figure 2B).

The findings of this case series suggest that calcipotriol-betamethasone foam is a safe and effective treatment for EAC, providing rapid improvement in inflammatory and epidermal changes. The combination targets the underlying pathogenesis of EAC while reducing the risks associated with prolonged corticosteroid use.

LC-OCT imaging was instrumental in objectively evaluating disease activity and treatment efficacy. Baseline imaging revealed hallmark features of active EAC, including spongiosis, dilated vessels, and dermal infiltrates, which progressively resolved or improved during treatment. This real-time monitoring capability provides clinicians with a powerful tool to guide therapeutic decisions and track disease progression or remission.

Conclusion

Calcipotriol-betamethasone foam, combined with LC-OCT monitoring, offers a novel approach to managing EAC. The small number of patients, open study, no control group, and limited follow-up are the main limitations of our report.



Figure 1. Clinical involvement of the forearm in a 48-year-old male. (A) Annular, erythematous, and scaling plaques are well observed. (B) After six months, complete resolution was achieved.

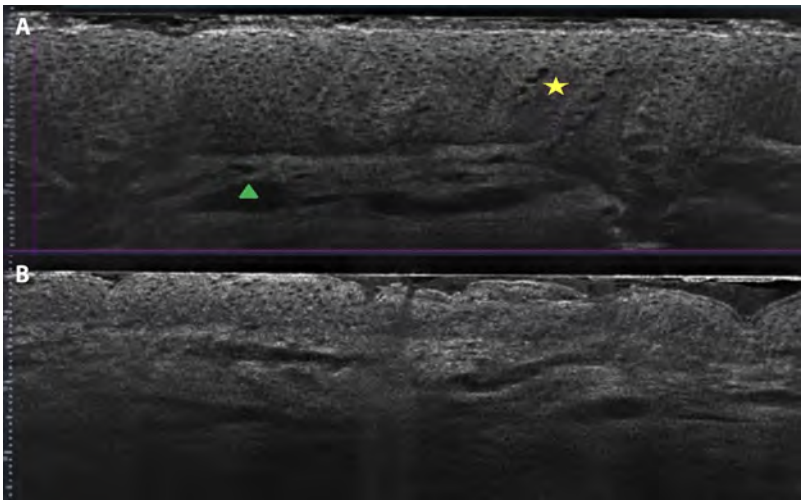


Figure 2. LC-OCT findings before and after treatment with calcipotriol-betamethasone foam in a representative patient with EAC. LC-OCT image of the active lesion border before treatment. (A) Evident spongiosis (hyporeflective spaces within the epidermis, yellow star), dilated dermal vessels (dark deep spaces, green triangle), and perivascular infiltrate are present. The epidermis shows mild hyperplasia with architectural disruption. (B) LC-OCT image of the same lesion after eight weeks of daily application of calcipotriol-betamethasone foam. Normalization of epidermal structure is observed, with resolution of spongiosis and restoration of dermal architecture with mild dilated vessels.

Thus, larger studies are warranted to confirm these findings and further explore the role of LC-OCT in optimizing treatment protocols for inflammatory skin disorders.

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Dermatology Practical & Conceptual

Treatment Strategies for Atopic Dermatitis in Adults Who Exhibit Non-Allergic Comorbidities: Real-Life Data from a Tertiary Greek Hospital

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Key words: Atopic Dermatitis, Comorbidities, Treatment, Real life

Citation: Paschou E, Lallas A, Bakirtzi K, Kiritsi D, Vakirlis E, Sotiriou E. Treatment Strategies for Atopic Dermatitis in Adults Who Exhibit Non-Allergic Comorbidities: Real-Life Data from a Tertiary Greek Hospital. *Dermatol Pract Concept*. 2025;15(4):5766. DOI: https://doi.org/10.5826/dpc.1504a5766

Accepted: Sptember 8, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease characterized by relapsing eczema with intense pruritus, which greatly impacts patients' quality of life [1].While associations between AD and allergic conditions have been recognized for decades, numerous non-allergic comorbidities have also been identified [2].However, treatment guidelines lack high-quality evidence regarding therapeutic algorithms which consider these associations [3]. This study presents real-life treatment data for selected AD comorbidities.

Findings

A retrospective observational study was conducted at the First Department of Dermatology and Venereology of Aristotle University, Greece from April 2022 to May 2024 in compliance with the Declaration of Helsinki. This study was approved by the Bioethics Committee (Registry number: 3.651/18.01.2022). Written informed consent was obtained from adult participants (≥18 years) with clinically diagnosed moderate-to-severe AD according to Hanifin and Rajka criteria who had at least one non-allergic comorbidity and complete electronic medical records available for the study period. Non-qualifying patients were excluded. Data were available for 50 patients, 27 (54.0%) males and 23 (46.0%) females, with a mean age of 39 years. Patients were grouped according to their comorbid condition. The first group consisted of those who exhibited metabolic and cardiovascular diseases (CVD), 28 patients (56.0%) (obesity N=10, dyslipidemia N=5, type 2 diabetes N=2, hypertension N=6, peripheral and coronary artery disease N=3, deep vein thrombosis N=1, atrial fibrillation N=1). The second

group had immune-related disorders: 19 patients (38.0%) (alopecia areata N= 8, vitiligo N=2, chronic urticaria N=2, rheumatoid arthritis N=4, systemic lupus erythematosus N=1, psoriasis N=1, inflammatory bowel disease N=1), and the third had bone health conditions: three patients (6.0%) (osteoporosis N=2, osteoporotic bone fractures N=1). Treatment decisions were made using SCORAD (Scoring Atopic Dermatitis), EASI (Eczema Area and Severity Index), and IGA (Investigator's Global Assessment scale) scoring systems, considering age, sex, and comorbidities through multidisciplinary consultation when appropriate. For moderate-to-severe disease, phototherapy, predominantly narrowband UVB, and less frequently UVA1, administered three times per week for six months, was the most commonly used treatment in CVD patients. For relapsing disease, dupilumab was chosen due to its safety profile. For immune-mediated disorders, biologics and small molecules were prescribed more frequently. In the bone health group, systemic corticosteroids and cyclosporine were excluded due to negative bone effects. Targeted therapies were initiated more frequently. Systematic agents are summarized in Table 1. All treatments were combined with topical mild-to-moderate corticosteroids. No serious adverse event was identified during the 26-month follow-up.

Conclusion

Our findings align with recent epidemiological studies demonstrating high prevalence of CVD and autoimmune comorbidities in AD patients, reflecting AD's systemic inflammatory nature [4]. Dermatologists' choices in our study are greatly dependent on disease activity and comorbid conditions. While international recommendations emphasize systemic immunosuppression for severe AD, our real-world data show a cautious, personalized approach in CVD patients. The predominant use of phototherapy reflects safety considerations in clinical practice. The use of JAK inhibitors for autoimmune conditions in our cohort is consistent with recommendations [5]. Our preference for dupilumab across all comorbidity groups aligns with real-world effectiveness studies regarding cardiovascular safety [6]. Future studies are needed to establish evidence-based treatment algorithms for AD patients with specific comorbidity profiles.

Ethical Approval: This study was approved by the Bioethics Committee of the Medical School of Aristotle University of Thessaloniki, Greece (Registry number: 3.651/18.01.2022). The research process complied with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Table 1. Treatment Choices for Patients Exhibiting Non-Allergic Comorbidities.

Treatment	Dose	Metabolic and cardiovascular comorbidities Percentage %[a] (N)[b]	Immune-mediated comorbidities Percentage % (N)	Osteoporosis Percentage % (N)
Phototherapy				
NB-UVB[c]	2 or 3 times per week	57.1% (16)		
UVA1[d]	2 or 3 times per week	17.8% (5)		
Systemics				
Corticosteroids	0.35-1 mg/kg per day		10.5% (2)	
Cyclosporine (CyA)	2.5-5 mg/kg per day	3.6% (1)	21.1% (4)	
Methotrexate (MTX)	5-15 mg per week	3.6% (1)		
Azathioprine (AZA)	1-3 mg/kg per day		5.3% (1)	
Dupilumab	600 mg s.c day 1 followed by 300 mg Q2W	17.9% (5)	10.5% (2)	66.7% (2)
Baricitinib	4 mg or 2mg per day		26.3% (5)	
Upadacitinib	30 mg or 15 mg per day		26.3% (5)	
Abrocitinib	200 mg or 100 mg per day			33.3% (1)

a. Percentage (%): percentage of patients receiving this treatment from each group; b. (N): number of patients receiving this treatment.; c. NB-UVB: narrow-band ultraviolet B.; d. UVA1: ultraviolet A1.

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Dermatology Practical & Conceptual

Colchicine-Responsive Granuloma Faciale: A Case Report with Dermoscopic Clues

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Key words: Colchicine, Dermoscopy, Granuloma faciale

Citation: Kılıç Manavlı E, Gürel G, Belen Aydoğmuş B, Aksu D. Colchicine-Responsive Granuloma Faciale: A Case Report with Dermoscopic Clues. *Dermatol Pract Concept*. 2025;15(4):5778. DOI: https://doi.org/10.5826/dpc.1504a5778

Accepted: April 22, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Granuloma faciale (GF) is a rare, benign inflammatory skin disorder characterized by red-brown or purplish papules, plaques, or nodules generally on the face [1]. The lesions are often asymptomatic and appear in middle-aged white males. The exact cause of GF is unknown. Histopathologically, GF presents with mixed dermal inflammatory infiltration, grenz zone, and vascular damage [2]. Dermoscopy has recently gained importance as a noninvasive diagnostic tool [3]. GF lesions are chronic, and spontaneous healing is rare. The disease is very difficult to treat, and response to treatment is variable [1]. This case report presents a GF case diagnosed via dermoscopy and histopathology, successfully treated with colchicine.

Case Presentation

A 62-year-old male presented with a five-month history of a rash on the nose. He had previously received treatment for rosacea with topical metronidazole and sodium sulfacetamide without improvement. The patient had no systemic disease. Laboratory tests were normal, and the Venereal Disease Research Laboratory (VDRL) test was negative. At dermatological examination, an infiltrated plaque with mild violaceous erythema at the border with scales was observed on the nose. Dermoscopic examination (Dermlite DL5; 3 Gen; polarized, 10x) revealed a red-brown background with yellow follicular openings, irregular white lines, linear branching vessels, brown dots/globules, and occasional scales. The histopathology revealed mixed-type inflammatory cell infiltration involving the entire dermis, with a grenz zone between the epidermis and dermis (Figures 1A–C).

The diagnosis of GF was confirmed clinically, dermoscopically, and histopathologically. The patient was treated with topical steroid, tacrolimus, and systemic colchicine (twice a day). After one month, the lesion began to regress, and by the seventh month, significant improvement was observed (Figure 2). No recurrence was observed during follow-up, and the patient remains under monitoring.

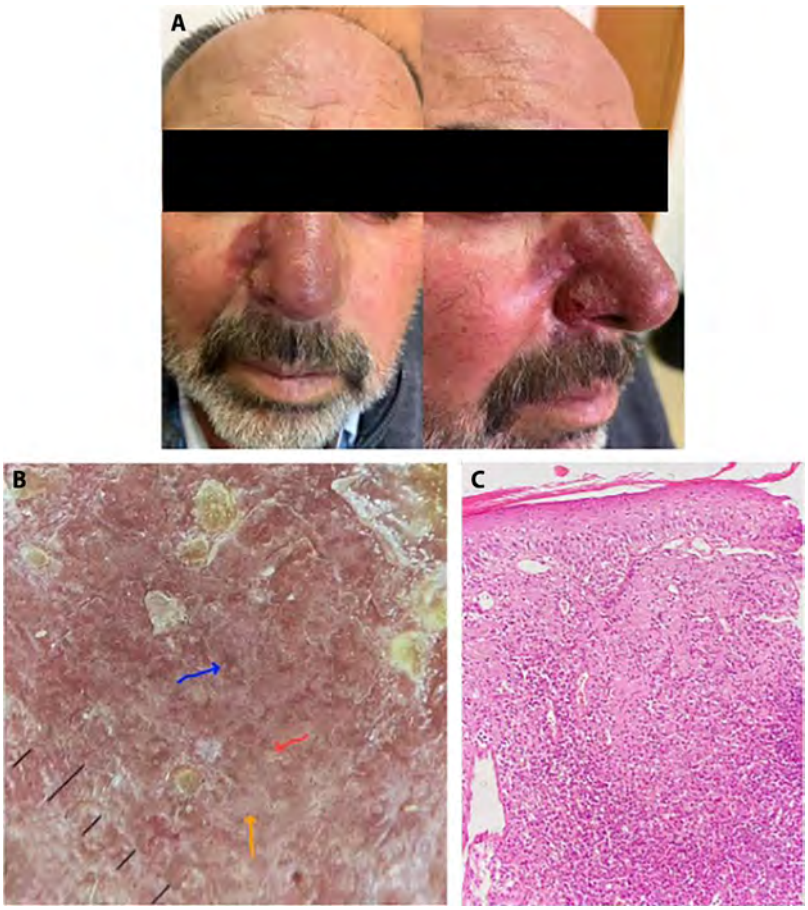


Figure 1. (A) An infiltrated plaque with sharp borders and mild violaceous erythema extending from the right nasal ala to the dorsum of the nose, with desquamation at the edges. (B) Dermoscopic examination: dilated yellow follicles (red arrow) on an erythematous-brown background, scattered brown dots and globules (blue arrow), and irregular white lines (orange arrow). (C) Histopathological examination; widespread inflammation in the dermis rich in eosinophils with histiocytes arranged in a palisading pattern in the upper dermis and plasma cells, separated from the epidermis by a narrow grenz zone (H&E 200x).



Figure 2. Significant regression of the lesions at 7th month of colchicine treatment.

