Folliculotropism in Actinic Keratoses in Patients not Responding to Treatments: A Pilot Study

Dear Editor,

Actinic keratoses (AK) have a high prevalence in the general population, with greater rates in Caucasian patients after the fourth and fifth decades of life (37.5-60.0%) (1,2). Standard histopathologic reporting of AKs does not provide information on the presence of atypical keratinocytes extending to the hair follicle, also defined as folliculotropism (FLC). Commonly, atypical cells in AKs do not present FLC, but this feature can be observed in bowenoid AKs with full-thickness epidermal atypia (3,4). FLC has been considered a possible element enhancing the chances of a progression toward invasive SCC (iSCC). Fernandez-Figueras *et al.* (3) reported that the depth of FLC in AKs was correlated with the invasiveness of associated iSCC. Pandey *et al.* (5) reported a positive association between AKs with FLC and history of invasive cutaneous cancer or melanoma, more often in men at an older age. The role of FLC in cutaneous melanoma is still debated, but it is considered a parameter that may correlate with treatment response in lentigo maligna and disease progression or recurrences in invasive tumors (6,7). These studies draw particular attention to the potential role of hair bulge compartment stem cells in favoring tumor progression through the expression of adhesion molecules, cytokines, and growth factor receptors (8).

Aks are known to have a high recurrence rate after topical treatment (1). The risk of evolution to an iSCC is not completely clear, but it has been estimated to be around 0.6% at 12 months and up to 2.5% at 48 months (1,3,7). Considering the possible progression and the heavy burden of AK treatments, including the economic burden, it is imperative to focus on histopathologic features associated with treatment failure. The aim of this preliminary study was to assess the histopathologic features, specifically FLC, of AK samples from patients considered "non-responders" to specific topical treatments. A secondary endpoint was to assess the clinical/dermoscopic features. Patients were considered "non-responders" if the lesions persisted after two alternated completed cycles of treatments with ingenol mebutate, imiquimod, diclofenac 3%, or 5-fluoruracil. Patients with a positive history of immunosuppression or genetic diseases were excluded. The study was approved by the local Ethics Committee.

Slides of AKs diagnosed at the Laboratory of Dermatopathology, University of Bologna, Italy from January 2016 to October 2018 were reviewed by two dermatopathologists (CM, PAF). 155 "non-responder" AKs of five main histopathologic subtypes were included, classified from grade I to III according to the

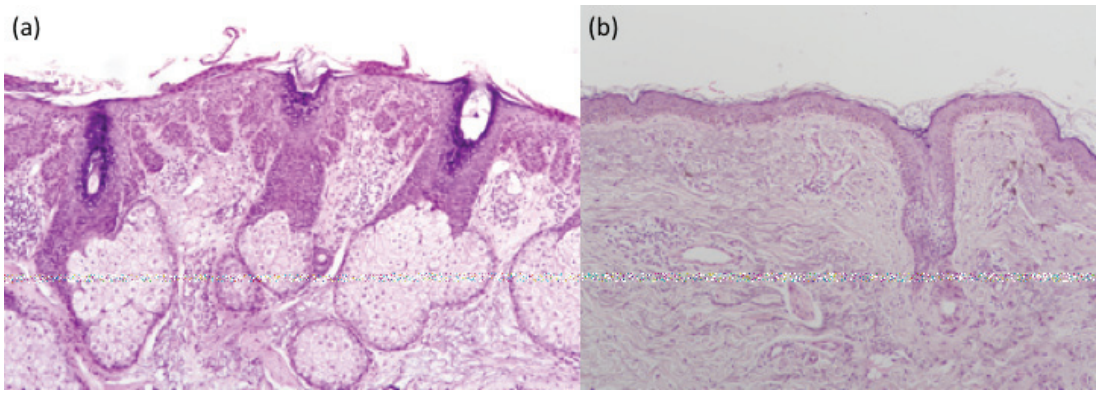

Figure 1. (a) Proliferative actinic keratoses showing periadnexal involvement of atypical keratinocytes (hematoxylin and eosin, ×20); (b) atrophic actinic keratoses showing intradnexal involvement of atypical keratinocytes (hematoxylin and eosin, ×20).

Roewert-Huber classification (9) (Table 1). The proliferative and atrophic histopathologic subtypes of AKs were detected in 33.6% and 30.4% samples, respectively. FLC was observed in 75.3% of the cases, subdivided into two categories, periadnexal (48.9%) and intraadnexal (26.4%). Periadnexal FLC was detected in 31.0% of atrophic and in 50.3% of proliferative AKs, while intraadnexal FLC was found in 48.7% and 29.2%, respectively (Figure 1, a, b). At dermoscopy, most lesions had been classified as grade I or II (38.8% and 45.8%), and only 15.4% as grade III, showing an unexpected non-response to treatment according to the dermoscopic criteria. In contrast, almost half of the AKs were classified as grade III at histology, revealing a discrepancy between the dermoscopic grading and histological findings in a majority of cases (77.4%) (Figure 2, c, d). Furthermore, atrophic and proliferative AKs accounted for 64.0% of total cases, and these are the variants associated with a higher probability of evolution toward an iSCC (10). The clinical/histological discrepancy has already been reported in the literature (9) and may represent a misleading factor for treatment choice and outcomes.

