Dermatology Practical & Conceptual

Clinical and Dermoscopic Diagnosis of Actinic Keratosis

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Introduction

Actinic keratosis (AK) is the most common keratinocyte skin cancer (KC) mainly caused by chronic sun damage; over 80% of AKs arise on chronically sun exposed areas such as face, scalp, neck, forearms and hands [1,2]. In fact, the most important risk factors for the development of AKs is ultraviolet (UV) exposure, notably UVB rays, augmented by the length of exposure and a lighter skin phototype [3]. Rates of transformation of AKs into squamous cell carcinoma (SCC) vary from 0.0015% to 16% but no specific criteria have been linked to the risk of progression, therefore the treatment of AK is mandatory for all forms detected during the visit [4]. Studies demonstrated two pathways for the development of a SCC: a direct one, from AK stage I into SCC and another with a progressive model (from AK stage I to AK stage III and then transformation into SCC) [5]. As development of invasive AK directly from the cancer field cannot be ruled out, the ideal treatment should be able to eradicate AK lesions and reverse the underlying field cancerization [6].

The diagnosis of AK is based on the clinical and dermatoscopic features; the combination of clinical and dermatoscopic characteristics helped physicians to elaborate algorithms and systems of classification useful not only for the diagnosis but also for choosing the correct therapy and for monitoring the response to the treatment. The aim of this systematic review is to summarize the clinical and dermatoscopic clues for the diagnosis of AKs, including clinical classification systems.

Materials and Methods

We searched the literature for studies published in the last 20 years between 2004 and 2024, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched PubMed

database using the term *actinic keratosis* in combination with the following terms: *dermoscopic and/or dermatoscopic features, clinical features, classification, dermoscopic and/or dermatoscopic criteria*. Eligibility was restricted to studies with more than thirty cases described. Reviews, meta-analyses, cohort studies, case series were eligible for inclusion. Only articles in English were selected. Letters and case reports without statistically relevant data were excluded from the analysis. Other potentially relevant articles were identified by manually checking the references of the included literature. The last search was run on 26th January 2023. Two investigators independently selected relevant articles according to predefined inclusion and exclusion criteria, as described above. Disagreements were solved by discussion, with a prior arrangement that any unsettled discrepancy would be determined by a third author.

Clinical Diagnosis of AKs: Olsen Classification

AK is clinically characterized by a squamous and erythematous macula or plaque; the degree of hyperkeratosis and symptomatology is variable. In fact, it can be asymptomatic, itchy and sometimes painful [7]. The first clinical classification of AKs is based on a three-stage model; the Olsen classification is based on the distinction of AKs into three stages: grade I in which the AK is a small erythematous macula, not very visible and more easily appreciated on palpation; grade II with greater hyperkeratosis and erythema, whereby the lesion is easily diagnosed with the naked eye and also easily appreciated; otherwise grade III is characterized by the maximum of hyperkeratosis and the diagnosis is immediate [8]. This classification has been among the most widely adopted in both clinical practice and scientific studies but has as a major limitation: it does not evaluate the entire skin area but defines only the grade of individual observable keratosis. Moreover, based on a 3-stage model, it seems to be a progressive model up to the most severe degree of keratosis with higher risk of transformation into iSCC. As other studies have shown, this is not true because even grade I AKs can evolve directly into iSCC, thus necessitating treatment of all forms.

The aim of the original Olsen classification (elaborated in 1991) was not to establish a clinical classification of AKs but to evaluate the response of AKs to masoprocol; the original classification had as a main clue the grade of hyperkeratosis, explaining why it has three grades. No predictive values are associated with this classification, no correlation has been found between Olsen grade and rate of progression and Olsen grade do not correlate with histology (i.e Rowert-Huber classification). Finally, Olsen classification addressed only single lesions, not considering AKs as components of field of cancerization (FC) [8,9]. For all these reasons, according to some authors, its use should be dismissed.