Conclusions

A skin biopsy is necessary to differentiate GF from conditions like sarcoidosis, discoid lupus erythematosus, and cutaneous lymphoma [2]. Dermoscopy is a valuable, noninvasive method for diagnosing GF and distinguishing it from other similar conditions [3]. In 2012, Caldarola et al. described dermoscopic features of GF [4]. Typical dermoscopic findings for GF include a red-yellow-brown background, scattered brown dots and globules, mildly branching linear vessels, perifollicular white halos, and dilated follicular openings. These findings correlate with histopathology, such as hemosiderin deposition and dermal infiltration [3]. The dermoscopic characteristics of our case were consistent with the literature. Additionally, the scale was more prominent.

GF is usually asymptomatic but can lead to cosmetic concerns due to its chronic course. Common treatment options include topical tacrolimus and corticosteroids, although treatment can sometimes be challenging. Other treatments

reported include intralesional and systemic corticosteroids, topical pimecrolimus, dapsone, hydroxychloroquine, clofazimine, TNF-α inhibitors, laser therapy, cryotherapy, and surgery [1]. Colchicine, though rarely used, has shown promise in treating GF [5]; it inhibits polymorphonuclear leukocyte chemotaxis, prevents lysosome formation, and stabilizes lysosomal membranes, mimicking the anti-inflammatory effects of dapsone [6]. Given its effectiveness and reliability, colchicine could be considered a treatment option for GF.

This case contributes to the literature by providing clinical, dermoscopic, and histopathological findings of GF treated with colchicine.

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Dermatology Practical & Conceptual

One Clue, Two Outcomes: Benign vs Malignant Through Dermoscopy

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Key words: Pyogenic granuloma, Nodular melanoma, Dermoscopy

Citation: Girštautė P, Virpšaitė M, Gylienė I, Jokubaitė J, Raudonis T. One Clue, Two Outcomes: Benign vs Malignant Through Dermoscopy. *Dermatol Pract Concept*. 2025;15(4):5780. DOI: https://doi.org/10.5826/dpc.1504a5780

Accepted: April 13, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Pyogenic granuloma is a common benign vascular lesion that can clinically and dermoscopically imitate melanoma and other tumors [1]. In our case, pyogenic granuloma and nodular melanoma exhibited dermoscopic similarities. Some dermoscopic patterns, which include characteristics such as a yellow collarette, a reddish homogenous area, and the presence of white rail lines, can aid in diagnosing pyogenic granuloma [12]. Even though pyogenic granuloma is benign, histology is still necessary, especially in cases where vascular structures are present, as melanoma cannot be ruled out [1,3].

Case Presentation

In this paper, we present two cases with outstanding similarities in clinical and dermoscopic presentation but contrasting histological findings.

The first case involves a 25-year-old female who presented with a rapidly growing, bleeding lesion on her back. The lesion, approximately 1.2 cm in diameter, appeared 2.5 weeks before her consultation (Figure 1A). Upon physical examination, it was identified as an exophytic, red, nodular lesion. The patient denied any history of trauma, sunburns, or a family history of skin cancer. Dermoscopy showed a reddish homogeneous area, the presence of polymorphic vessels, and a characteristic yellow collarette enveloping the periphery (Figure 1B). The lesion was surgically excised, and histopathological analysis confirmed the diagnosis of pyogenic granuloma. The presence of the yellow collarette, which is indicative of hyperplastic epithelium, was crucial in suggesting the benign nature in this case.

The second case describes a 44-year-old female who presented with a similarly fast-growing, bleeding lesion on her back. The lesion, approximately 2 cm in diameter, had been increasing in size for three months (Figure 2A). Like the first case, the patient had no notable family or personal history of skin cancer or risk factors like severe sunburns during childhood. On dermoscopic examination, the lesion exhibited erythema and polymorphic vessels, closely resembling the findings in the first patient (Figure 2B). The lesion was

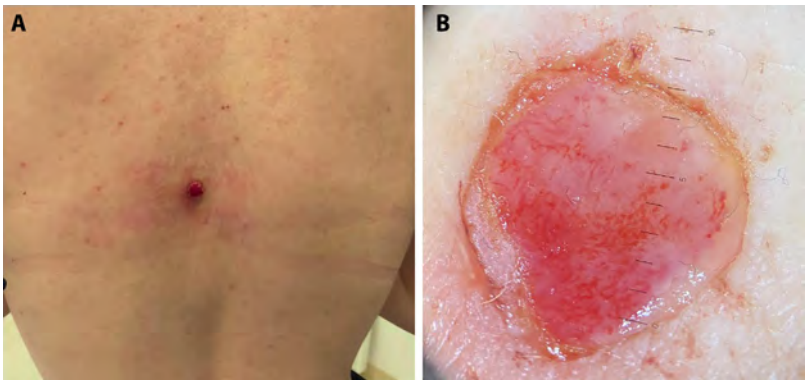


Figure 1. An exophytic, bleeding nodular lesion on the back of a 25-year-old female (A), polymorphic vessels, erythema and a yellow collarette (B).

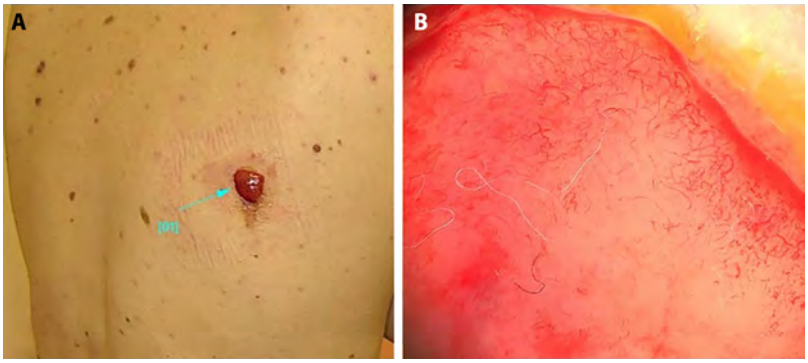


Figure 2. An erythematous, ulcerated nodular lesion located on the back of a 44-year-old female (A), polymorphic vessels and erythema (B).

excised and histologically confirmed as an ulcerated nodular melanoma, pT3b, Breslow thickness 3.8 mm, Clark level III. The presence of vascular structures in a red tumor resembling pyogenic granuloma indicates that melanoma must be excluded and highlights the need for prompt histological confirmation in similar cases [1,3].

Conclusion

Although pyogenic granuloma and nodular melanoma can exhibit overlapping clinical and dermoscopic characteristics, subtle differences, such as the presence of a yellow collarette, can help differentiate them. Still, the yellow collarette alone cannot be considered a tell-tale sign that the lesion is benign, as it can also be seen in melanomas and other skin malignancies [1,2]. Given the potential for melanoma, histological examination remains crucial when vascular structures are present in rapidly growing lesions [3].

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Dermatology Practical & Conceptual

A Case of Infective Endocarditis Presenting with Skin Findings

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Key words: Infective Endocarditis, Janeway Lesions, Skin Findings

Citation: Balik ZB, Akoglu G. A Case of Infective Endocarditis presenting with Skin Findings. *Dermatol Pract Concept*. 2025;15(4):5816. DOI: https://doi.org/10.5826/dpc.1504a5816

Accepted: April 22, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

This case is shared to remind dermatologists of dermatological findings in rapid and accurate diagnosis and the importance of Janeway lesions in the diagnosis of infective endocarditis (IE) and to contribute to the literature.

Case Presentation

A 40-year-old male presented to the emergency department with complaints of weakness, diffuse muscle aches, yellowing of the eyes, and burning during urination for a week. Shortly before his admission, he had noticed non-painful discoloration of the big toe of the left foot, the third finger nail of the right hand, the distal tips of the fingers, and bilateral palmar areas. Cardiovascular and respiratory system examination was normal. He had no fever. Blood pressure, pulse, and O_2 saturation were normal. WBC:20.29x10^3 cells/µL, PLT:60x10^3 cells/µL were measured as abnormal findings. Elevated liver enzymes (AST: 510 U/L, ALT: 359 U/L, ALP: 238 U/L, Total Bilirubin: 6.21 mg/dL, Direct Bilirubin: 4.68 mg/dL, LDH: 798 U/L, GGT: 77 U/L) were detected. Renal function tests showed deterioration (Creatinine: 4.1 mg/dl, Urea: 160 mg/dl, GFR: 17). CRP:380 mg/L and Procalcitonin:2.1 ng/mL. The patient was admitted to the intensive care unit due to acute renal failure, elevated liver enzymes, and acute phase reactants. Cholestatic appearance was observed on abdominal USG. The patient's blood culture result was negative. Hepatitis panel, ANTI HIV, Torch panel, EBV, VZV, Leptospirosis, and Crimean-Congo haemorrhagic fever antibodies were negative. During follow-up, the patient developed persistent fever and agitation, and his general condition and laboratory values deteriorated rapidly. The patient was evaluated neurologically, and no neurologic pathology was considered. Skin biopsy was taken from the livedo macular and papular lesions (Figure 1) of the patient, who was consulted dermatologically. Histopathological evaluation revealed perivascular and periadnexal nonspecific lymphocytic dermatitis in the upper, middle, and deep dermis. The patient was evaluated by the rheumatology and cardiology clinics, and fibrinogen: 657 mg/dL, D-dimer: 4.44 mg/L, procalcitonin: 6.2 ng/mL and NTProBNP: 4458 pg/mL



Figure 1. Janeway lesions: Subungal, irregular, painless, erythematous or hemorrhagic macules and papules on the left big toe, palms, and distal tips of fingers.

values gradually increased. Subsequently, a transesophageal echocardiogram (TEE) was performed. Although no vegetation was detected on the initial transthoracic echocardiogram (TTE), the TEE revealed an 8-mm mass/vegetation involving all three cusps, more prominent on the noncoronary and right coronary cusps of the aortic valve.

Conclusion

In this case, the patient was diagnosed with IE relatively late as pre-diagnoses such as viral hepatitis, cholecystitis, and urinary tract infection were prioritized due to the absence of fever and cardiac symptoms/signs at the beginning and to the absence of growth in multiple blood cultures, although the patient's skin findings were a warning. Janeway lesion is a cutaneous manifestation of endocarditis, a disease usually caused by bacterial or fungal infection of the cardiac endocardium. Janeway lesions are irregular, nontender, erythematous or hemorrhagic macules or papules lasting days to weeks, usually found on the palms and soles of the feet [1].

It should be kept in mind that Janeway lesions may be an important clue for early diagnosis of IE.

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Dermatology Practical & Conceptual

Graham-Little-Piccardi-Lassueur Syndrome: Favorable Response to Isotretinoin Treatment

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Key words: Graham–Little-Piccardi-Lassueur syndrome, Lichen planopilaris, Scarring alopecia, Isotretinoin

Citation: Guerrero-Cornejo S, Orellana-Westermeyer V, Catalán-Lobo J. Graham-Little-Piccardi-Lassueur Syndrome: Favorable Response to Isotretinoin Treatment. *Dermatol Pract Concept*. 2025;15(4):5851. DOI: https://doi.org/10.5826/dpc.1504a5851

Accepted: April 22, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Graham-Little-Piccardi-Lassueur syndrome (GLPLS) is a rare subtype of lichen planopilaris (LPP), with approximately 50 reported cases [1]. It is characterized by a triad of scarring alopecia on the scalp, non-scarring alopecia in the axillary and pubic regions, and follicular papules on the body [2-3]. Due to its rarity, treatment is based on case reports and includes topical and systemic medications, with variable efficacy. Given the lack of strong evidence, alternative therapeutic approaches are needed to prevent progression to cicatricial alopecia.

Case Report

A 33-year-old female presented with a three-year history of trichodynia, pruritus, and hair loss. Examination revealed reduced hair density at the vertex, and trichoscopy revealed loss of follicular openings, and hyperkeratosis (Figure 1). Histopathology confirmed LPP, showing perifollicular fibrosis, lymphocytic infiltration, and follicular narrowing (Figure 2). Treatment was initiated with hydroxychloroquine (200 mg every 12 hours), oral minoxidil (1 mg/day), topical clobetasol 0.05%, ketoconazole 2% shampoo, and monthly intralesional corticosteroid injections.

Despite improvement in scalp symptoms and partial hair regrowth, new follicular hyperkeratotic papules appeared on the trunk and extremities alongside patches of non-scarring alopecia in the axillary and pubic regions (Figure 1). Trichoscopy revealed yellow dots and hair thinning. These findings led to a diagnosis of GLPLS, prompting a switch from hydroxychloroquine to isotretinoin (20 mg three times weekly). After three months, the patient showed resolution of scalp symptoms, repopulation of non-scarring alopecia areas, and a decrease in hyperkeratotic papules.

Conclusions

GLPLS is the rarest form of LPP, primarily affecting Caucasian females aged 30 to 70 years [1,4]. Its etiology remains unclear, though associations with vaccines and hormonal changes have been suggested. Clinically, it manifests as a

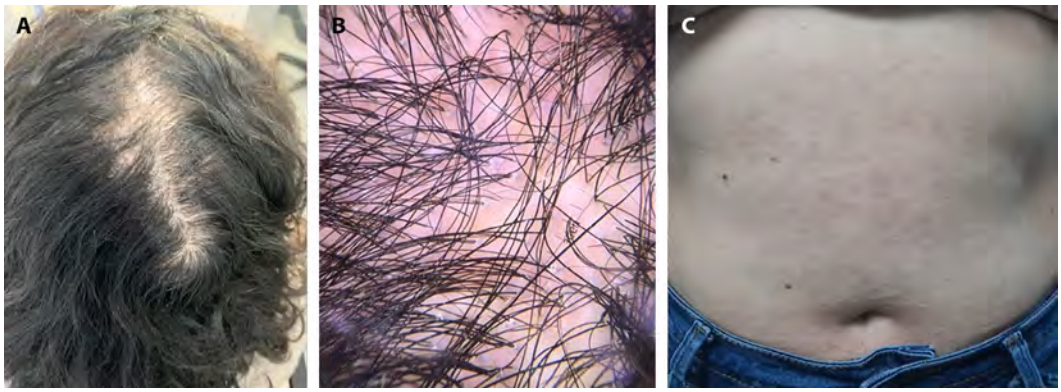


Figure 1. (A) Alopecic patch on the vertex of the scalp (B) Trichoscopy: erythematous base, loss of follicular openings, perifollicular scaling, peripilar casts, and tufted hairs (C) Hyperkeratotic follicular papules on the abdomen.

