Evaluation of dermatoscopic criteria for early detection of squamous cell carcinoma arising on an actinic keratosis

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Background: Advanced squamous cell carcinoma (SCC) can be discriminated easily from actinic keratosis (AK) based on clinical and dermatoscopic features. However, at the initial stage of dermal invasion, SCC might still be clinically flat and discrimination from AK remains challenging, even with the addition of dermatoscopy.

Objective: The aim of this study was to investigate the clinical and dermatoscopic criteria that could suggest early invasion and serve as potent predictors to discriminate early SCC from AK.

Methods: Clinical and dermatoscopic images of histopathologically diagnosed AKs and early SCCs were evaluated for the presence of predefined criteria by 3 independent investigators.

Results: A total of 50 early SCCs and 45 AKs were included. The main positive dermatoscopic predictors of early SCC were dotted/glomerular vessels (odds ratio [OR] 3.83), hairpin vessels (OR 12.12), and white structureless areas (OR 3.58), whereas background erythema represented a negative SCC predictor (OR 0.22).

Limitations: The retrospective evaluation of images. Moreover, the differential diagnosis included in the study is restricted between AK and early SCC.

Conclusions: We identified potent predictors for the discrimination of AK and early SCC that may better guide management decisions in everyday clinical practice. (J Am Acad Dermatol 2022;86:791-6.)

Key words: actinic keratosis; dermatoscopy; dermoscopy; skin cancer; squamous cell carcinoma.

INTRODUCTION

Actinic keratosis (AK) and squamous cell carcinoma (SCC) are neoplasms of keratinocytic origin that most commonly affect chronically sun-damaged areas of the skin. AKs usually present as multiple erythematous, ill-defined, scaly macules, papules, or plaques. SCCs manifest as solitary, fast-growing, indurated papules or nodules. An advanced SCC can be discriminated easily from an AK on the basis of these clinical features. However, at the initial stage of dermal invasion, an SCC might still be clinically flat and its discrimination from AK might be challenging.

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The clinical relevance of this problem is obvious, since AKs are typically treated nonsurgically, whereas invasive SCC requires surgery.

Dermatoscopy enhances the clinical diagnostic assessment of skin tumors. The dermatoscopic features of AKs and cutaneous SCC have been extensively described in the literature and a progression model from AK to invasive SCC has been proposed.[1] However, clues to discriminate between AK and early SCC have not been established and identification of the initial signs of invasion remains challenging.

The aim of this study was to investigate the clinical and dermatoscopic criteria that could suggest early invasion and serve as potent predictors to discriminate early SCC from AK.

CAPSULE SUMMARY

- The dermatoscopic criteria of actinic keratosis and advanced squamous cell carcinoma have been extensively reported. At the initial stage of dermal invasion, a discrimination between these tumors remains challenging.
- Dotted/glomerular, hairpin vessels, and white structureless areas are predictive of early squamous cell carcinoma. Background erythema is suggestive of actinic keratosis.

METHODS

This was a prospective observational study conducted in 4 referral centers for skin cancer diagnosis and management in Greece and Italy. Ethics Committee Approval was waived because the study protocol did not affect in any way a patient's management. All individuals included in the study provided a written signed informed consent.

Patients with the differential diagnosis of AK/early SCC and scheduled for a diagnostic biopsy between September 1, 2018 and August 31, 2020 were eligible to participate in the study. Demographic data and history were recorded for each patient and a prebiopsy clinical and dermatoscopic image was captured according to the routine clinical protocol of our centers. The macroscopic images were captured with a Canon G16 camera and the dermatoscopic images were captured with the Dermlite Foto System (3Gen) at 10-fold magnification. Lesions with a final histopathologic diagnosis of AK or SCC were included in the study, whereas those with any other histopathologic diagnosis were excluded.

Histologic diagnosis of AK was based on the presence of disorganized/disoriented epidermal architecture and atypical keratinocytes either adjacent to the basal cell layer or spreading throughout the epidermis. By definition, the basement membrane should be preserved in AKs. Atypia of keratinocytes was defined by the presence of large pleomorphic and hyperchromatic nuclei. Additional criteria included deficient keratinization, impaired maturation, and atypical mitoses. These cytologic features could be present in invasive SCC as well, with the exception of the intact basement membrane, which is by definition preserved in AKs. Histology of SCC consisted of nests of neoplastic keratinocytes invading the dermis. In undifferentiated (anaplastic) SCC, tumor cells could individually infiltrate the dermis without the formation of nests.

The analysis included both dermatoscopic and clinical assessment of the lesions.Three independent investigators with experience in dermatoscopy, blinded to the histopathologic diagnosis, retrospectively evaluated all dermatoscopic and clinical images for the presence of predefined criteria. The evaluators were asked to assess the presence or absence of each criterion.

The selection of dermatoscopic features was based on previously published literature and included dotted/glomerular (coiled), linear (branched, non-branched, and linear), hairpin and serpentine/corkscrew vessels, white and yellow scales, white halos surrounding vessels, white and wide follicles, erythema background, rosettes, ulceration/bleeding, erosions, blood spots, white structureless areas, white circles surrounding follicles, and presence of pigmentation. The clinical characteristics of each lesion included the size, the surface (flat or elevated lesions), the clinical grade, and the presence or absence of ulceration, erosion, and pigmentation.

