Psoriasis induced by first-line pembrolizumab in metastatic non-small cell lung cancer: A case report

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Abstract. Therapeutic options for non-small cell lung cancer (NSCLC) have changed with the introduction of immune checkpoint inhibitors. Immunotherapy is generally well tolerated, but can also be associated with severe adverse events, such as the development of new autoimmune diseases. In patients without a history of autoimmune diseases, psoriasis caused by immunotherapy treatment is rarely described in the literature. The present study describes the case of a 68-year-old man with metastatic NSCLC that started chemoimmunotherapy with carboplatin plus pemetrexed plus pembrolizumab. After two cycles of therapy, the patient developed a G3 maculopapular rash. Biopsy confirmed psoriasis and pembrolizumab treatment was discontinued. At the last follow up, the patient was

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Abbreviations: AE, adverse event; APC, antigen-presenting cells; BSA, body surface area; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; DRESS, Drug Rash with Eosinophilia and Systemic Symptoms; ECOG, Eastern Cooperative Oncology Group; HRQoL, health related quality of life; ICIs, immune checkpoint inhibitors; IHC, immunohistochemistry; irAEs, immune-related adverse events; NA, not applicable; NSCLC, non-small cell lung cancer; OS, overall survival; PD-1, programmed death protein 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis

Key words: lung cancer, pembrolizumab, immuno-related adverse events, psoriasis, chemoimmunotherapy

still on maintenance therapy with pemetrexed alone, which is well tolerated. Psoriasis has rarely been reported as an immune-related adverse event. Although the patient had to stop the immunotherapy treatment, the patient is still exhibiting a response to it. Notably, it has previously been described how skin toxicities are associated with a better outcome. Other studies need to be conducted to identify the risk and predictive factors associated with severe immune adverse events and objective response.

Introduction

Immunotherapy has profoundly changed the history of several types of cancer such as the improvement of survival, duration of response, and quality of life compared with chemotherapy. Immune checkpoint inhibitors (ICIs) are comprehensive of different monoclonal antibodies targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1) (1).

Interaction between PD-1 (on T cells) and PD-L1 (on tumor cells) induces immune system tolerance and promotes tumor growth. Consequently, the inhibition of the immune system down-regulation permits the reactivation of T-cells (2). However, the immunity activation can disrupt peripheral immune tolerance and cause immune-related adverse events (irAEs) (3).

Pembrolizumab is a humanized monoclonal antibody IgG4 PD-1 inhibitor. It blocks the interaction with PDL1 and PDL2 expressed by antigen-presenting cells (APC), tumor and other cells in the tumor microenvironment (4). It has shown efficacy in different malignancies, specifically in Non-Small cell lung cancer (NSCLC). The first-line approval came with the Keynote024 trial (5) that involved patients with meta-static NSCLC non-oncogene addicted, PD-L1 \geq 50%. In this study, patients were randomized to receive pembrolizumab 200 mg q3w vs. platinum-based chemotherapy. Clinically significant results in overall survival (OS) and progression-free

survival (PFS) were obtained in this population expressing high levels of PD-L1.

First-line treatment standard for patients with PD-L1 <50% is the combination of chemo and immunotherapy. In the KEYNOTE-189 trial (6), patients were randomized to receive chemotherapy + pembrolizumab + pemetrexed or chemotherapy + placebo, followed by maintenance with pembrolizumab + pemetrexed or placebo + pemetrexed. A median follow-up of 4 years confirms trial results: experimental arm OS is significantly better than the placebo arm (HR 0,60). Subgroup analysis shows that the combination is efficient even in patients with brain and liver metastasis. Positive effects are independent of PD-L1 expression.

Evidence shows that more than 60% of patients treated with immunotherapy develop irAEs. Dermatological irAEs concern between 30 and 50% of patients on ICIs and are the most frequent and the earliest (7). More than 30%reported mild skin toxicity, alone or associated with other symptoms (8). Unfortunately some severe irAEs such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) are life-threating are described and require the cessation of ICIs (8). The average incidence of skin irAEs reported in meta-analysis includes 16.7% for Pembrolizumab (9). For patients treated with the chemoimmunotherapy combination, the skin reactions mostly reported (frequency $\geq 1/10$) were: alopecia, skin eruption, and pruritus. Common adverse events ($\geq 1/100$, <1/10) were severe cutaneous reactions, erythema, dermatitis, and dry skin. Uncommon adverse events ($\geq 1/1.000$, <1/100) were psoriasis, eczema, lichenoid keratosis, acneiform dermatitis, and vitiligo. Rare adverse events ($\geq 1/10.000$, < 1/1.000) were nodosum erythema, papules, and change in color of skin or hair (4). Psoriatic plaques are the most frequent presentation of psoriasis but the incidence has been difficult to estimate (9). The mechanisms of pembrolizumab-induced psoriasis remains unclear. A reason could be related to the activation of Th17 lymphocytes, which typically are inactivated by PD-1 (10).