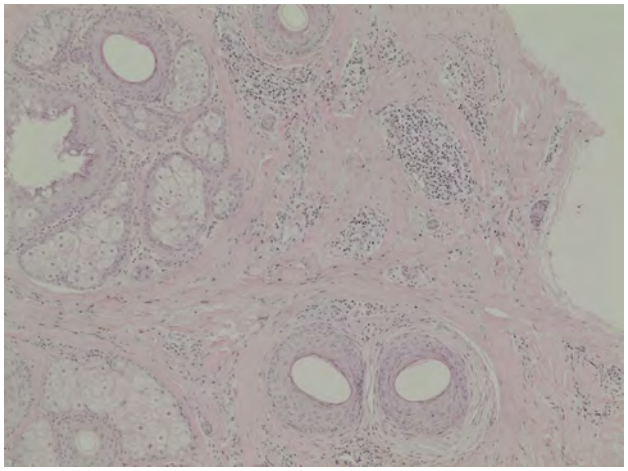


Figure 2. Hematoxylin-eosin stain 40x, decreased number of hair follicles with perifollicular fibrosis and lymphocytic infiltrate.

triad of scarring alopecia on the scalp, non-scarring alopecia in the axillary and pubic areas, and hyperkeratotic follicular papules [2,3]. Scalp findings include perifollicular erythema, scaling, and progressive multifocal alopecic patches. Trichoscopy typically reveals perifollicular erythema, fibrotic white dots, hair casts, and loss of follicular openings [5].

Histopathologically, early stages show perifollicular lymphocytic infiltration at the infundibulum and isthmus, with vacuolar degeneration and keratinocyte necrosis. Advanced stages demonstrate perifollicular fibrosis, loss of pilosebaceous units, and replacement by fibrous tracts. The disease course varies but often leads to irreversible scarring alopecia [2,3].

Treatment remains challenging and is primarily extrapolated from LPP management. The main goal is to halt disease progression and relieve symptoms. Described therapies include topical, intralesional, or systemic corticosteroids, retinoids, hydroxychloroquine, cyclosporine, methotrexate, and photochemotherapy, all with varying success rates [1,3].

Early recognition of GLPLS is crucial to initiating timely treatment and preventing irreversible alopecia. This case highlights the importance of comprehensive follow-up in LPP patients, as the GLPLS triad may develop after scarring alopecia onset. While acitretin has been used with a favorable response, to our knowledge, this is the first case where isotretinoin has been reported as a systemic therapy. Its inclusion in treatment options is valuable, particularly where acitretin availability is limited.

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Dermatology Practical & Conceptual

Cutaneous and Orbital Myeloid Sarcoma as the Initial Clinical Presentation of Acute Myeloid Leukemia in an Infant

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Key words: Acute Myeloid leukemia, Cutaneous myeloid sarcoma, Chloroma, Granulocytic sarcoma, Pediatric leukemia

Citation: Di Carlo Del Vecchio L, Lapins J, Fernandes EL, de Alvarenga Lira ML, Magalhães F, Moleta M. Cutaneous and Orbital Myeloid Sarcoma as the Initial Clinical Presentation of Acute Myeloid Leukemia in an Infant. *Dermatol Pract Concept.* 2025;15(4):5858. DOI: https://doi.org/10.5826/dpc.1504a5858

Accepted: April 17, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Cutaneous myeloid sarcoma is a rare disease that predominantly occurs in association with myeloid malignancies, with a particularly high incidence in acute myeloid leukemia (AML). This paper presents a rare case of cutaneous and orbital myeloid sarcoma in an infant without a prior diagnosis of AML, contributing to the limited literature on the subject.

Case Presentation

A five-month-old male infant presented with a three-month history of asymptomatic cutaneous lesions. The lesions initially appeared on the abdomen and subsequently spread over the trunk and limbs, accompanied by a one-week period of swelling in the right lower eyelid. No fever, hemorrhage, or arthralgia was reported.

On examination, erythematous-violaceous macules and patches were observed on the torso and extremities, along with painless nodules. An erythematous mass was noted in the lower right eyelid region (Figures 1A-B). Laboratory tests revealed anemia (hemoglobin 7.9 g/dL) and elevated lactic dehydrogenase (606 U/L), with negative HIV and hepatitis B/C serologies.

A skin biopsy showed blue round cells infiltrating vessels, adnexals, and the interstitium, extending into the hypodermis, with hyperchromatic nuclei and frequent mitosis, suggesting hematopoietic lineage (Figures 2A-C). Immunohistochemical analysis was positive for CD45, CD43, CD4, and CD15, but negative for myeloperoxidase (MPO), CD34,

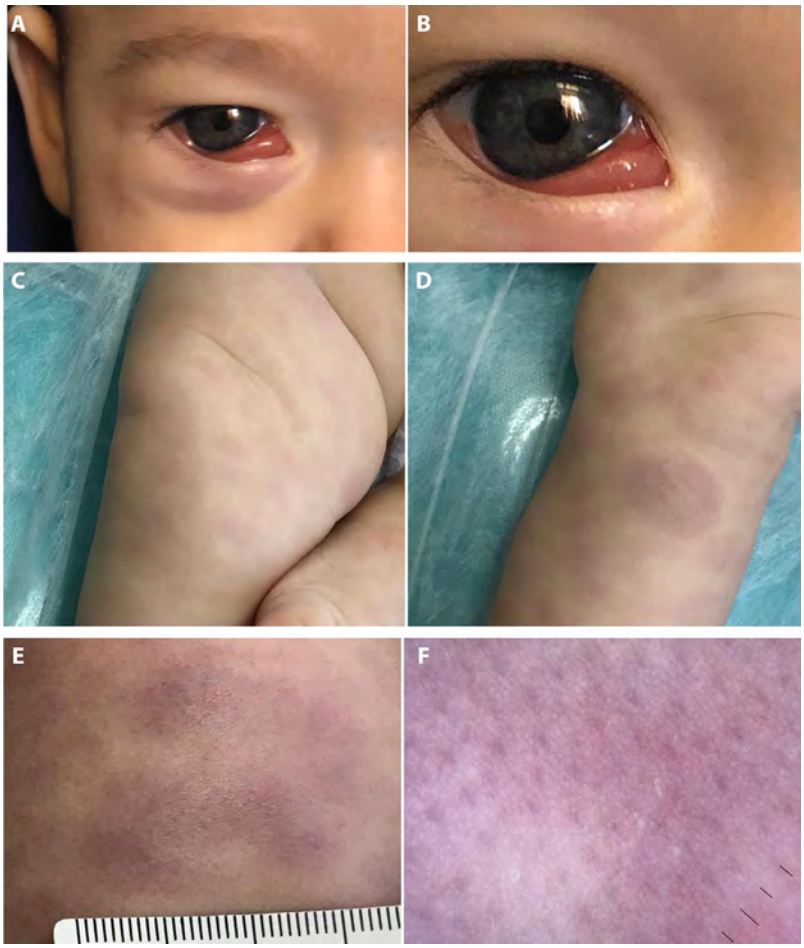


Figure 1. (A) Right eye displaying an erythematous mass in the lower eyelid region, extending to the medial portion of the sclera. (B) Close-up view of the affected area. (C-D) Clinical image showing erythematous-violaceous macular patches and the presence of painless nodules that were detected upon palpation of the lower limbs. (E) Close-up view of erythematous-violaceous infiltrated lesions. (F) A dermatoscopic evaluation of the disseminated erythematous-violaceous lesions discloses the presence of dotted vessels on a conspicuous violaceous background. However, no discernible abnormality in the skin texture is observed.

CD117, and TdT, indicating a myeloid lineage consistent with cutaneous myeloid sarcoma. Bone marrow biopsy confirmed acute myeloid leukemia.

The patient received chemotherapy (cytarabine and daunorubicin), achieving disease-free status. Two years later, the patient's leukemia returned. A bone marrow transplant was successful, resulting in long-term remission.

Discussion

Myeloid sarcoma may occur with hematological conditions like AML, CML, myelodysplastic syndrome, or without prior diagnoses [1]. In the pediatric age group, infiltration of the skin is the most common extramedullary manifestation of myeloid sarcoma, affecting 12.3% of pediatric AML patients, with higher prevalence in children under age one year [2]. The occurrence of orbital involvement in patients with AML is estimated to be between 3% and 9% and is most prevalent in young children [3].

Cutaneous myeloid sarcoma presents as papules, plaques, or nodules, typically on the trunk, head, neck, or extremities [4]. At histopathological examination, the leukemic infiltrate can be subtle and easily overlooked, and the rate of histopathological diagnostic error may be high, especially in patients lacking a history of AML [5]. Thus, clinical suspicion together with immunohistochemical analysis is important for the correct diagnosis. Dermatoscopy of cutaneous myeloid sarcoma shows nonspecific features such as polymorphic vessels (dotted, linear, or serpentine) on a pink-to-violaceous stroma (Figure 2F). These patterns overlap with conditions like leukemia cutis or inflammatory dermatoses, making dermatoscopy a useful but nonspecific tool [6]. While it helps guide biopsy, definitive diagnosis depends on histopathology and immunohistochemistry.

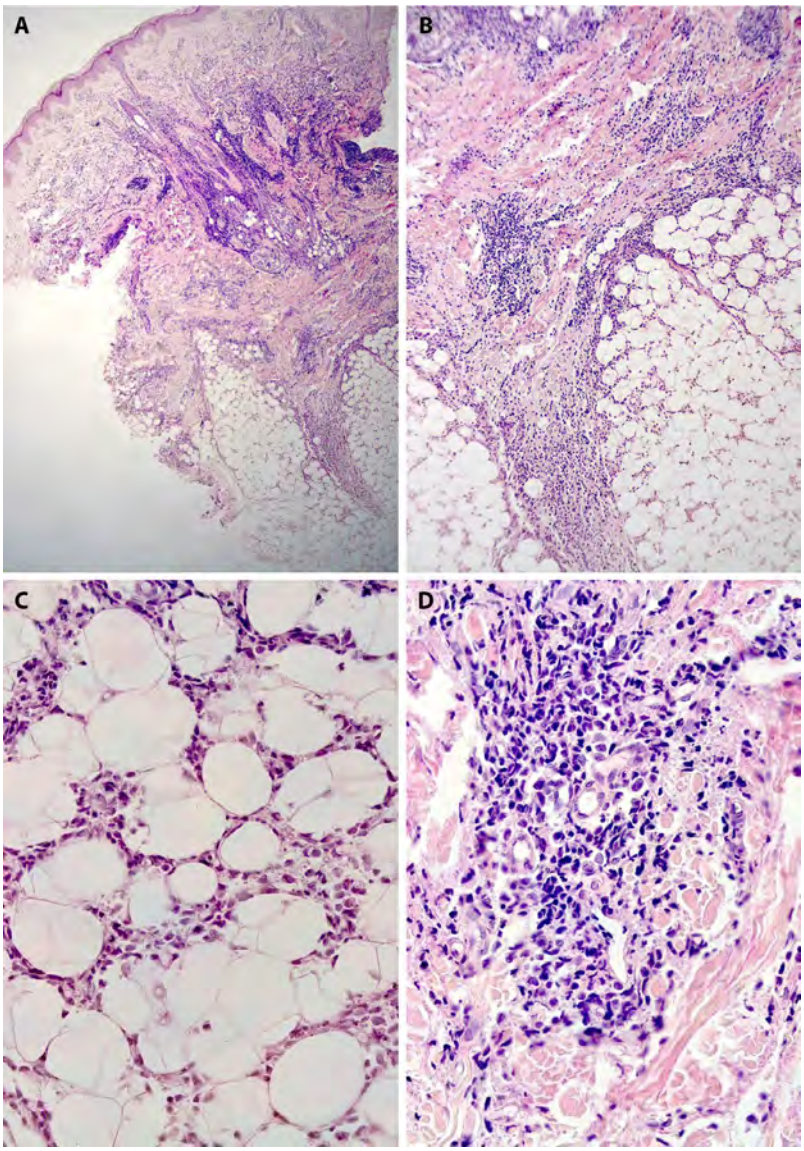


Figure 2. (A) Histopathology reveals dermal infiltration of isolated round cells surrounding vessels, adnexal structures, and the interstitium (H&E staining). (B) Histopathology shows infiltration of isolated round cells extending into the hypodermis. (C) Hypodermal infiltration by blue round cells. (D) Dermal infiltration by small-to-medium-sized cells with hyperchromatic nuclei and a high nucleus-to-cytoplasm ratio.

Conclusion

Cutaneous myeloid sarcoma may precede bone marrow involvement and be the first sign of AML or its recurrence. Prognosis is poor, particularly in pediatric cases [1]. Early detection is essential, as it can indicate imminent leukemia. Dermatologists play a key role in early diagnosis, which is critical to initiating treatment and improving outcomes.