Dermatoscopic Features of AKs

Non Pigmented AK

The dermatoscope is certainly the quickest and most user-friendly tool for diagnosing AKs. They were first described by Zlaudek ed al in 2006 with the identification of four main dermatoscopic features: a pattern characterized by erythema surrounding hair follicles to form a "pseudonetwork," yellowish-white scales; fine linear wavy vessels with a perifollicular distribution and follicles with yellowish keratotic plugs surrounded or not by a with halo. These features combined form a typical pattern, which later became famous over the years for ease of recognition, termed the "strawberry pattern" [10]. This pattern is, however, more characteristic of lesions located on the face. Reinehr et al. have described how the most frequent dermatoscopic features of non-facial actinic keratoses are represented by opaque white scales and erythema for non-pigmented lesions, and homogeneous brown pigmentation for pigmented ones [11]. Rosettes, described as structures characterized by four white dots arranged like a 4-leaf clover visible under polarized light in actinic keratoses (AK) and squamous cell carcinomas (SCC), are actually quite nonspecific since they can also be identified in basal cell carcinomas (BCC), melanomas, and non-lesional photodamaged skin [12,13]. Dermatoscopy has also proven to be a valuable tool for the clinical and post-treatment follow-up of such lesions [14–17].

Pigmented AK

Since the initial use of dermatoscopy in diagnosing AKs, it has been challenging to accurately identify pigmented AKs (pAKs), particularly when differentiating them from lentigo melanoma (LM) in cases of diagnostic uncertainty. In a 2005 study on two cases of pigmented actinic keratoses (pAK), Zalaudek et al. asserted that although dermatoscopy could be helpful in some instances, the principle that the diagnosis of a pigmented lesion cannot rely on a single criterion meant that histopathology remained the gold standard for diagnosing these lesions [18].

The same conclusion was reached in a subsequent study by Akay et al. on 89 facial pigmented skin lesions, including 67 pAK, aiming to define the dermatoscopic criteria that distinguish them from LM. The study identified up to eleven different dermatoscopic features in pAK, such as grey dots, annular-granular patterns, rhomboidal structures, and pseudonetworks [19]. Subsequently, Lallas et al. studied 144 facial pigmented skin lesions, including 70 LM) and

56 pAK, to determine if the limitations of dermatoscopy in differentiating these two types of lesions were due to previous studies focusing exclusively on pigmented criteria without considering other possible characteristics. The results of their study indeed showed that features such as scales, red colors, and white circles were significantly associated with pAKs, whereas grey rhomboids, non-prominent follicles, and intense pigmentation were linked with LM (Figure 1) [20]. The most recently described criterion in the literature, useful for the differential diagnosis between pAK and LM, is the "inter grey halo," as characterized by Nascimento et al. 21. This feature is described as a homogeneous circular structure, either gray-blue or beige, which on one side surrounds the hair follicle and on the other forms the inner contour of the pigmented pseudonetwork. Histologically, this structure corresponds to an inverted cone of epidermis spared by the follicular keratin plug and the anaplastic, hyperpigmented epidermis of the pseudonetwork.

Bowenoid AK

Bowenoid actinic keratosis (AK) is a histological subtype of AK characterized by single-cell keratinization and full-layer atypia that does not involve the cutaneous adnexa [22]. Dermatoscopically, it is distinguished by regularly distributed glomerular vessels on the surface of the lesion, unlike Bowen's disease, where the vessels are typically arranged in clusters (Figure 1) [23].

Dermatoscopy Signs of Invasiveness in AK

In 2012, based on Olsen's clinical classification, the dermatoscopic features of nonpigmented AKs were analyzed to assess whether there were typical and/or pathognomonic criteria related to grades. It was shown that grade I AK showed mostly the erythematous pseudonetwork and white scales, grade II are characterized by the "strawberry" pattern while grade III are associated mostly with marked hyperkeratosis and follicular keratin plugs [24]. [Table 2]

The most interesting finding was to have observed more hyperkeratosis dermatoscopically in the higher grades (II and III) which then reached the maximum presence in in situ squamous cell carcinoma (iSCC) [25]. Another criterion that aids in the diagnosis and assessment of progression, along with those previously mentioned, is the red starburst pattern. This pattern is characterized by the presence of peripheral radial lines or vessels in the context of typical actinic keratosis (AK) criteria. It is indicative of progression to invasive squamous cell carcinoma (iSCC) [24]. Papageorgiou et al. published a study evaluating the presence of dermatoscopic criteria indicative of early invasion, capable of differentiating between early SCC and AK. Conducted on 45 AK cases and 50 early SCC cases, the study highlighted that the predictive criteria for early SCC are dotted/glomerular vessels, hairpin vessels, and white structureless areas, while an erythematous background was identified as a negative predictor (Figure 2) [26,27].

