# Actinic keratosis: do we have clinicopathological criteria to select lesions for therapy?

Gerardo Ferrara, [1] Maria Paola Mariani,[1] Stefano Simonetti[2]

[1] Anatomic Pathology Unit – Macerata General Hospital – Macerata, I

[2] Department of Dermatology – University Hospital of Perugia – Perugia, I

Actinic keratoses (AKs) are defined clinically as erythematous and scaly plaques occurring on chronically sun-damaged skin as a result to exposure to ultraviolet radiation. They are typically located on the face, the scalp, the neck, and the extremities. It is said that *'their potential for malignant transformation is well documented'* (1), because of several mechanisms of ultraviolet-induced damage on DNA (mutations through pirimidine dimer formation), cell membranes (proinflammatory prostaglandin synthesis from damaged phospholipids), and immune suppression (cytokine dysregulation). The relative risk of progression of AKs to SCC increases with the increasing number of AKs (1-5 facial AKs = 1.7; 6-20 facial AKs = 4.2; >20 facial AKs = 11) (2); these data, however must be balanced with the potential of AKs to spontaneously regress (rates of regression of single lesions estimated between 15% and 63% after 1 year) (3).

Indeed the term 'malignant transformation', still used by some Authors, is improper for AKs because these are best considered as examples of early squamous cell carcinoma (SCC) (4) or SCC in situ: thus, it is more accurate to state that AKs **can progress** to a full-blown (invasive) SCC. A model of multistep carcinogenesis has been proposed (5) according to which a single ultraviolet-induced mutation of the p53 gene is followed by apoptosis, whereas a second p53 mutation promotes a clonal expansion of keratinocytes which gives rise to a clinically detectable actinic keratosis. Neoplastic progression probably warrants subsequent mutations involving first the RAS genes, in particular HRAS, and then the CDKN2A gene (6). The role of p16, which is a product of the CDKN2A gene, in neoplastic progression of AKs to SCC has been also investigated with immunohistochemistry: an increasing p16 expression is detected when mving from normal skin through AK to SCC (7). It is well known that p16 overexpression in human cancers is commonly due to functional inactivation of the Rb protein by the human papillomavirus (HPV) E7 protein; thus, not surprisingly, an association has been found between beta-HPVs (mainly types 5, 8, and 38; also involved in epidermodysplasia verruciformis) and actinic keratoses (8). Interestingly, HPV prevalence and viral load decrease during skin carcinogenesis, being higher in AKs than in SCC; these findings suggest that virsues may play a role in the early stages of tumor development (the 'hit-and-run' hypothesis) (9). The role of viruses in neoplastic progression of AKs is obviously in keeping with the higher incidence of AKs in immunosuppressed patients (8).

The genetic model of neoplastic progression under exposure to an injury of the skin surface is in keeping with the concept of field cancerization, i.e.: the biological process in which large areas of cells at a tissue surface or within an organ are affected by a carcinogenic alteration(s) (10). In ther words, cancer is not the result of an isolated cellular phenomenon, but rather as a *polychronotopic process*, i.e.: as an anaplastic tendency which arises and runs in different sites and different times of the same body site. It is estimated that each clinically evident AK is associated with at least 10 sub-clinical lesions in sun-damaged skin, up to a distance of 7 cm from the primary lesion (11). The field damage is clinically manifested as large areas of multiple AKs in the background of erythema and sun damage.

The above-illustrated multistep model of progression (p53 mutations, followed by HRAS mutations and finally associated with CDKN2A mutations) might represent the ideal genetic substrate for a 'tidy' clinical

and histopathological progression of AKs; and a tidy clinicopathological progression might represent the prerequisite to select patients and lesions for treatment.

The clinical grading of AKs has been proposed since 1991 by Olsen et al (12) according to the following criteria:

Grade I: flat erythematous macules, easier felt than seen;

Grade II: moderately thick hyperkeratosis

Grade III: very thick hyerkeratosis ('cutaneous horn').

In recent years, Zalaudek et al. have proposed a progression model from AKs to thick invasive SCC based on dermoscopy (13) and characterized by the following steps:

I – Erythema sparing the follicular openings ('strawberry' pattern); on polarized light dermoscopy, presence of rosettes (four white points arranged as four-leaf clover or as leaves radiating out from central stem);

II – Red starburst pattern;

III – Yellow opaque structures and 'dotted' vessels;

IV – White structureles areas and 'dotted' or 'hairpin' vessels;

V – Central mass of keratin and 'hairpin' vessels;

VI – Central mas of keratin, ulceration, and 'linear irregular' vessels.

According to this model, the 'hairpin' vessels herald progression of AKs to early SCC.