In this paper, we describe a case of psoriasis in a 68-years-old man with advanced NSCLC who developed this specific dermatology adverse event during immunotherapy.

Case report

A 68-year-old Caucasian male patient with Eastern Cooperative Oncology Group (ECOG) Performance Status 0, came to our observation, at Multispeciality Department of Oncology, ASL Latina, 'Sapienza' University of Rome, Aprilia, Italy in February 2020 with a histologically confirmed diagnosis of right upper lobe lung adenocarcinoma. Immunohistochemistry (IHC) showed ALK and ROS1 negative, PD-L1 <1%, and EGFR wild type in quantitative PCR.

A CT scan and brain MRI demonstrated a lung lesion of 34x25x29 mm and a single right hemispheric lesion of 7 mm asymptomatic. In April 2020 the patient started stereotactic radiation therapy, completed in 3 sessions (33,75 Gy total dose). Following, a front-line chemo-immunotherapy was set up with carboplatin AUC 5 i.v. day 1, pemetrexed 500 mg/sqm i.v. day 1 and pembrolizumab 200 mg day 1, every 21 days.

Initially the patient developed diarrhea G1 as a single adverse event (AE). Then, after 2 cycles of chemo-immunotherapy, a cutaneous rash G3 (Fig. 1) appeared on the back of the chest, upper and lower limbs appeared associated with pruritus G1.

In June 2020 the patient stopped chemo-immunotherapy treatment and daily oral prednisolone 50 mg/daily for three days + ebastine 10 mg was administered. Steroids have been weaned in 10 days, with complete regression of the rash. After 3 months a CT scan showed stability of disease of the primary lesion and complete response of the hemispheric lesion post-radiotherapy.

In August 2020 the patient restarted the chemoimmunotherapy combination after seven weeks of interruption. In September 2020, after four cycles of therapy, a CT scan showed a partial response of the primary lesion. The patient started maintenance therapy with pemetrexed 500 mg/sqm and pembrolizumab 200 mg day 1, every 21 days. After 3 maintenance cycles, he manifested a re-occurrence of the rash with scaly papules on the head, abdomen, back and gluteus (Fig. 2). This was treated with prednisolone 50 mg/daily for three days, weaned over 10 days. After the interruption of prednisolone appeared an exacerbation of the cutaneous rash and pruritus G1.

In December 2020 a consultant dermatologist diagnosed psoriasiform reaction on the elbows, gluteus and scalp; a cutaneous biopsy confirmed diagnosis of psoriasis (Fig. 3). The patient denied any personal or family history of psoriasis.

Topical treatments: clobetasol foam for scalp twice daily for 15/20 days, calcipotriol + betamethasone foam once a day for 4 weeks, dexamethasone + clotrimazole on skin folds twice daily and then soothing cream.

After the complete regression of the lesions, the patient continued the maintenance treatment without pembrolizumab. The patient has completed 28 maintenance cycles with only pemetrexed with stable disease at CT revaluations. The skin manifestations of psoriasis are controlled without any local or systemic treatment (Fig. 4).

Discussion

Immunotherapy has brought the development of new strategies against NSCLC. Previously negative PD-L1 patients were considered less responsive to these new treatments, now we know that PD-L1 is not an affordable biomarker of immunotherapy sensitivity, indeed also patients with lower expression of PD-L1 could benefit from this treatment, above all combined protocols as established by KEYNOTE-189 (6). The scenery of non-oncogene addicted NSCLS is thus changed because immunotherapy constitutes the standard of care (combined with chemotherapy or not). This has certainly increased the number of patients treated with immunotherapy, as well as the experiences of both responses and adverse events.

Skin AEs are one of the most frequent AEs in patients treated with anti-PD-1 (nivolumab and pembrolizumab). Onset is quite early, within the first weeks after the infusion. Despite these serious manifestations being rare (<3%), and usually do not require the interruption of treatment (11).

Psoriasis is a chronic autoimmune disease that affects about 0,27-11,4% of the population, hits the skin, and it could impact lives of patients both physically and psychologically (12).