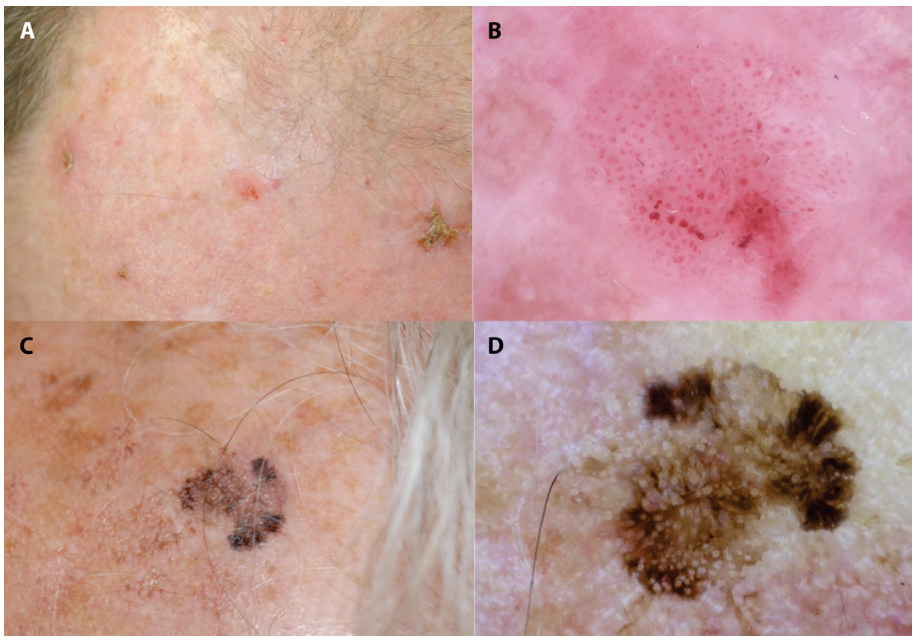

Figure 1. Male kidney transplant patient presenting with a pinkish frontal macular lesion (A) dermatoscopically characterized by glomerular vessels evenly distributed over the surface (B) and corresponding to a bowenoid AK on histopathology. Seventy-nine-year-old male with a pigmented hyperkeratotic patch of the left frontal region (C) characterized dermatoscopically by pigmented pseudonetwork, dilated yellowish-white follicular ostium, rosettes, and sharp margins (D) and corresponding to a pigmented AK on histopathology.

Table 1. Clinical classification systems of AK

	Olsen classification	AKASI score	AK-FAS score
Grades/Scores	3	18	4
Analysis of FC	No	Yes	Yes
Analysis of sun damage	No	No	Yes
Analysis Hyperkeratosis	Yes	No	Yes
Areas considered in the analysis	Lesion-based classification	Scalp and face	Scalp and face

FC: field of cancerization.

Table 2. Dermoscopic features of AK according to the grade

Grade of AK	Dermoscopic feature	Histological correlation
I	Red pseudonetwork	Atypical keratinocytes localized in the third of the epidermis
II	Strawberry pattern	Atypical keratinocytes in the lower two-thirds of the epidermis
III	Yellow-White scales and follicular keratin plugs	Atypia throughout the epidermis