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Dermatology Practical & Conceptual

Oral Erosive Lichen Planus Successfully Treated with Baricitinib

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Citation: Savian S, Maglie R, Baffa ME, Pipitò C, Rubino V, Senatore S, Antiga E. Oral Erosive Lichen Planus Successfully Treated with Baricitinib. *Dermatol Pract Concept.* 2025;15(4):5848. DOI: https://doi.org/10.5826/dpc.1504a5848

Accepted: April 9, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Lichen planus (LP) is a chronic inflammatory disorder that most often affects middle-aged adults. LP can involve the skin or mucous membranes including the oral, vulvovaginal, esophageal, laryngeal, and conjunctival mucosa. It has different variants based on the morphology of the lesions and the site of involvement.[1] Oral lichen planus (OLP) is one of the most common variants of LP, showing different clinical presentations; among them, erosive OLP severely affects the quality of life of the patients, resulting in painful erosion of the mucous membranes. Management of erosive OLP has proven to be difficult; however, recent reports of treatment with Janus kinase inhibitors (JAKi) such as baricitinib are encouraging.[2] This paper reports the successful treatment of erosive OLP with baricitinib in a patient with recalcitrant disease.

Case Presentation

A 79-year-old female presented painful erosions and ulcerations of the ventrolateral region of the tongue with oral disease severity score (ODSS) =12 (Figure 1A) and lesions compatible with LP on the back of the hands, on the volar surface of forearms, and on the soles, with papules showing clinical features of hypertrophic LP. After confirmation of the diagnosis, treatment with prednisone 50 mg and methotrexate 12.5 mg/day was started, with marked improvement of the skin manifestations after 12 weeks of treatment. In contrast, the involvement of the oral cavity did not show significant improvement despite the multiple treatments, including prednisone, methotrexate, azathioprine, topical clobetasol propionate 0.05%, and intralesional triamcinolone. Considering the patient's poor clinical control and reduced quality of life due to the persistence of erosive mucosal lesions, off-label therapy with baricitinib 4 mg/day was introduced, while maintaining prednisone 5 mg/day. After three months of baricitinib treatment, there was a marked improvement, with ODSS=4, followed by a complete remission after five months (ODSS=0) (Figure 1B), which was maintained at 7-month follow up. No obvious side effect was reported by the patient.



Figure 1. Painful erosions and ulcerations of the tongue (A) complete remission of the oral disease after five months of baricitinib (B).

The treatment of erosive OLP includes systemic corticosteroids, immunosuppressants, and/or oral retinoids.[3] Management of erosive OLP has proven to be difficult;[4] however, JAKi such as baricitinib may represent a new possible line of treatment. There are currently 16 published cases of cutaneous only LP treated with baricitinib; nine of them achieved complete or partial remission of the disease, while in the other seven, baricitinib was not able to improve the skin lesions.[2] Moreover, a case report of a 63-year-old female presenting with chronic alopecia areata (AA) and coincidental acute OLP was recently published. Baricitinib 3.4 mg twice daily was commenced, with improvement in OLP after 1 month and sustained response after four months. Except for mild hypercholesterolaemia, baricitinib was well tolerated.[5]

Conclusion

We report the second documented case of erosive OLP that has been successfully treated with baricitinib, suggesting the latter as a potential new therapeutic option in patients with recalcitrant erosive OLP. However, given the conflicting results reported in the literature, further controlled studies on larger case series are needed to evaluate the actual efficacy of baricitinib in OLP and LP patients.

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Dermatology Practical & Conceptual

Is Dermoscopy Destroying Clinical Dermatology?

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Citation: Conforti C, Ambrosio L, Giuffrida R, Longo C, Pellacani G, Zalaudek I. Is Dermoscopy Destroying Clinical Dermatology? *Dermatol Pract Concept.* 2025;15(4):5823. DOI: https://doi.org/10.5826/dpc.1504a5823

Accepted: April 9, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Dear Editor,

Dermoscopy represents a silent revolution in dermatology, profoundly transforming daily practice. Though its impact on early skin cancer detection and reduction of unnecessary excisions is well established, it has yet to gain consistent recognition in high-ranking medical journals. Nevertheless, this simple, cost-effective tool has become a global standard in skin cancer screening, with growing applications in general dermatology, including skin infections and inflammatory diseases, due to its accuracy and efficiency [1]. For these reasons, it is often referred to as the "dermatologist's stethoscope" [2]. However, while the enthusiasm for dermoscopy has led to intense research resulting in the identification of numerous diagnostic criteria, the principle that it should complement clinical examination is being overlooked. Many published studies emphasize its use as a second-level tool, yet often neglect the description of clinical features, risking a loss of crucial educational and diagnostic context [3]. Clinical reasoning remains the cornerstone of dermatology, especially for differentiating tumors from inflammatory diseases that may share overlapping dermoscopic features. For instance, the classification of keratinocyte tumors benefits more from contextual evaluation (photodamaged versus non-photodamaged skin) than from isolated dermoscopic findings [4]. Without such contextualization, dermoscopy risks fostering superficial interpretation. This trend is compounded by the increasing medicolegal weight of histopathology, leading to what has been termed "anatomopathological chaos," with numerous subtypes of dysplastic lesions (e.g., SAMPUS, MELTUMP, THIMUMP) whose clinical significance remains debated [5,6]. The widespread use of dermoscopy from the early stages of residency has also encouraged a reversal of priorities: today, a dermatofibroma is often diagnosed dermoscopically before being confirmed by palpation, although tactile examination should remain fundamental. Similarly, conditions such as dermatitis, warts, and molluscum contagiosum, once diagnosed primarily through clinical evaluation, are increasingly approached dermoscopically. This prioritization of pattern

recognition over bedside reasoning extends to inflammatory diseases such as lichen planus, psoriasis, and mycosis fungoides [3]. A further shift has been observed in the evaluation of pigmented lesions, where the desperate search for features is giving way to the recognition of benign criteria first. Lallas et. al have shown how, instead of focusing on malignant features, clinicians must first assess the presence/absence of benign criteria typically associated with seborrheic keratoses, solar lentigo, or actinic keratoses [7]. Yet, modern teaching tools often promote rapid pattern recognition, sometimes in a gamified format, undermining deeper diagnostic reasoning. Coupled with a decreasing interest in research, this risks weakening the scientific rigor of the discipline. To address these challenges, a balanced approach is needed: dermoscopy should supplement, not replace, traditional clinical examination. Patient history, inspection, and palpation must remain central, supported by dermoscopy and by close collaboration with dermatopathologists. By maintaining this integration, dermatologists can provide holistic and effective care while ensuring that future generations remain grounded in essential clinical skills.

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Dermatology Practical & Conceptual

Melanomas Arising On Tattoos: The "Disruption Sign"

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Key words: Melanoma, Tattoo, Dermoscopy

Citation: Vaccari S, Cirella R, Lambertini M, Morante M, Raone B, Dika E. Melanomas Arising On Tattoos: The "Disruption Sign". *Dermatol Pract Concept*. 2025;15(4):5890. DOI: https://doi.org/10.5826/dpc.1504a5890

Accepted: April 22, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.s

Authorship: All authors have contributed significantly to this publication.

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To the Editor,

Tattoos may be related to a number of dermatological complications: cutaneous neoplasms, particularly melanomas (cMs), have been reported, but the pathogenesis remains controversial [1-4]. Forty-three cMs on tattoos (cMT) have been reported, occurring more frequently in males and younger patients, with a higher mean Breslow thickness, possibly related to a delayed diagnosis [5,6]. No case series of cMT dermoscopic features have been reported and we report four cases (Table 1, Figures 1 and 2).

The most common dermoscopic feature was the atypical reticular pattern (4/4, 100%), followed by grayish-blue areas (3/4, 75%) and homogeneous areas (2/4, 50%). Cobblestone pattern, blue-gray veil, gray circles, regression structures, dots/globules, and peppering were observed in 1/4 cMTs. Grayish-blue areas were likely related to the black ink as they were not present in the cMT arising on the yellow tattoo.

All the cMTs were atypical clinical lesions, representing clinical "ugly ducklings," but they had not been noticed by the patients. The atypical clinical features according to the ABCDE rule were a hint of the malignant nature and even more worrisome than the dermoscopic elements. Indeed, tattoos represent an obstacle to self- and medical clinical examination as well as to dermoscopic assessment. The presence of superimposed ink can mimic a blue-gray veil and mask the vascular pattern and the borders. As shown in Cases 1 and 2, at low magnification, the ink can create two different dermoscopic areas with a prominent diversity (Figures 1B–D).

The harmonic features and image of the tattoos had been altered by the cMT ("disruption sign"), representing a clue of the subsequent origin of the lesion. Indeed, usually

Table 1. Clinical and Dermoscopic Features of the Reported Cases.

Case 1	F	50	Arm	Melanoma in situ	Homogeneous areas Cobblestone Atypical reticular Gray circles Grayish-blue areas
Case 2	F	41	Dorsum	Melanoma, pT1a, Breslow 0.3 mm	Grayish-blue areas Atypical reticular Homogeneous areas Dots/globules
Case 3	M	48	Dorsum	Melanoma, pT1a, Breslow 0.5 mm	Atypical reticular Peppering Blue-gray veil Regression structures
Case 4	M	46	Torax	Melanoma, pT1a, Breslow 0.5 mm	Grayish-blue areas Atypical reticular

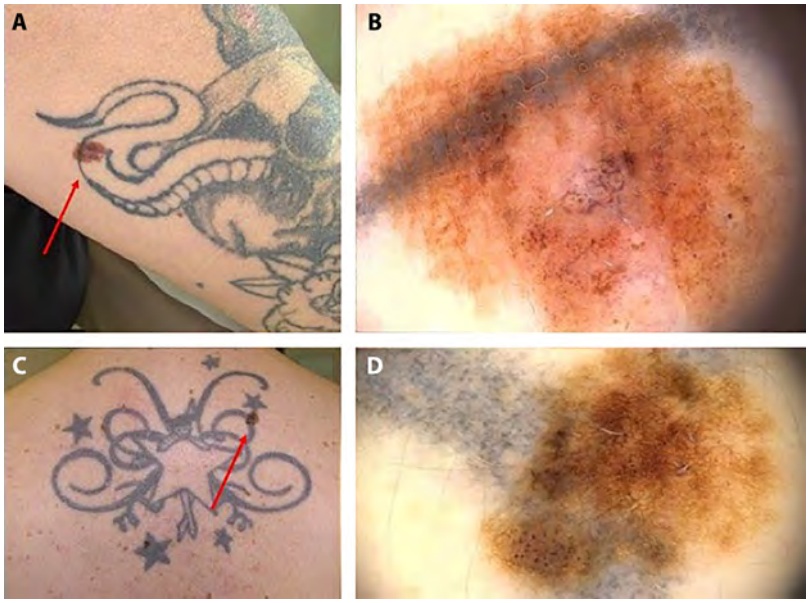


Figure 1. Clinical (A,C, red arrows) and dermoscopic (B,D) features of the excised melanomas on tattoos.

a professional tattoo is performed around a pre-existing nevus, sparing its borders and aesthetic appearance (Figure 2A, blue arrows). The drawing itself can help the clinician to monitor the evolution of the pigmented lesion at sequential images, representing points of reference.

In those tattoos with complex drawings and multiple nevi or photodamage (Figures 2A), cMT may be misjudged as part of the tattoo itself.

Our goal is to raise awareness of cMT and emphasize the importance of a thorough clinical and dermoscopic examination. Further studies and the new available technologies are required to elucidate cMT diagnostic features in order to avoid unnecessary excisions with a heavy cosmetic impact. CMs may alter the harmony of the colour and shape of the pre-existing tattoo ("disruption sign") and represent a clinical "ugly duckling."

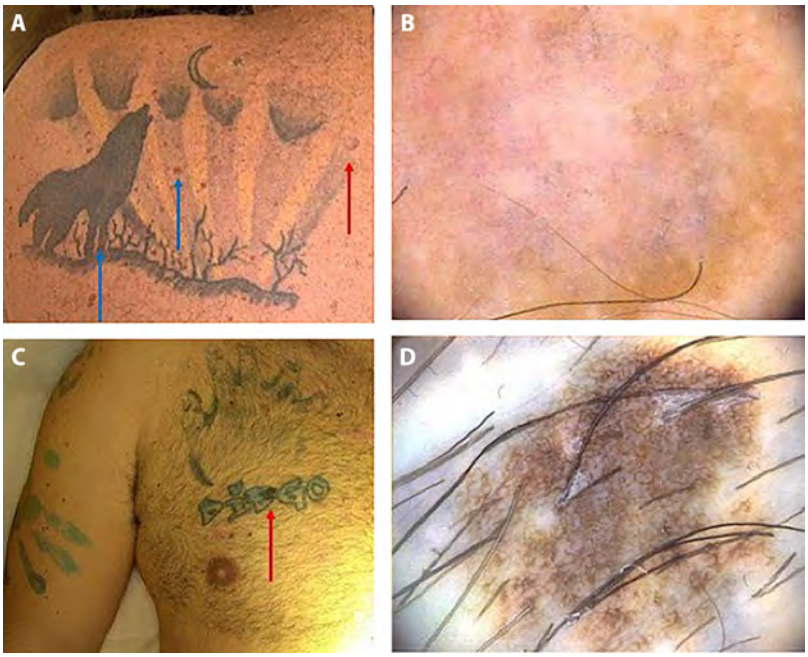


Figure 2. Clinical (A,C, red arrows) and dermoscopic (B,D) features of the excised melanomas on tattoos. Blue arrows represent those areas where the nevus is spared by tattoo.

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Dermatology Practical & Conceptual

The Efficacy and Safety of Nemolizumab in Patients with Prurigo Nodularis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Citation: Titou H. The Efficacy and Safety of Nemolizumab in Patients with Prurigo Nodularis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Dermatol Pract Concept.* 2025;15(4):5967. DOI: https://doi.org/10.5826/dpc.1504a5967

Accepted: April 9, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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To the Editor,

Recent advancements in the understanding of Prurigo nodularis (PN) immunopathogenesis have led to more treatment choices. Since August 2024, nemolizumab has been approved by the US Food and Drug Administration [1]. We systematically reviewed the efficacy and safety of nemolizumab among existing randomized, double-blinded, and placebo-controlled clinical trials.