Figure 1. (A) Psoriasis of the scalp; (B) psoriasis of the left elbow.

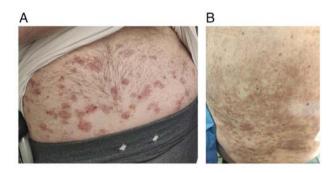


Figure 2. (A) Psoriasis of the abdomen; (B) psoriasis of the back.

It's often associated with multiple comorbidities such as obesity (13). This disease causes red, itchy scaly patches, most commonly on the knees, elbows, trunk and scalp (14). The histopathological features are similar to typical psoriasis vulgaris, with the presence of hyperkeratosis, hypogranulosis, acanthosis with elongated rete ridges, and a perivascular lymphocytic infiltration (7).

A health-related quality of life (HRQoL) impairment is associated with psoriasis. Itching and skin pain have been reported in 62-97 and 42-59% of patients with psoriasis, respectively (15). Furthermore, although a correlation between anxiety and psoriasis has not been demonstrated, the levels of anxiety recorded in patients with psoriasis were higher than average (16).

The mechanism of disease is a higher expression of Th1 and Th17 lymphocytes and, consequentially, cytokines such as IL-1, IL-6, and IL-17 (17). It is known that immunotherapy

might exacerbate psoriatic lesions in those with positive familial or personal history of psoriasis. The most frequent presentation is plaque-type psoriasis, and it is associated with a family history (17). The mechanism under this adverse event is explained by the inhibition of PD-1/PD-L1 axis that, as reported by Dulos et al (18) and Okiyama and Tanaka (19), activates Th1, Th17 and Th22 lymphocytes with the production of IL-6 (20). In turn, IL-6 stimulates IL-17, a cytokine that downregulates T-reg cells. The balance between these types of cells is the key to autoimmune regulation and cancer (21). Another mechanism described in literature is overweight or obesity. Western Diet fed mice became obese and they have higher expression of Th-17 cytokines and PD-1 on $\gamma\delta$ -low T cells. Imiquimod treatment elevate psoriasis inflammation and PD-1 as inhibitory regulation. Anti-PD1 treatment, as Pembrolizumab, induced a prominent PD-1 blockage effect and severe psoriasiform dermatitis (8). Our patient is overweight with a BMI of 28.7.

As in Table I, not many cases of pembrolizumab-induced psoriasis are described in the literature. We have reported patients without a personal or family history of psoriasis. The median onset time was 6 weeks, 2 cycles. Only 3 cases of NSCLC were registered.

For G1 toxicity (skin rash with or without symptoms, >10% body surface area (BSA) ESMO Guidelines recommend avoiding skin irritants, sun exposure, topical emollients, topical steroids (mild strength) cream and/or, topical or oral antihistamines for itch. For G2 (rash covers 10-30% of BSA) is recommended supportive management as above, a topical steroid (moderate strength) cream and or potent cream bd +/- topical or oral antihistamines for itch.

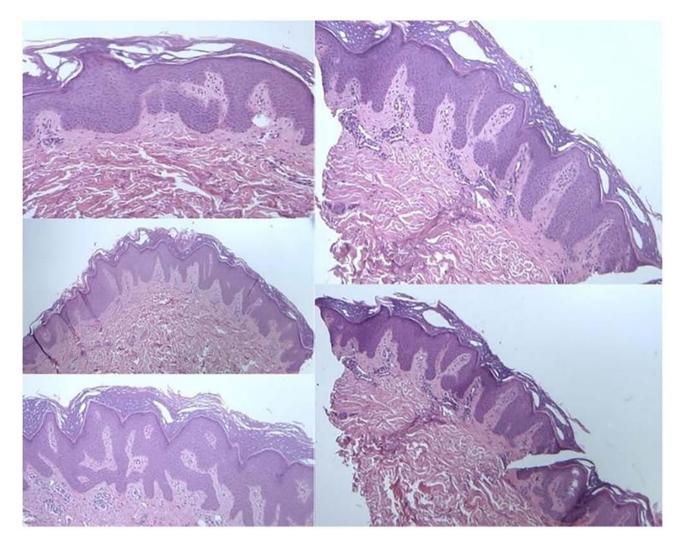


Figure 3. Sections of abdomen skin punch biopsy showing compact/moderate orthokeratosis and parakeratosis, mildly hyperplastic granular layer, irregular psoriasiform hyperplasia, focal spongiosis, dishomogeneous thinning of basal membrane and focal intradermal deposits of melanin pigment. Mild perivascular lymphohistiocytic infiltrate of the superficial subepithelial connective tissue was also identified. Negative for eosinophils.