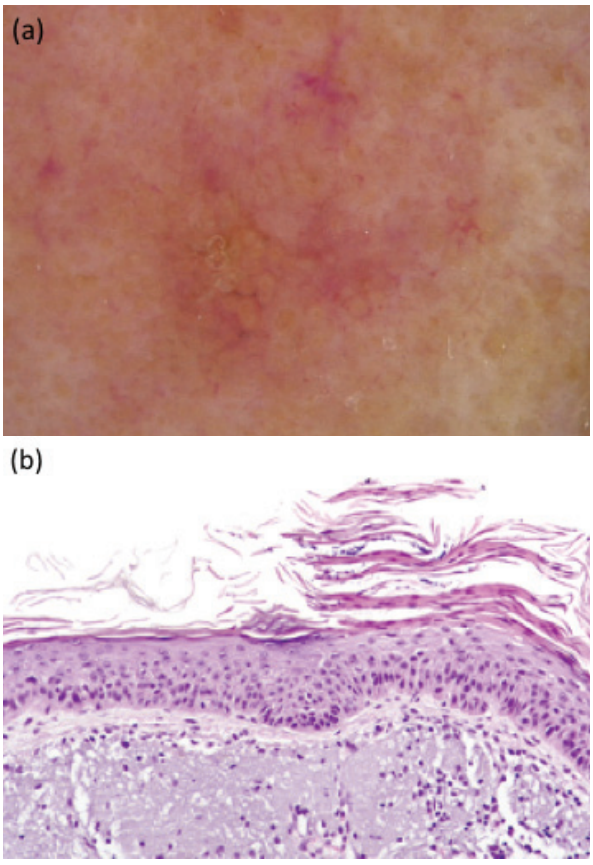

Figure 2. Discrepancy between dermoscopic (a) grading and histological findings (b) (hematoxylin and eosin, ×20) in a sample of actinic keratoses of the face. Dermoscopy shows grade II (a), but histology shows grade III (b).

Table 1. Clinical and histological features of the studied cases

Sex (%)	
• Male	82 (53.0)
• Female	73 (47.0)
Age at diagnosis, mean (range)	
• Male	72 (95-40)
• Female	69 (93-41)
Tumor location (%)	
• Face	84 (54.2)
• Scalp	31 (20.0)
• Chest	20 (12.9)
• Upper limb	14 (9.0)
• Lower limb	6 (3.9)
Grade at dermoscopy (%)	
• I	60 (38.8)
• II	71 (45.8)
• II	24 (15.4)
Grade at histology (%)	
• I	57 (36.8)
• II	21 (13.5)
• III	77 (49.7)
Histologic variants (%)	
• Hypertrophic	12 (7.7)
• Lichenoid	15 (9.7)
• Proliferative	52 (33.6)
• Atrophic	47 (30.4)
• Bowenoid	8 (5.1)
• Acantholytic	7 (4.5)
• Pigmented	14 (9.0)
Adnexal involvement (%)	
• Absent	46 (24.7)
• Periadnexal	68 (48.9)
• Intradnexal	41 (26.4)
Adnexal involvement according to the histologic subtype (%)	
• Periadnexal	
▪ Hypertrophic	5 (3.2)
▪ Lichenoid	5 (3.2)
▪ Proliferative	78 (50.3)
▪ Atrophic	48 (31.0)
▪ Bowenoid	7 (4.5)
▪ Acantholytic	6 (3.9)
▪ Pigmented	6 (3.9)
• Intradnexal	4 (2.4)
▪ Hypertrophic	15 (9.7)
▪ Lichenoid	45 (29.2)
▪ Proliferative	75 (48.7)
▪ Atrophic	0 (0.0)
▪ Bowenoid	4 (2.4)
▪ Acantholytic	12 (7.6)
▪ Pigmented	
Solar elastosis (%)	
• Absent	48 (31.0)
• Scarce	57 (36.9)
• Moderate	42 (27.0)
• Severe	8 (5.1)

We believe that a comparative analysis with dermoscopy and histology should be performed in non-responding AKs, in order to choose the best therapeutic option. In fact, some superficial treatments (such as cryotherapy) may not provide a good response in deep hair follicles (4). We also suggest encouraging greater focus on FLC and its description in pathology reports.

This is a preliminary observational study, but it reinforces the need to further larger clinical studies investigating the role of specific histopathologic parameters in AKs, including FLC, that may correlate with treatment outcomes.

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The patients in this manuscript have given written informed consent to publication of their case details.

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