We performed every step according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We searched electronic databases (Embase, Scopus, PubMed, and Cochrane) from their inception to 01 January 2025. The search strategies and methods are provided in Supplementary Figure A1 and Materials (Available via Mendeley at https://data.mendeley.com/datasets/tghtskv98w/1). Finally, this study included four studies involving 560 patients in experimental groups and 299 patients in control groups. We summarized the primary and second endpoints of each study in Supplementary Table 1 (Available via Mendeley at https://data.mendeley.com/datasets/tghtskv98w/1).

Overall, compared with placebos, the use of nemolizumab treatment showed a significant improvement in the lesion score and pruritus from week 4: Peak Pruritus Numerical Rating Scale (PP-NRS) improvement ≥4 points (odds ratio (OR): 9.27; 95% confidence interval (CI): 5.08–16.90; $P<0.00001$) and Investigators' Global Assessment score (IGA 0/1) (OR: 3.24; 95% CI: 0.45–23.49; $P=0.02$) (Figures 1 and 2).

The intense itching associated with PN significantly affects patients' quality of life, leading to sleep disturbances, particularly during the evening [2]. The results of the meta-analysis indicated that nemolizumab has better performance than does the placebo on the Sleep Disturbance Numerical Rating Scale (SD-NRS) (OR: 6.33; 95% CI: 3.51–11.41; $P<0.00001$). (Supplementary Figure A2, available via Mendeley at https://data.mendeley.com/datasets/tghtskv98w/1).

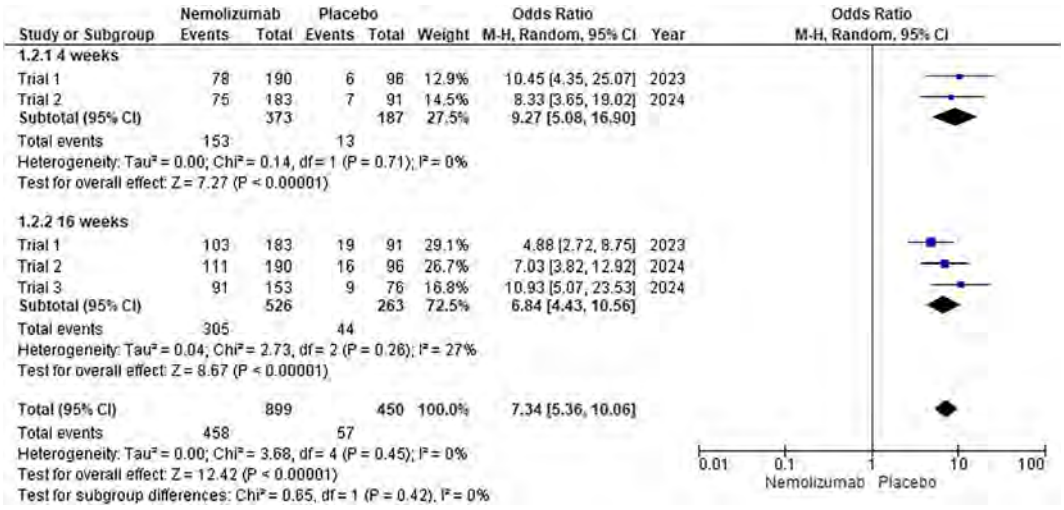


Figure 1. Forest plot of effect of nemolizumab treatment on PP-NRS improvement ≥4 points in prurigo nodularis patients.

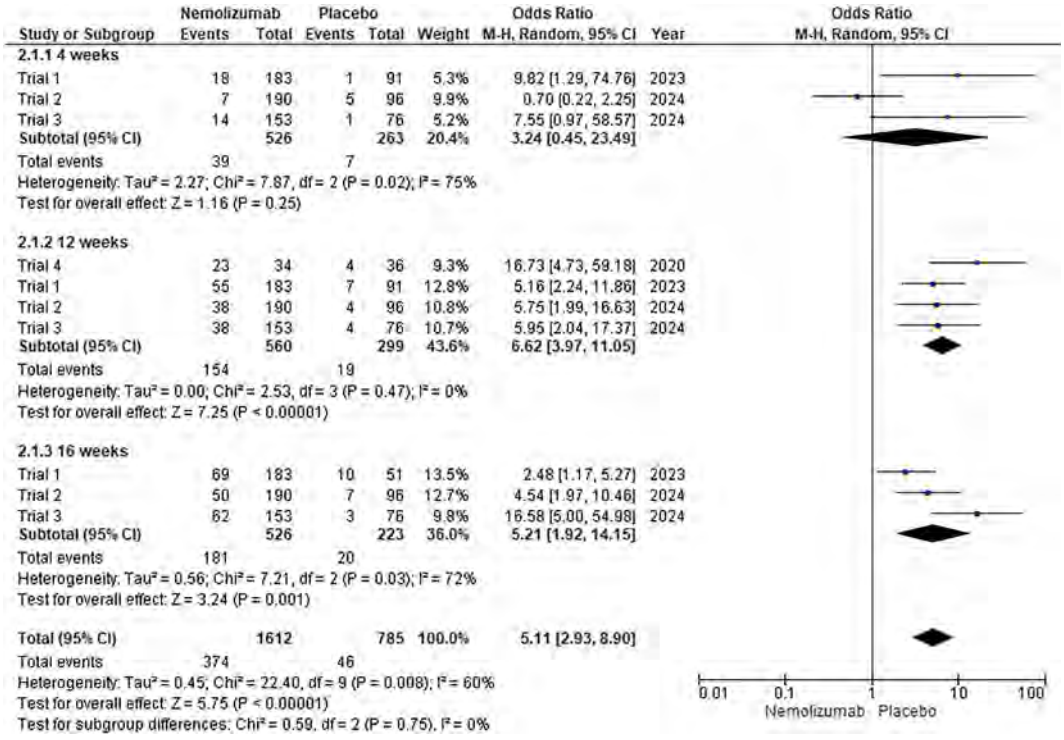


Figure 2. Forest plot of effect of nemolizumab treatment on Investigator's Global Assessment score (IGA 0/1) in prurigo nodularis patients.

The safety profile and efficacy of nemolizumab were similar to dupilumab [3]. Nemolizumab demonstrated the highest risk of AEs, and the incidence was significantly higher than that of the placebo. Twenty-nine patients in the nemolizumab-treated group experienced serious AEs, and 22 of them discontinued the treatment. The most commonly reported serious AEs of nemolizumab were infection (OR: 0.81; 95% CI: 0.53–1.24; *P*=0.52), atopic dermatitis (OR: 2.68; 95% CI: 0.54–13.24; *P*=0.21), peripheral or facial edema (OR: 1.83; 95% CI: 0.50–6.69; *P*=0.70), and asthma (OR: 1.35; 95% CI: 0.35–5.16; *P*=0.77), all of which were mild-to-moderate in severity (Supplementary Figure A3, available via Mendeley at https://data.mendeley.com/datasets/tghtskv98w/1).

In conclusion, this meta-analysis showed that nemolizumab is a promising treatment option for PN. Further studies with long follow-up will be needed to fully elucidate the safety profile of nemolizumab.

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Dermatology Practical & Conceptual

Cutaneous Lesions from *Schistosoma haematobium*

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Citation: Danese A, Sokol S, De Rui E, Scarso S, Vaienti S, Bellinato F, Girolomoni G, Gisondi P. Cutaneous Lesions from *Schistosoma haematobium*. *Dermatol Pract Concept*. 2025;15(4):6479. DOI: https://doi.org/10.5826/dpc.1504a6479

Accepted: August 26, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Case presentation

A 22-year-old male from Senegal presented with multiple pruritic papular lesions near the umbilicus, right lumbar area, and thighs (Figure 1A and B). Skin biopsy showed epidermal hyperplasia and a dense eosinophilic infiltrate with parasitic ova-like structures in the dermis (Figure 1C and D). The presence of *Schistosoma haematobium* was confirmed by polymerase chain reaction (PCR) targeting parasite-specific DNA extracted from formalin-fixed, paraffin-embedded skin tissue. Serum laboratory examinations revealed peripheral eosinophilia (2.36×10^9 per liter; normal range 0.04-0.4) and positivity for IgG antibodies against *Schistosoma* species, with other findings within normal limits. Stool and urine samples were negative. A diagnosis of cutaneous schistosomiasis was made. The patient was treated with oral praziquantel (120 mg per kilogram on day 0, repeated at six weeks), leading to complete resolution of the lesions [1].

Teaching point

Cutaneous schistosomiasis is a rare ectopic manifestation of *S. haematobium* infection [2]. Early recognition is essential for prompt diagnosis and curative therapy.

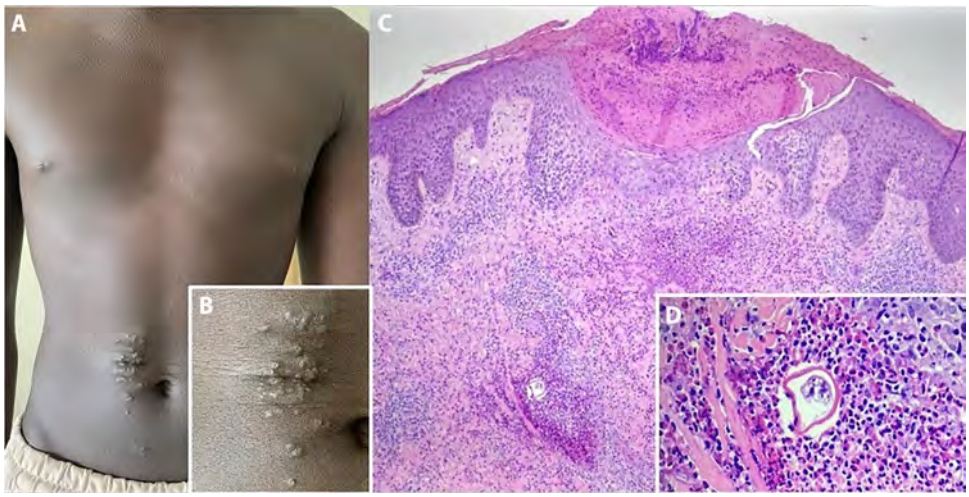


Figure 1. Multiple pruritic papular lesions near the umbilicus, right lumbar area, and thighs in a 22-year-old male from Senegal (A and B); Skin biopsy revealed epidermal hyperplasia and a dense eosinophilic infiltrate with parasitic ova-like structures in the dermis (C and D).

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Dermatology Practical & Conceptual

Hair Collar Sign with Naevus Flammeus: A Possible Sign of Aplasia Cutis Congenita

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Li Han and Lang Rao contributed equally to this work.

Citation: Han L, Rao L, Wu YB, Deng YY, Luo B. Hair Collar Sign with Naevus Flammeus: a Possible Sign of Aplasia Cutis Congenita. *Dermatol Pract Concept*. 2025;15(4):6116. DOI: https://doi.org/10.5826/dpc.1504a6116

Accepted: June 27, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Case Presentation

A 2-month-old female infant presented with a reddish patch and bald area on her scalp, which her parents had noticed one week earlier (Figure 1A). Dermoscopy revealed an atrophic patch lacking central follicular openings, surrounded by radiating coarser hairs and featuring thin linear, rounded, and globular vessels on a pinkish background (Figure 1B). She was diagnosed clinically with aplasia cutis congenita (ACC) with a hair collar sign (HCS) and naevus flammeus, supported by dermoscopic findings. Magnetic resonance imaging (MRI) demonstrated that the skull was closed and intact, with normal intracranial structures (Figure 1C). She was advised to undergo close follow-up without intervention.

Teaching Point

Aplasia cutis congenita (ACC) is a rare congenital skin defect that can occur anywhere on the body, most commonly on the scalp. A ring of coarser, darker hair surrounding a bald scalp lesion, termed HCS, is considered a specific clinical sign of ACC. Prior studies suggest nearly half of HCS cases correlate with naevus flammeus (port-wine stains); this association may arise from aberrant migration of neural crest cells affecting fetal skin development, particularly in capillary network formation [1]. In ACC cases, because the presence of HCS and vascular stains are considered as a marker for neuroectodermal defects (e.g., heterotopic brain tissue or cephalocele), an MRI is essential for evaluation [2].

In conclusion, HCS is frequently associated with naevus flammeus and may indicate aplasia cutis congenita. Patients demonstrating this cutaneous marker should undergo thorough physical examination coupled with MRI evaluation of the craniospinal axis.

Ethical Statement: Written informed consent was obtained from the patient's parents for publication of this case letter and any accompanying anonymized data/images. The parents were informed that all personal identifiers would be removed to protect privacy.

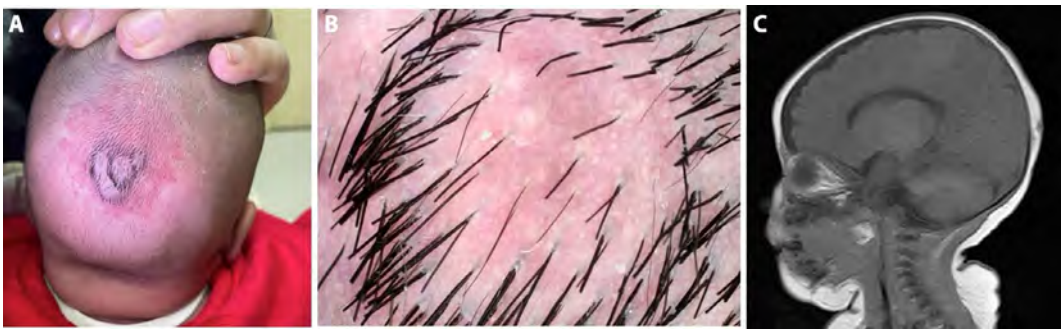


Figure 1. (A) A reddish patch with a hair collar sign is present on the occipital region of an infant; (B) Dermoscopy revealed an atrophic patch surrounded by radiating hair follicles, with thin linear, rounded, and globular vessels on a pinkish background (polarized 30x); (C) MRI scan showed the skull was intact, with normal intracranial structures.