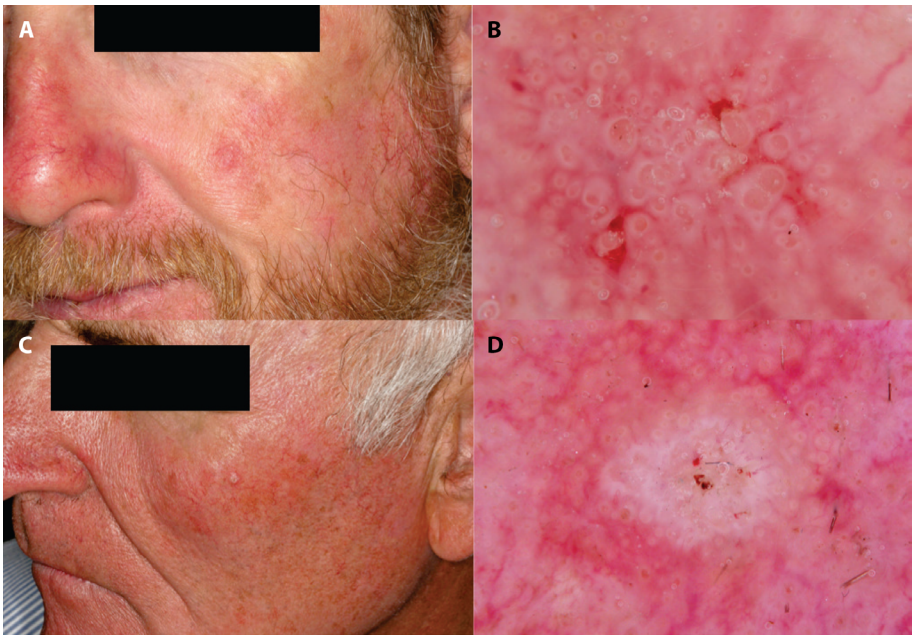

Figure 2. A 41-year-old male with an erythematous and hyperkeratotic macular lesion of the left malar region (A) dermatoscopically characterized by erythematous pseudonetwork, white scales, and (B) dilated follicular ostium corresponding to an AK on histology. Sixty-four-year-old male with an erythematous and hyperkeratotic maculo-papular lesion of the left malar region (C) characterized dermatoscopically by erythematous pseudonetwork and dilated follicular ostium at the periphery associated with a central white structureless area (D) corresponding histologically to an SCC.

AK in other Non-Invasive imagine Techniques

Optical Coherence Tomography (OCT)

OCT operates as a noninvasive, in vivo imaging method utilizing interferometry principles. It employs infrared light for imaging, achieving an axial and lateral resolution around 15 micrometers, with a penetration depth between 500 and 1000 micrometers. This method allows for the visualization of skin layers, adnexal structures, and blood vessels, but it does not provide cellular details [28]. Several studies have described the morphological characteristics of actinic keratoses (AK) in Optical Coherence Tomography (OCT), including: disruption of the dermo-epidermal junction (DEJ), epidermal thickening, hyperkeratosis, white streaks and dots, rapid attenuation of light, lower penetration depth, and a dark band in the stratum corneum [29–33]. The most predictive features described in the majority of published papers include architectural disarray, characterized by a complete or partial absence of the dermo-epidermal junction (DEJ);

white streaks and dots, which histologically correspond to particularly dense areas of hyperkeratosis; epidermal thickening; and pronounced hyperkeratosis. The latter characteristic is not specific to actinic keratoses (AK) as it can also be found in other lesions and may compromise the quality of the images due to artifacts. These artifacts create shadows that obscure underlying portions of the tissue [29]. The basement membrane cannot be distinguished with this technique, making it difficult to reliably determine early tumor invasion. he practical utility of Optical Coherence Tomography (OCT) for actinic keratoses (AK) also lies in its ability to non-invasively monitor the outcomes and effectiveness of various therapeutic approaches available for this condition, offering additional possibilities and information beyond what is possible with dermatoscopy alone. In this regard, numerous studies have been published on the use of OCT to evaluate the results of therapies such as ingenol mebutate [34,35], hybrid fractional ablative and nonablative laser resurfacing36, daylight photodynamic therapy after tailored pretreatment with ablative fractional laser or microdermabrasion [37], cryosurgery [38], imiquimod [39], tirbanibulin [40], and fluorouracil [41]. Furthermore, this method is useful in the identification of both clinical and subclinical actinic keratoses, thereby serving as an important tool for precisely defining the field of cancerization in patients with significant photodamage [42].