The histopathological features of AKs are classically described as the following:

- Atypia, crowding, and increased number of mitotic figures within the basal/suprabasal layer with preservaton of the granular layer;
- Marked solar elastosis;
- Epithelial 'budding', which may raise concern about an early invasive SCC;
- Dermal inflammation.

An important clue to AKs is the 'volcano sign', that is the presence of 'blue' compact orthokeratosis secondary to preservation of normal adnexal keratinocyte differentiation alternating with 'red' parakeratosis of the interfollicular epidermis. In some cases, however, this sign is lost because atypical keratinocytes extend down to the basal layer of the follicular infundibula or acrosyringia. The follicular involvement in AKs is a sign of severe sun damage, because the stem cells of the 'bulge' are deep enough to be usually spared by the ultraviolet damage.

The following histopathological subtypes of AKs are described:

1. Hypertrophic, with a marked epidermal hyperplasia and thick parakeratotic horn;
2. Atrophic, with flattened and thin epidermis, and scant parakeratosis;
3. Acantholytic, with extensive intraepidermal clefts;
4. Lichenoid, with a prominent subepidermal band-like infltrate of lymphocytes;
5. Bowenoid, with full-thcknes keratnocytic atypia;

6. Pimented, with increased basal layer pigmentation;
7. Actinic cheilitis, with a broad rete ridges and frequent erosion.

The lichenoid infiltrate is probably the first step of possible involution ('regression') of AKs. In our view, the so-called 'lichenoid (lichen planus-like) keratosis' is not a clinicopathological entity but, instead, the inflammatory phase of involution shared by different cutaneous neoplasms (more often AKs or seborrheic keratoses, but also melanomas).

With the clinical progression model in mind, it becomes easy to imagine the existence of a histopathological progression model akin to the intraepithelial neoplasia of the uterine cervix and based on the accumulation of neoplastic cells which progressively fill the whole thickness of the epidermis. The concept of 'Keratinocyte Intraepithelial Neoplasia' (KIN) was proposed by Cockerell in 2000 (14): the assumption was that AKs are indeed cells of SCC which start proliferating and fill the lower third (KIN1), then the lower two thirds (KIN2) and finally the full thickness of the epidermis (KIN3),the latter occurrence followed by dermal invasion of SCC. The histopathological progression model was refined by Röwert-Huber et al in 2007 under the terms AK-I, AK-II, and AK-III (15), which to date are most commonly used in the literature. A retrospective study by Pandey et al (16) confirmed that patients with AKs showing follicular involvement were 1.8 times more likely to have a previous history of SCC compared with patients whose AKs showed no follicular involvement. Thus, follicular involvement mus be considered as diagnostic of KIN3/AK-III irrespective of the presence of other definitional features for the latter category.

The histopathological progression model might ideally allow to select high-risk lesions/patients alone for treatment. There are, however, several limitations to this approach. The first paradox is that the clinical presentation of AK, used to determine which patients are eligible for treatment, does not provide an understanding of the histopathology of the lesion. In a recent study on 892 AK lesions, Schmitz et al reported that only 53.8% of the investigated lesions had a match between the Olsen clinical and Röwert-Huber histological classification and there was no significant correlation between these classification systems (17). Furthermore, Heerfordt et al demonstrated that the clinical thickness of AKs does not correlate with either the severity of dysplasia or the immunoihistochemical expression of p53 (18). More importantly, a thoughtful histopathological study by Fernández-Figueras carried out on 196 excision specimens of SCC demonstrated that AK-I was by far the most common subtype of intraepidermal neoplasia associated with SCC (63.8% of cases) (19). Therefore, it seems reasonable to accept a dual progression pattern from AKs to SCC:

- The 'stepwise progression' pattern from KIN1/AK-I to KIN2/AK-II to KIN3/AK-III to SCC
- The 'differentated' pattern from KIN1/AK-I to SCC

If the above is true, histopathology is little predictive about the progressive potential of AKs. The follicular involvement is a clue to a severe ultraviolet damage and is a potential histopathological candidate for individuating high-risk lesions. In our view, however, the follicular involvement is difficult to be appreciated in the 'differentiated' pattern; thus, the problem of a histopathology-based selection of high-risk lesions is still unresolved to date. The obvious consequence is that, in the absence of any effective means of selection for high-risk lesions, all AKs must be treated (20).

In conclusion, a genetic model of neoplastic progression from AKs to SCC is highly likely: this probably involves sequential mutations of p53, RAS, and p16. The clinical and the histopahological correlates of this genetic model are not clear-cut. To date, the follicular involvement in AKs seems to be the unique histopathological clue for high-risk lesions; this feature, however, may be difficult to be detected. Based on

the above, the progression of individual AKs cannot be predicted clinically or histopathologically; therefore, it has been proposed that all AKs, regardless of their grade, should be carefully monitored and appropriately treated in clinical practice.

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