Acknowledgement: We thank the patient's parents for granting permission to publish this information.

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Dermatology Practical & Conceptual

Type 2 Lepra Reaction with Borderline Lepromatous Leprosy

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Citation: Chen Q, Liu J. Type 2 Lepra Reaction with Borderline Lepromatous Leprosy. *Dermatol Pract Concept*. 2025;15(4):6738. DOI: https://doi.org/10.5826/dpc.1504a6738

Accepted: September 19, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Case Presentation

A 37-year-old female was admitted due to recurrent erythema, papules, and nodules over her body for six months and intermittent fever for two months. Physical examination revealed erythematous papules and plaques on the limbs and trunk (Figure 1A) and erythematous nodule on the earlobe (Figure 1B). The skin examination showed high-density leprosy bacilli (2+). Histopathological examination of the skin tissue showed lymphocyte and histiocyte infiltration around the blood vessels (Figure 1C). A diagnosis of type 2 leprosy reaction with borderline lepromatous leprosy was made.

Teaching Point

Type 2 lepra reaction is an acute inflammatory response triggered by immune complex deposition during the course of leprosy, most commonly occurring in patients with lepromatous (LL) or borderline lepromatous (BL) leprosy. Skin symptoms are painful red nodules or papules on the limbs or trunk, which may ulcerate and suppurate [1]. The first-line drugs are thalidomide and prednisone [2], so the patient was treated with oral thalidomide and prednisone, along with multidrug therapy for leprosy. The erythema nodosum basically subsided after three months.

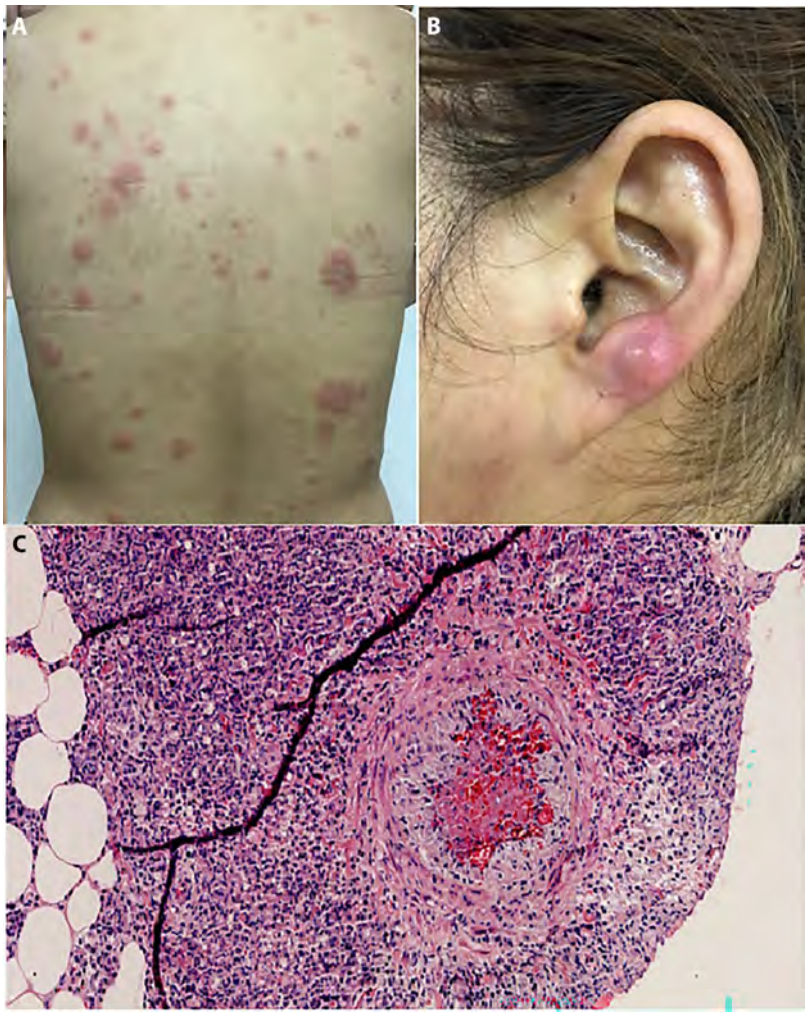


Figure 1. (A) Multiple erythematous papules and plaques on the trunk. (B) Erythematous nodule on the earlobe. (C) Histopathology (H&E, x100): Subcutaneous fat shows vascular embolism with infiltration of tissue cells and lymphocytes.

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Dermatology Practical & Conceptual

Poroma Vessels can be Better Identified by High Magnification Dermoscopy Compared to Conventional Dermoscopy

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*Equally contributed to the manuscript

Key words: Magnified Dermoscopy, Poroma

Citation: Giuffrida R, Tognetti L, Valguarnera D, Conforti C, Zalaudek I, Guarneri F. Poroma Vessels can be Better Identified by High Magnification Dermoscopy compared to Conventional Dermoscopy. *Dermatol Pract Concept*. 2025;15(4):6050.
DOI: https://doi.org/10.5826/dpc.1504a6050

Accepted: June 2, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Case Presentation

An 88-year-old female with history of multiple basal cell carcinomas (BCCs) presented with an asymptomatic, pink-to-red 2-mm firm papule on her left posterior leg of two months' duration. Dermoscopy at magnification 20x (Medicam 1000, Fotofinder System, Bad Birnbach, Germany) showed yellow central structureless area, surrounded by white interlacing areas around polymorphous vessels (Figure 1A). The latter at magnification 300x (Fig.1b) and 400x (Fig.1c) better appeared as branched vessels with rounded endings. Histopathologic examination revealed features compatible with eccrine poroma.

Teaching Point

Eccrine poroma (EP) is an uncommon, benign sweat gland tumor that clinically may show a variety of features, mimicking other neoplasms [1]. The most frequent clinical presentation is a single slow-growing, asymptomatic pink-to-red well-circumscribed papule or nodule, commonly affecting the distal extremities of adult patients [1].

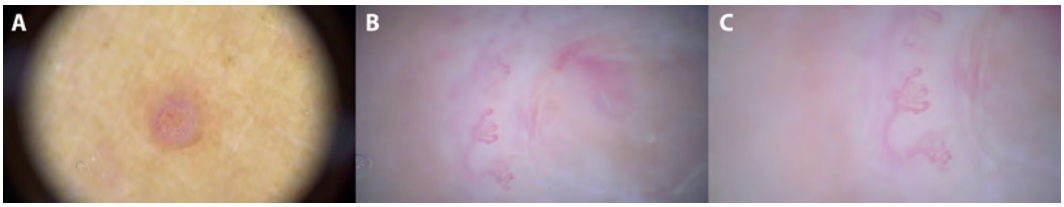


Figure 1. Dermoscopy of eccrine poroma. A) Yellow central structureless area, surrounded by white interlacing areas around polymorphous vessels visible at magnification 20x. B-C) Branched vessels with rounded endings well visible at magnification 300x (B) and 400x (C).

Dermoscopy improves the diagnosis of EP, typically showing a polymorphous vascular pattern, including branched vessels with rounded endings (branched vessels with looped/coiled terminal endings having a rounded silhouette), considered a clue for EP [1]. However, this finding was recently described in BCC, frequently reported as differential diagnosis of EP [2]. Of note, in EP the vessels are generally less prominent and branched than in BCC. This peculiar vascular morphology may be difficult to detect with conventional dermoscopy. High magnification dermoscopy is a new noninvasive imaging tool that has been shown to add information for clinically difficult-to-diagnose skin tumors. It may be useful to better identify branched vessels with rounded endings in EP, improving the diagnostic accuracy compared to dermoscopy with low magnification.

Ethics Statement: The patient in this manuscript gave written informed consent to the publication of her case details.

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Dermatology Practical & Conceptual

Dermoscopic Features of Morbilliform Rash in Dengue Fever: A Clinical Insight

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2 Medical Student of University of Campania Luigi Vanvitelli, Naples, Italy
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Citation: Giorgio CM, Di Brizzi EV, Argenziano G, Di Sarno C, Di Sarno R, Licata G. Dermoscopic Features of Morbilliform Rash in Dengue Fever: A Clinical Insight. *Dermatol Pract Concept.* 2025;15(4):5245. DOI: https://doi.org/10.5826/dpc.1504a5245

Accepted: January 7, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Case Presentation

A 30-year-old malecame to our department with a history of high fever (39°C), asthenia, headache ,and myalgia four days after a trip to a tropical area; he presented with erythematous macules confined to the hands and feet. Clinically well-demarcated macular, non-pruritic, erythematous areas primarily affecting the hands and feetwere observed (Figures 1A and B).Dengue fever was confirmed via serological tests. Considering the diagnosis of dengue and the atypical clinical presentation, dermoscopic examination was performed,and the following dermoscopic features were observed (Figures 1C and D): shiny white structures, visible under polarized light,potentially indicative of acute inflammation and dermal fibrosis;red hemorrhagic dots and globules, indicative of capillary fragility.

Teaching Point

Dengue fever typically manifests with a generalized rash involving the trunk and sometimes the face[1]. The observed shiny white structures may reflect acute dermal changes, while red dots/globules could be markers of thrombocytopenia. Current literature contains few studies describing the dermoscopic patterns of exanthematous diseases[2]. Measles may exhibit an intensely erythematous background due to confluent macules, rubella may show a pinkish-red background corresponding to its non-confluent maculopapular rash, and parvovirus B19 mayreveal a moderately erythematous reticulated pattern. These dermoscopic differences underscore the potential of this tool in differential diagnosis. Interestingly, a comparison with other viral exanthems revealed the absence of shiny white structures, suggesting that this finding couldbe

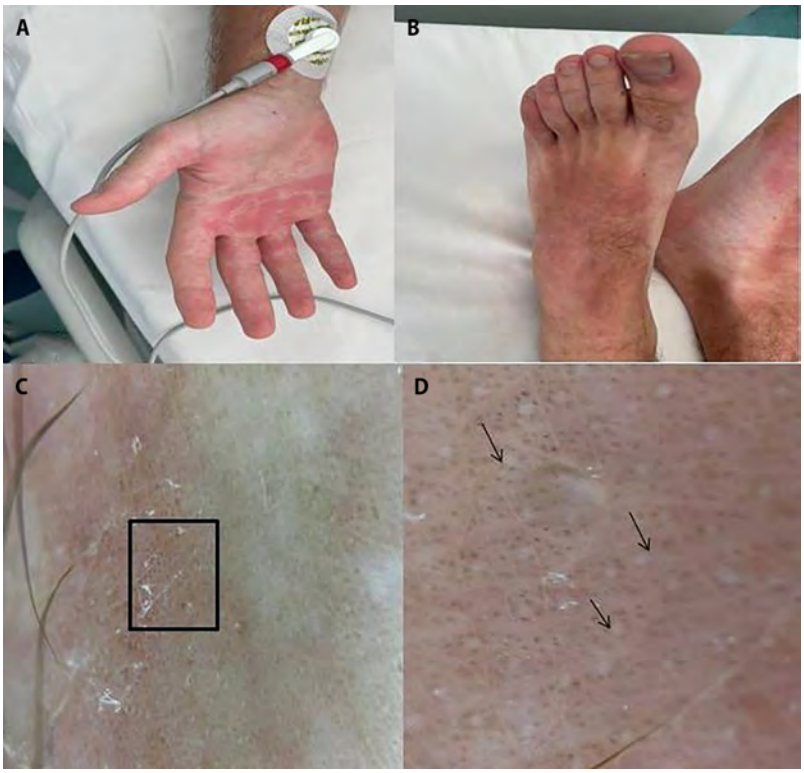


Figure 1. A-B: Clinical images of a 30-year-old maleaffected by dengue fever extending to the palms and soles.C-D: Dermoscopic images of dengue fever where it is highlighted theaspecific presence of red dots/globules (square) and shiny white structures (arrows).

characteristic of dengue fever. Moreover, red hemorrhagic dots and globules are instead present in other exanthematous diseases [2]. However, further studies are necessary to validate their diagnostic relevance and specificity in dengue.

Ethics Statement: The patients in this manuscript have given written informed consent to the publication of their case details. This study follows the ethics guidelines.

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Dermatology Practical & Conceptual

Dermatomyositis-Like Lesion: An Atypical Cutaneous Presentation in Adult-Onset Still Disease

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Citation: Chen S, Li L, Xiang L, Chen X, Jiang C. Dermatomyositis-Like Lesion: an Atypical Cutaneous Presentation in Adult-Onset Still Disease. *Dermatol Pract Concept*. 2025;15(4):5243. DOI: https://doi.org/10.5826/dpc.1504a5243

Accepted: June 4, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Case Presentation

A 56-year-old female with no prior dermatological history presented with persistent pruritic erythematous scaly plaques accompanied by fever, myalgia, and generalized lymphadenopathy for over 20 days. The rash had started on the neck and chest and had rapidly spread to the face, back, and thighs (Figure 1A-D). Histopathology found dyskeratotic keratinocytes of the upper third of epidermis. Muscle, bone marrow lymph node biopsies, and PET-CT found no substantial abnormality. The patient was initially diagnosed as having dermatomyositis. However, based on Yamaguchi criteria, especially the highly specific and sensitive skin histopathology, clinical presentation and subsequent examinations, the final diagnosis was adjusted to adult-onset Still's disease (AOSD). During our 10-month follow-up after treatment with glucocorticoids and siltuximab, laboratory results, including complete blood count, liver function, and ferritin levels, showed improvement; the patient no longer had fever or any discomfort.