Line-Field Confocal Optical Coherence Tomography (LC-OCT)

Line-field confocal optical coherence tomography (LC-OCT) is a non-invasive optical imaging method that produces real-time vertical, horizontal, and three-dimensional section images. These images are comparable to traditional histology images and offer cellular resolution, with a penetration depth of approximately 500 micrometers [43]. This technique can identify diverse skin structures and assess various conditions, such as the presence of atypical epidermal cells, the integrity of the dermo-epidermal junction in the vertical plane, the uniformity of the keratinocyte pattern, and the presence of dendritic cells in the horizontal plane. Cinotti and colleagues employed LC-OCT to identify and analyze key patterns in AK and SCC, aiming to distinguish specific criteria that could differentiate between these conditions. Notable features common to both AK and SCC included hyperkeratosis, acanthosis, parakeratosis, erosion/ulceration, disrupted epithelial architecture, dyskeratotic keratinocytes, crowded cell nuclei, abnormal nuclei, tumor budding, and expanded blood vessels. Among these, dyskeratotic keratinocytes, atypical nuclei, and disorganized epithelial architecture were particularly significant indicators [44]. Just as with OCT and RCM, excessive hyperkeratosis can lead to artifacts characterized by heightened reflectivity in the upper portions and reduced image quality in the lower portions of lesions marked by this criterion. Greater lesion thickness, disrupted epidermal architecture, and non-outlined DEJ could assist instead in differentiating SCC from actinic keratosis AK [44]. Ruini and colleagues have shown that evaluating AK with LC-OCT can non-invasively replicate the PRO histological classification, exhibiting strong correlation and interobserver agreement. As a result, this method facilitates the assessment of AK's progression risk without requiring an invasive biopsy [45]. A study by Daxenberger et al. investigated the use of an artificial intelligence (AI) algorithm on LC-OCT images for diagnosing and grading AK. The performance of the AI algorithm was compared with that of a group of experts, demonstrating high concordance. Consequently, this suggests the potential to enhance the accuracy of diagnoses and improve the management of patients with this condition in clinical practice [46]. Numerous studies have been reported in the literature on the use of LC-OCT for monitoring AK after treatments such as cryotherapy [47] and tirbanibulin [48].

Reflectance Confocal Microscopy (RCM)

Reflectance confocal microscopy (RCM) is a non-invasive imaging technique that enables the visualization of skin in the horizontal plane with cellular-level resolution. The imaging depth of RCM extends approximately 200-300 micrometers, reaching down to the papillary dermis [49]. The primary features of AK as observed through RCM include hyperkeratosis with parakeratosis at the level of the stratum corneum and an irregular honeycombed pattern in the spinous-granular layers. Given that this technique provides images on a horizontal plane, it does not enable the assessment of the vertical invasion depth of these lesions [50]. Pellacani and colleagues reported a high concordance rate and strong interobserver correlation in the grading of keratinocyte atypia in AK when evaluated using RCM compared to histopathological examination [51]. Specifically, grade 1 actinic keratosis (AK) displays focal areas of atypical honeycombed patterns mixed with areas of normal honeycomb at the spinous layer level. Grade 2 AK shows widespread keratinocyte atypia across both the spinous and granular layers, featuring keratinocytes of various shapes and sizes. Grade 3 AK is characterized by a markedly atypical honeycombed pattern described as disarranged. Keratinocyte pleomorphism increases proportionally with the AK grade [51,52]. Moscarella et al. outlined the principal features of pAK using RCM. These features include hyperkeratosis with parakeratosis, atypical honeycombed pattern, increased epidermal thickness, intraepidermal dendritic cells, and bright, small dermal papillae with enlarged interpapillary spaces. Notably, these observations were made in the absence of any features indicative of melanocytic lesions [53]. A confounding

factor is the presence of intraepidermal dendritic cells, as this feature can also be observed in melanomas, making it challenging to differentiate between the two conditions based solely on this characteristic. Another diagnostic challenge associated with RCM involves distinguishing between AK and SCC. Due to the limited penetration depth of RCM, it is difficult to assess deeper structures, which restricts the available information for accurate differentiation between these conditions. Currently, the distinction between AK and SCC relies on the extent of keratinocyte atypia and epidermal disarray, which appears widespread and full-thickness in SCC, but tends to be more localized and focal in AK [54,55]. RCM has also been used for the post-treatment follow-up of AK treated with various modalities such as fluorouracil [56], imiquimod [57], ingenol mebutate [58], shave biopsy [59], photodynamic therapy [60], daylight photodynamic therapy [61], and cryotherapy [62].