Figure 4. (A) Abdomen without psoriasis. (B) Improvement of elbows' psoriasis. (C) Improvement of scalp's psoriasis.

The treatment can be continued. For G3 (rash covers >30% BSA or grade 2 with substantial symptoms) withhold ICIs, topical treatments as above (potent) and steroids. If mild to moderate 0.5/1 mg/kg prednisolone once daily for three

days then wean over 1-2 weeks; or if severe, i.v. (methyl) prednisolone 0.5-1 mg/kg and convert to oral steroids on response, wean over 2-4 weeks. For G4 (skin sloughing >30% BSA with associated symptoms) i.v. (methyl)prednisolone 1-2 mg/kg with urgent dermatology review and discontinuation of ICIs (11).

Our patient, as described above, needed both topical and systemic steroids, soothing and antifungal cream to solve maculopapular rash. With the aim of preserving the recurrence and severity of psoriasis, the immunotherapy treatment was discontinued.

The majority of cases reported in Table I were treated with topical steroids. One case was treated with anti-IL-17 (secukinumab) (3), and two cases with anti-PDE4 (apremilast) (22,23). Despite the discontinuation of the treatment, the benefit of our patient, in terms of progression free survival, is consistent if compared with the median PFS of the Keynote 189 trial, which is 9.0 months (24). A meta-analysis conducted on 52 studies including 9,156 patients affected by different malignancies treated with anti-PD-1/PD-L1 agents (22), demonstrated how irAEs were statistically associated with better PFS and OS. Observing subgroups analysis, these

First author, year	Sex	Age, years	Cancer type	Onset time of psoriasis after the start of immunotherapy, weeks	Personal and familial history	Psoriasis management	(Refs.)
Huang and Chu, 2020	М	71	Squamous NSCLC	2	No	Topical steroids	(17)
Suzuki <i>et al</i> , 2020	F	78	NSCLC	9	No	Topical and oral steroids	(22)
Johnson <i>et al</i> , 2019	М	80	Melanoma	12	No	Topical steroids and moisturizers, then retinoids and oral steroids, then secukinumab	(3)
Siciliano <i>et al</i> , 2020	М	75	Melanoma	30	No	Apremilast	(23)
Takama <i>et al</i> , 2020	М	74	Bladder	2	No	Oral steroids + vitamin D, then apremilast	(25)
Totonchy <i>et al</i> , 2016	F	80	Melanoma	4.5	NA	Topical steroids	(26)
Bonigen <i>et al</i> , 2017	М	59	Melanoma	NA	No	Topical steroids	(27)
Bonigen <i>et al</i> , 2017	М	77	Melanoma	NA	No	Topical steroids	(27)
Voudouri <i>et al</i> , 2017	М	69	Squamous cell carcinoma of the tonsil	6	No	UVB-NB and topical steroids	(12)
Present study	М	68	NSCLC	6	No	Oral and topical steroids, and antihistaminic and antifungal cream	-

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M, male; F, female; NA, not applicable; NSCLC, non-small cell lung cancer.

results have been described in NSCLC, endocrine and skin toxicities but not for gastrointestinal and lung AE. The major grade of adverse events was not associated with favorable PFS or OS.

In conclusion, pembrolizumab, as an immunotherapy drug, has changed the prognosis and the quality of life of patients. Compared to chemotherapy, ICIs have a different spectrum of adverse events, mostly well tolerated. However, as in our case, they could be so severe to discontinue the treatment, even without a positive history of autoimmune disease. As mentioned above, our patient had a long response from immunotherapy despite its interruption. Although the mechanism behind irAEs remains not clear, it might be explained by a reactivation of T-cells, so that patients with a more responsive immune system are the ones who benefit more by ICIs. For these reasons, it might be important to conduct other studies to identify predictive factors of immune-related toxicities and objective response.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

FG, LR, IP and AC made substantial contributions to conception and design of the manuscript. SC, AA, MB, CP and GC

contributed to acquisition and interpretation of data, and wrote the abstract. DS, VP and VS performed the histological examination of the psoriasis and were major contributors in writing the manuscript, confirm the authenticity of all the raw data and gave final approval of the version to be published. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the publication of their data.

Competing interests

The authors declare that they have no competing interests.

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