Teaching Point

AOSD is a rare systemic inflammatory disease with diverse clinical presentations. Skin rash is a key feature, which is typically characterized as evanescent, non-pruritic eruption, and often followed by spiking fever[1]. Here, we report an atypical case of AOSD with persistent pruritic dark-red lesions on the face, neck, chest, and back, which are frequently associated with poor prognosis[2]. Dyskeratotic cells of the upper-to-mid-epidermis in histopathology is a crucial clue for diagnosis (Figure 1E). Dermatomyositis is the primary disease for differential diagnosis, and hematologic malignancies should be ruled out. Early recognition of these clinical and pathological signs can aid in timely clinical decision-making.

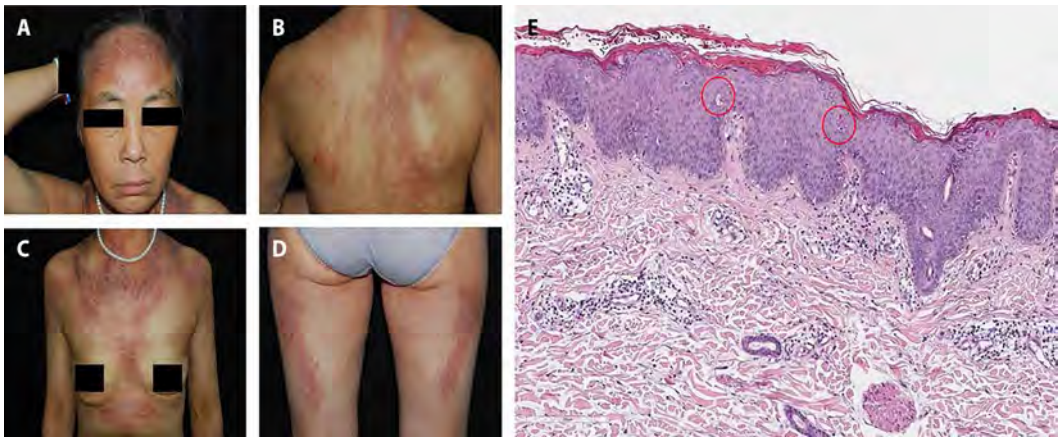


Figure 1. (A-D) The patient presented erythema scale rash on the forehead, face, chest, back, and lateral thigh. (E) Histopathology found several dyskeratotic keratinocytes of the upper third of the epidermis and a few infiltrations of lymphocytes, neutrophils, and eosinophils in the superficial dermis (H&E, 400x).

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Dermatology Practical & Conceptual

Bywaters Lesions: Clinical, Dermoscopic, and Histopathological Insights

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Key words: Bywaters lesions, Rheumatoid arthritis

Citation: Salvagno S, Baravalle S, Colato C, Carletto A, Bellinato F, Girolomoni G, et al. Bywaters Lesions: Clinical, Dermoscopic, and Histopathological Insights. *Dermatol Pract Concept*. 2025;15(4):5754. DOI: https://doi.org/10.5826/dpc.1504a5754

Accepted: May 27, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Case Presentation

A 58-year-old female with a recent diagnosis of seropositive rheumatoid arthritis (RA) treated with methylprednisolone (8 mg/daily) presented with asymptomatic cutaneous lesions on her hands, persisting for two months. Physical examination revealed multiple brown-to-black papules on the proximal and lateral nail folds and ventral fingers, with signs of necrosis and fine desquamation (Figures 1A and B). Dermoscopy showed homogeneous structureless brown areas with well-defined borders, mild scaling, and absence of a network and vascular structures (Figures 1C and D). Histopathology demonstrated small vessel vasculitis with focal subintimal fibrinoid necrosis and a perivascular lymphohistiocytic infiltrate. Areas of collagen necrobiosis bordered by palisading histiocytes were also present, consistent with rheumatoid vasculitis (Figures 1E and F) [1]. Methylprednisolone was suspended, and therapy with etanercept 50 mg weekly and acetylsalicylic acid 100 mg/daily was initiated. Complete resolution was observed at two months.

Teaching Point

Bywaters lesions are a distinctive cutaneous manifestation of RA. They present as nailfold thromboses and brown-to-black papules on acral surfaces, which correspond to a small vessel lymphocytic/neutrophilic vasculitis, causing intimal obliteration and territorial infarction [2]. Bywaters lesions tend to have a favorable prognosis when occurring in isolation, without requiring specific treatment. Recognition of these lesions is clinically relevant as they do not contraindicate the initiation of biologic therapy and are likely to improve with adequate control of the underlying rheumatoid disease. In contrast, the presence of systemic vasculitis may warrant more aggressive immunosuppressive management.

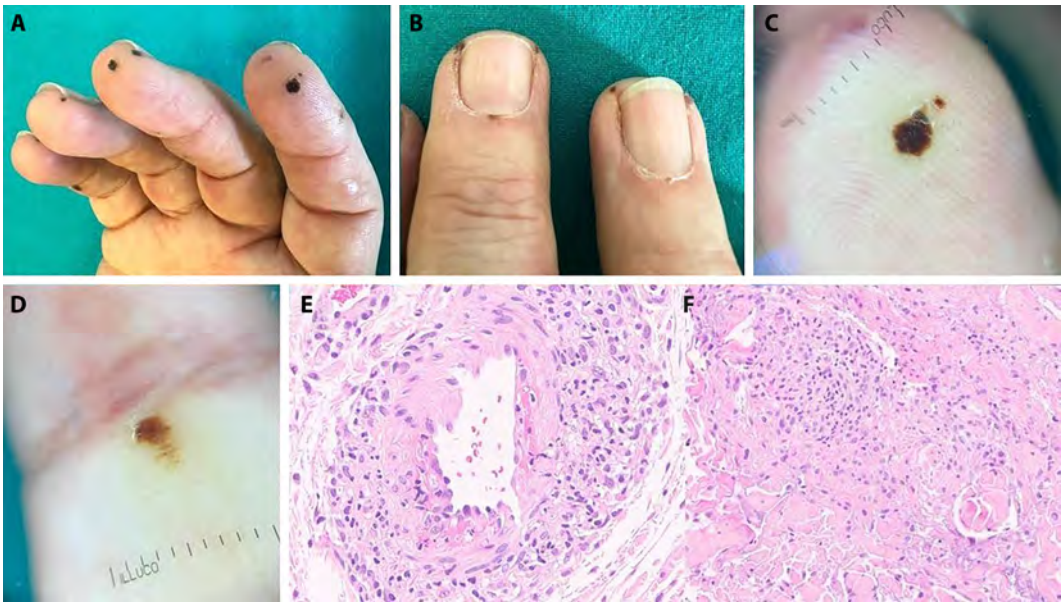


Figure 1. Multiple brown-to-black papules on the proximal and lateral nailfolds and ventral fingers, with signs of necrosis and fine desquamation (A, B). Homogeneous structureless areas of brownish color, with well-defined borders, without a network and vascular structures, covered by a mild scaly surface (C, D). Small vessel lymphocytic vasculitis with neutrophilic infiltration around the vessel wall (H&E, 40x) (E). Collagen necrobiosis surrounded by histiocytes (H&E, 20x) (F).

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Dermatology Practical & Conceptual

Inverted Follicular Keratosis of the Nail Unit: A Rare Case Report

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Citation: Rachadi H, Chemsy F, Marnissi F, Chiheb S. Inverted follicular keratosis of the nail unit: a rare case report. *Dermatol Pract Concept*. 2025;15(4):5542. DOI: https://doi.org/10.5826/dpc.1504a5542

Accepted: June 29, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Case Presentation

A sixty-two-year-old female presented with a painless periungual lesion on the left thumb, which had evolved over three months. Clinical examination revealed a nodular pink lesion located beneath the proximal fold of the nail of the left thumb, with a verrucous surface at its distal part. The lesion was painless on palpation and did not bleed upon touch (Figure 1A). An excisional biopsy of the lesion was performed. Histopathological examination showed epithelial proliferation with a predominantly verrucous exophytic and endophytic growth pattern. The epidermis was thickened, exhibiting ortho- and parakeratotic hyperkeratosis. It was mature, without significant cytonuclear atypia, and contained rare dyskeratotic bodies. Notably, no koilocyte was observed. The endophytic component invaginated into the dermis as large lobules or small lobules of coiled cells without atypia, with some keratin pearls. The limited visible dermis beneath the endophytic component showed a lymphocytic inflammatory reaction and neovascularization, consistent with an inverted follicular keratosis (Figures B and C). Postoperative outcomes following excision were uncomplicated, and no recurrence was observed after one-year follow-up.

Teaching Point

Inverted follicular keratosis (IFK) is a rare benign lesion that typically manifests as a small, solitary, papillomatous papulo-nodule, most commonly in elderly individuals. The exact etiopathogenesis of IFK remains unclear.

In 90% of cases, IFK is localized in the head and neck region. Other locations have rarely been documented in the literature, and to our knowledge, the localization in the nail unit has never been reported in the literature.

Clinically and dermoscopically, IFK lacks specific distinguishing features, making it challenging to differentiate it from other keratinizing lesions such as viral warts, seborrheic keratoses, keratoacanthoma, fibrokeratoma, squamous cell carcinoma, basal cell carcinoma, and melanoma [1]. Thus, the diagnosis of IFK is primarily established through histopathological examination.

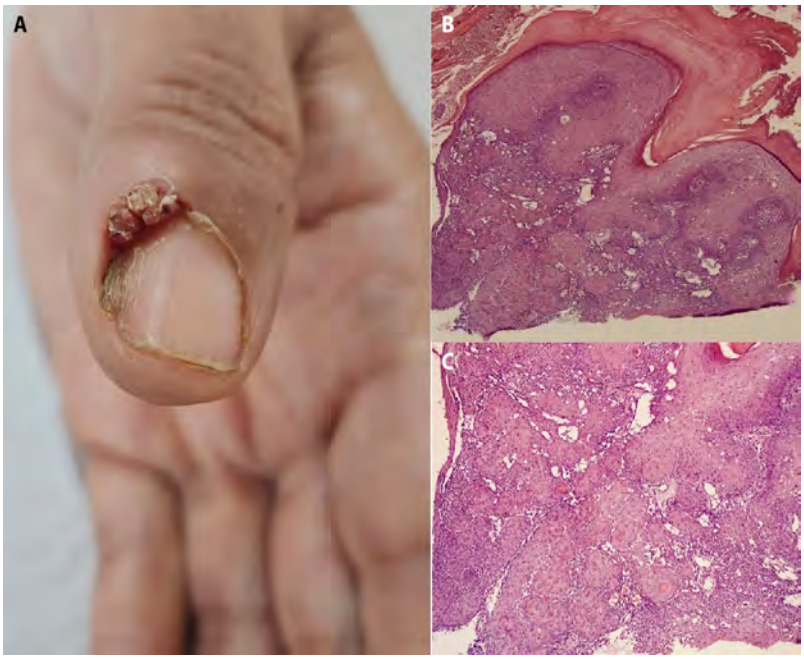


Figure 1. A nodular lesion in the proximal fold of the nail of the left thumb, with a verrucous surface at its distal part. B: Histological image (4x): epidermal proliferation with both exophytic and endophytic components covered by orthokeratotic and parakeratotic hyperkeratosis. C: Histological image (10x): endophytic component with whorls and dyskeratosis.

Histologically, IKF can also pose a differential diagnostic challenge with trichilemmoma, squamous cell carcinoma, keratoacanthoma, verruca vulgaris, and especially seborrheic keratosis, particularly when it is irritated. In this specific case, the characteristic endophytic growth pattern of IKF allowed for distinguishing between these two entities [2].

Surgical excision is the treatment of choice for IFK, although topical application of imiquimod 5% cream has also been reported to be effective.

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Dermatology Practical & Conceptual

Legius Syndrome: A Clinical Observation of a Father-Son Pair

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Key words: Pigmentary Disorder, Legius Syndrome

Citation: Wang L, Wu Y, Xu W, Tan C. Legius Syndrome: A Clinical Observation of a Father-Son Pair. *Dermatol Pract Concept.* 2025;15(4):5771. DOI: https://doi.org/10.5826/dpc.1504a5771

Accepted: April 22, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Case Presentation

A 3-year-old male was referred to our clinic to evaluate multiple café-au-lait macules (CALMs) present since birth. His growth and developmental milestones were age-appropriate, with no other abnormality observed. (Figure 1A). The family history was significant as the patient's father exhibited multiple CALMs, axillary freckling (Figures 1B and 1D), and several subcutaneous lipomas confirmed by ultrasound (Figure 1E). Genetic testing revealed a heterozygous frameshift mutation in exon 7 of the *SPRED1* gene (NM_152594:c .1149_1152delAGAG, p.G385Ifs*20). This mutation was also detected in the affected father, but absent in the mother (Figures 1F–H), confirming Legius syndrome.

Teaching Point

Legius syndrome is an autosomal dominant disorder caused by germline loss-of-function mutations in the *SPRED1* gene. The clinical features include multiple CALMs, with or without associated intertriginous freckling [1]. Associated findings may encompass lipomas, macrocephaly, or neurodevelopmental manifestations, including learning disabilities, attention-deficit/hyperactivity disorder (ADHD), and mild developmental delays [2]. In contrast to neurofibromatosis type 1 (NF1), Legius syndrome is characterized by the absence of tumorigenic manifestations such as neurofibromas and optic pathway gliomas, and it is associated with a milder clinical phenotype. Current clinical guidelines highlight the importance of monitoring and managing neurodevelopmental issues, given that there is no targeted therapy available for cutaneous lesions. Accurate diagnosis is essential for distinguishing Legius syndrome from NF1, thereby preventing unnecessary surveillance measures such as tumor screening and mitigating familial anxiety associated with NF1-related complications. Genetic counseling and prenatal testing should be made available to affected families.