Field-Cancerization Based Classifications: AKASI and AK-FAS Score

To evaluate not only the single AKs but the whole skin surrounding them, in 2017 the AKASI (AK Area and Severity Index) score was developed [63]. To calculate AKASI, four regions should be considered in the analysis: scalp, forehead, left face and right face. Within each region, according to the area affected by AKs, a score ranging from 1 (1-9% affected area) to 6 (90-100% affected area) is assigned. Other features considered are the distribution, erythema and thickness of AKs with a scale ranging from 0 (none) to 4 (maximum). Combining the area and the signs scores, a score ranging from 0 (no AKs) to 18 (most severe degree) is obtained. With this system, a global look on the affected area is achieved, quantifying the characteristics of sun damaged regions and obtaining an objective score for monitoring the efficacy of a treatment prescribed. This classification has a major limitation the restriction of the score only for the head, for this reason it cannot be used for AKs located in other areas, such as hands, forearms or chest.

Also, in 2017 another score was developed, named AK-FAS (Actinic Keratosis Field Assessment Scale), to assess the severity of Aks [64].

This score is based on three criteria: hyperkeratosis, sun damage and AK area. Depending on percentage of area affected by AKs, a score from 0 (0% area affected) to IV (<50% area involved) is assigned. The scale has been validated on photographs of twelve patients and the validation of the AK-FAS showed good reproducibility, helping to standardize AK diagnosis, making it relevant to routine clinical practice but also for clinical trials and studies.

How to Improve Classification of AKs in Clinical Trials and Studies

Considering the limitations of each classification and the low rate of reproducibility of some of them it seems inevitable to have classifications that cannot be compared with each other and with different analyzed characteristics. As already suggested by other authors, it would be necessary to always analyze the presence or absence of the field of cancerization and to evaluate the extent of the area of Aks [65].

Otherwise, focusing only on individual lesions does not allow the assessment of the disease burden and does not allow the evaluation of the response to treatments accurately.

Olsen's classification, despite the limitations already mentioned, remains the most widely used but should be unused especially in scientific studies. Furthermore, Olsen's classification has no predictive value for the development of SCC, unlike AKASI score, which has been associated with the incidence of iSCC. The use of AKASI in clinical trials would also allow the same score to be used during clinical practice to compare data with those in the literature. This method already appears to be in use for other dermatologic conditions such as psoriasis in which the PASI score is used both in research and during daily practice.

Conclusions

AKs are the most frequent tumors diagnosed during daily dermatological practice; their diagnosis is usually made by clinical evaluation, but in some cases the clinical aspect is not sufficient for a diagnosis of certainty. Dermatoscopy, already defined a silent revolution in dermatology because of its ease of use and being an inexpensive method [66], adds more specificity to the diagnosis through visualization of typical criteria, such as red pseudonetwork, the presence of large and white follicles, strawberry pattern and whitish scales. Several diseases in fact have a clinical presentation that can mimic AK: for example, irritated flat seborrheic keratosis, superficial basal cell carcinoma, lentigo melanoma, or even inflammatory pathologies such as psoriasis or cutaneous sarcoidosis [67]. The presence of dermatoscopic criteria helps to direct the diagnostic and the therapeutic process. Despite its easy use, the biggest limitation that can be observed in the classification systems previously described in this paper such as AKASI and AK-FAS, is the disregard of dermatoscopic parameters in classifications based on scores that only clinically evaluate AKs and the field of cancerization. It would be preferable in the future to integrate noninvasive diagnostics into the classifications systems in order to obtain objective and reproducible data based on a non-expensive and user-friendly diagnostic method.

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