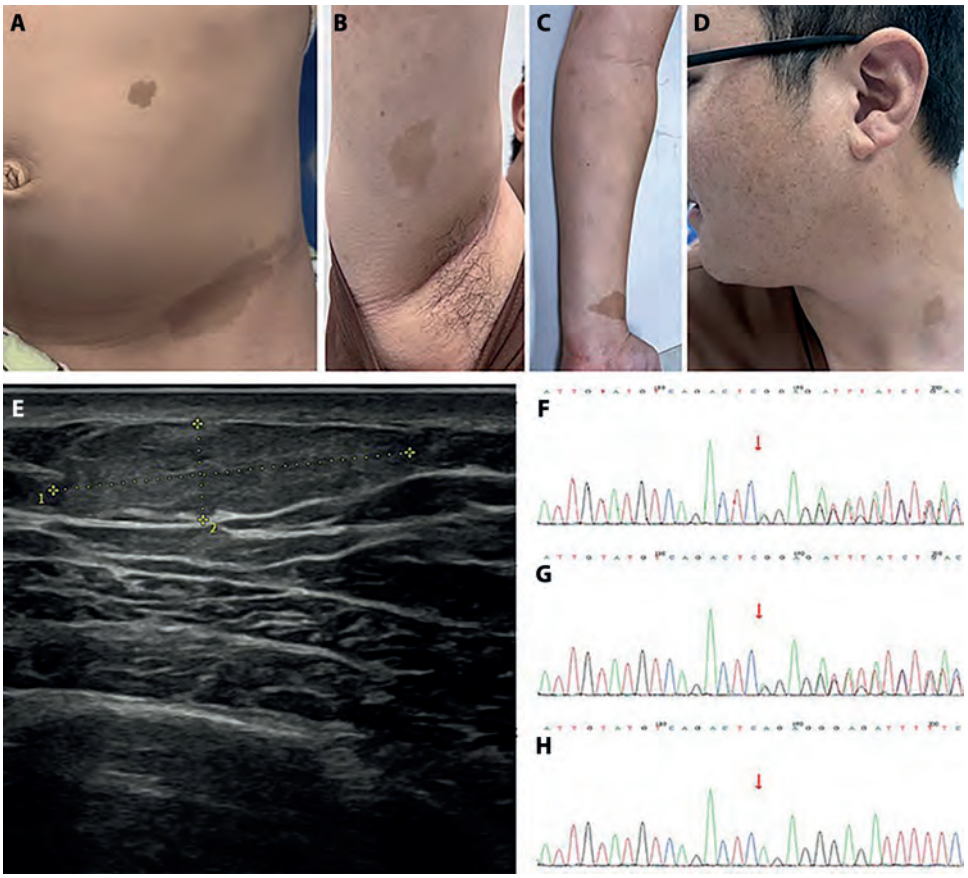


Figure 1. Clinical features included café-au-lait macules in the patient (A) and café-au-lait macules with facial freckles in the father (B–D).Ultrasound examination of the father's right flank revealed a slightly hyperechoic region (28 mm × 7 mm) with well-defined margins and clear demarcation from surrounding tissues, consistent with lipomas (E). The patient harbored a heterozygous frameshift mutation, c.1149_1152delAGAG (p.G385Ifs*20), in exon 7 of the *SPRED1* gene (F). This mutation was identified in his father (G) but absent in his mother (H).

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Dermatology Practical & Conceptual

Line-field Confocal Optical Coherence Tomography Features of Merkel Cell Carcinoma

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Key words: Merkel Cell Carcinoma, LC-OCT, Skin Imaging

Citation: Palmisano G, Lasudry J, Boussingault L, del Marmol V, Peris K, Suppa M. Line-field Confocal Optical Coherence Tomography Features of Merkel Cell Carcinoma. *Dermatol Pract Concept*. 2025;15(4):5743. DOI: https://doi.org/10.5826/dpc.1504a5743

Accepted: April 27, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Case Presentation

A 74-year-old male presented with a 1 cm rapidly growing red ulcerated nodule located on the right upper eyelid (Figure 1A). Dermoscopy showed arboriform and linear vessels and structureless pinkish-white areas (Figure 1B). Based on clinical and dermoscopic criteria, the differential diagnoses included basal cell carcinoma (BCC), amelanotic melanoma, and Merkel cell carcinoma (MCC). Line-field confocal optical coherence tomography (LC-OCT) examination displayed a flattened dermal-epidermal junction due to the nodular dermal proliferation of hyporeflective nests separated by hyperreflective collagen septa with some bright round cells, better highlighted in the horizontal image (Figures 1C and D). In addition, basaloid lobules with millefeuille pattern, indicating BCC, or nests of atypical melanocytes were absent. Hence, the dermal proliferation of hyporeflective nests and bright round cells at LC-OCT, as previously described by Soglia et al. [1], raised the suspicion of MCC, which was later confirmed by the histopathological examination (Figure 1E).

Teaching Point

MCC is an aggressive neuroendocrine tumor with often unspecific clinical and dermoscopic features [2] that is histopathologically characterized by dermal nodules with cells clustered in sheets or nests (Figure 1E). LC-OCT, through its high resolution and penetration, may be a valid additional tool in the diagnosis of MCC [1]. LC-OCT's non-invasive, real-time, near-histologic resolution allows visualization of dermal proliferation of hyporeflective nests and bright cells as well as peri-nodular black silhouettes

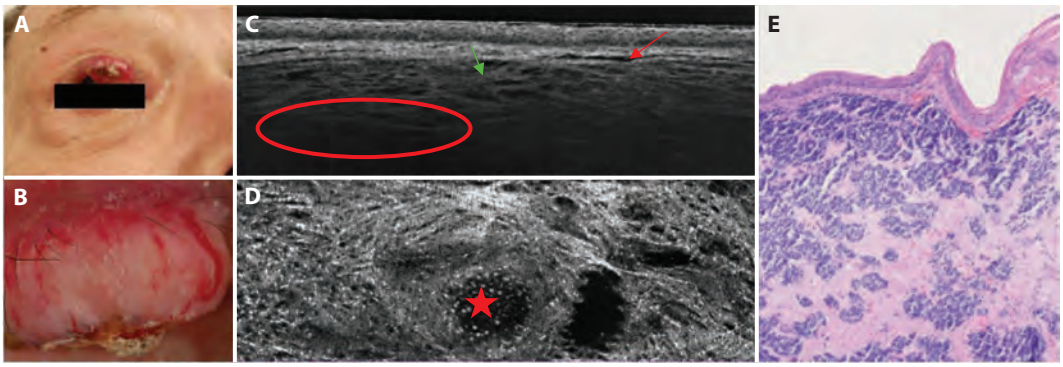


Figure 1. Clinical, dermoscopic, vertical, and horizontal LC-OCT and histopathological appearance of Merkel cell carcinoma of the right upper eyelid in a 74-year-old male. Clinical appearance of a nodular lesion localized on the right upper eyelid (A). Dermoscopy revealed the presence of arboriform and linear vessels and structureless pinkish-white areas (B). Vertical LC-OCT showed a flattened dermal-epidermal junction due to dermal nodular proliferation with perinodular vessels (red arrows). The dermis presented hyporeflective nests (red circle) separated by collagenous septa (green arrow) and bright round cells (C), prominent in the horizontal image (red star) (D). Histopathological examination showed dermal proliferation of layers and nests of small homogeneous cells, somewhat discrete, interspaced by connective septa (H&E staining, 100x) (E).

corresponding to extensive neoangiogenesis due to rapid tumor growth displayed by dermoscopy as arboriform and linear vessels.

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Dermatology Practical & Conceptual

Hutchinson's Sign without Melanonychia: A Key for the Diagnosis of Invasive Melanoma of the Nail Matrix

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Key words: Hutchinson sign, Nail matrix melanoma, Dermoscopy, Confocal Microscopy

Citation: Jaramillo-Arboleda A, Torres-Calderón MF, Piscazzi F, Micieli Galeazzi MP, Alos L, Puig S. Hutchinson's Sign without Melanonychia: a Key for the Diagnosis of Invasive Melanoma of the Nail Matrix. *Dermatol Pract Concept*. 2025;15(4):5888. DOI: https://doi.org/10.5826/dpc.1504a5888

Accepted: April 17, 2025; **Published:** October 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Case Presentation

A 70-year-old male presented with a recently noticed pigmented lesion on the periungual region of the fifth finger of his right hand. Clinical examination revealed a 6 × 4 mm lesion on the proximal and lateral nailfolds, with no melanonychia (Figure 1). Dermoscopy showed irregular brown pigmentation and a parallel ridge pattern in the volar skin. Reflectance confocal microscopy revealed a regular honeycomb pattern, upper epidermis without atypical cells, and bright melanocytes at dermoepidermal junction (1–3 per dermal papilla). Initial punch biopsy demonstrated melanocytic hyperplasia with mild atypia. To rule out matrix melanoma, nail matrix biopsy showed extensive melanocytic hyperplasia with PRAME positivity. Complete matricectomy revealed acral lentiginous melanoma with a Breslow thickness of 0.2 mm. Therapeutic margin widening surgery showed no residual neoplasia, confirmed by SOX10 immunohistochemistry.

Teaching Point

Subungual melanoma is a rare condition, accounting for only 0.7% to 3.5% of melanoma cases [1]. Subungual melanoma often presents with a pigmented brown or black longitudinal

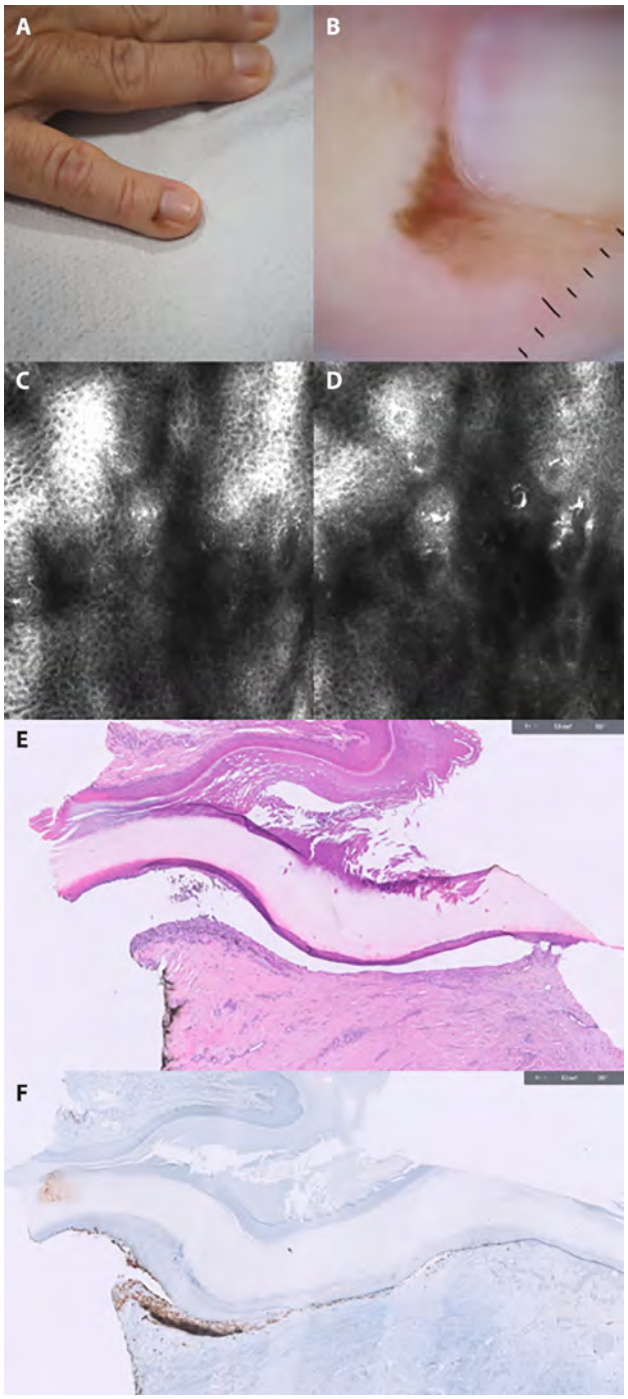


Figure 1. Clinical examination revealed a pigmented lesion on the lateral nailfold of the fifth finger of the right hand, extending to the periungual skin, with no evidence of melanonychia (A). Dermoscopy showed irregular, asymmetrical brown pigmentation radiating into the lateral nailfold, consistent with Hutchinson's sign (B). Reflectance confocal microscopy of the previously biopsied periungual skin demonstrated the honeycomb pattern of the epidermis, with the focal presence of shiny-white pagetoid dendritic cells (C) and irregular clusters of bright atypical dendritic cells at the dermoepidermal junction (D). Hematoxylin and eosin staining from the biopsy confirmed a proliferation of atypical melanocytes along the basal layer, with evidence of pagetoid spread in the epidermis (E). Immunohistochemical staining revealed SOX10 positivity in the atypical melanocytic proliferation, further supporting the diagnosis of acral lentiginous melanoma (F).

band, with irregularly pigmented lines involving 2/3 of the nail plate or the nailfolds with periungual pigmentation called Hutchinson's sign [2]. However, this case highlights Hutchinson's sign pigmentation of the periungual skin without nail plate pigmentation as an early indicator of invasive ungual melanoma, but biopsy should be performed in the nail matrix, origin of the tumor. This uncommon presentation could lead to diagnostic delays, further worsening the prognosis. Clinical suspicion is critical, even in the absence of melanonychia, particularly in patients over 50 years of age. Early biopsy of the nail matrix is essential to accurate diagnosis and timely treatment. Dermatologists should maintain a high index of suspicion for any periungual pigmentation, considering melanoma in the differential diagnosis [2].

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