Statistical analysis

All separate dermatoscopic variables were included in the analysis. Crude and adjusted odds ratio and corresponding 95% confidence intervals were calculated by univariate and conditional multivariate logistic regression, respectively. The alpha level was set at 0.05 and an alpha level of 0.10 was used as a cut off for variable removal in the automated model selection for multivariate logistic regression. Statistical analyses were performed using SPSS 24.0 (IBM SPSS Statistics).

RESULTS

One hundred three lesions from 103 patients were enrolled in the study, of whom 8 were subsequently excluded from further analysis when the histopathology confirmed a diagnosis other than AK or SCC.

Abbreviations used:

AK: actinic keratosis
SCC: squamous cell carcinoma

A total of 95 lesions from 95 patients with a definite histopathologic diagnosis of AK or SCC were included in the study. Fifty lesions were diagnosed as early SCC and 45 were diagnosed as AK.

The mean ages of patients in the AK and SCC groups were 71.7 years and 75.5 years, respectively. The mean sizes of the lesions were 6.29 mm for AKs and 6.0 mm for SCCs. The most frequent anatomic sites of involvement in the AK and SCC groups were the head/neck (62.2% and 74.0%, respectively), followed by the extremities (20.0% and 22.0%, respectively).

Regarding the morphological and clinical characteristics of the lesions (Supplemental Table I; available via Mendeley at http://doi.org/10.17632/px7h2wcks3.1), most of the AKs were clinically flat (77.8%), not pigmented (86.7%), without clinical erosion or ulceration (62.2%), and with mild hyperkeratosis (grade I; 37.8%). About 50% of the SCCs were clinically elevated, most were not pigmented (96.0%), and 62.0% displayed either an ulceration (20.0%) or erosion (42.0%). Moreover, 32.0% of the SCCs had no hyperkeratosis and 30.0% displayed mild hyperkeratosis (grade I). In our sample of 45 AKs, 11 (24.4%) were histologically classified as grade I, 15 (33.3%) as grade II, and 19 (42.2%) as grade III, based on the PRO I–III classification scheme.[2]

The analytic results of the dermatoscopic analysis are shown in Table I. Most AKs lacked dermatoscopic vessels (53.3%), while 28.9% displayed monomorphous and 17.8% polymorphous vessels. SCCs exhibited mainly polymorphous vessels (60.0%). The most frequent morphologic types of vessels in the 45 AKs were dotted/glomerular (14; 31.1%), followed by linear (12; 26.7%). The most frequent morphologic types of vessels in 50 early SCCs were dotted/glomerular (35; 70.0%), linear (27; 54.0%), and hairpin (21; 42.0%).

The most common dermatoscopic criteria of AKs were scales (93.3%), background erythema (77.8%), erosions (40.7%), and white and wide follicles (37.8%). SCCs more commonly exhibited scales (78.0%), white structureless areas (58.0%), ulceration/bleeding (54.0%), and white halos surrounding vessels (42.0%).

The univariate analysis revealed several clinical and dermatoscopic predictors of early SCC (Table II). Conditional backward elimination multivariate logistic regression was used to model the influence of dermatoscopic criteria on SCC diagnosis (Table II). Based on these results, the main positive dermatoscopic predictors of early SCC were dotted/glomerular vessels (3.8-fold higher odds), hairpin vessels (12.1-fold higher odds), and white structureless areas (3.5-fold higher odds). Background erythema represented a negative SCC predictor (Odds ratio 0.218).

According to the discriminant analysis, a model that included these 4 variables, namely the presence of dotted/glomerular vessels, hairpin vessels, and white structureless areas and the absence of background erythema, yielded a diagnosis of SCC with a sensitivity of 84.0%, a specificity of 80.0%, a positive predictive value of 82.3%, and a negative predictive value of 81.8%. When only dotted/glomerular vessels and white structureless areas were considered, the sensitivity was 90.0%, the specificity was 62.2%, the positive predictive value was 72.5%, and the negative predictive value was 84.8%.

DISCUSSION

Recent evidence suggests that AK represents a neoplasm within the continuum of SCC, which essentially means that AK and SCC belong to the same nosological spectrum, while at different stages of evolution. In this scenario, AK represents the in situ phase of an ongoing process and may gradually progress into the invasive phase (SCC), acquiring a metastatic potential after that point.[3-6] Based on literature data, the risk for the malignant transformation of an individual AK ranges from 0.1% to 20% and the average time needed for this process is about 24.6% months.[7-12] Considering that the risk is higher when multiple AKs are present (i.e., more than 10) and given that there is no way to predict which of the AKs will ultimately progress to SCC, all of them should be properly treated.[7,13,14]

Management of AKs is mostly topical. The gold standard for SCC treatment is surgical excision with adequate margins. In this context, as different therapeutic strategies are applied for each neoplasm, discrimination between AK and early SCC is of utmost importance. Based on the findings of the present study, dotted/glomerular vessels, hairpin vessels, and white structureless areas represent potent dermatoscopic early SCC predictors, whereas background erythema is strongly suggestive of AK. With the exception of some differences in the reported frequency of each dermatoscopic criterion for both tumors, our results agree with previous studies.[1,15-28]

Consistent with previous data, the most frequent dermatoscopic criteria of AKs were scales, erythema

Table I. Frequency of dermatoscopic variables according to diagnosis

Dermatoscopic variables	Actinic keratosis (n = 45)	Early squamous cell carcinoma (n = 50)
Vessels		
None	24 (53.3%)	10 (20.0%)
Monomorphous	13 (28.9%)	10 (20.0%)
Polymorphous	8 (17.8%)	30 (60.0%)
Vessel arrangement		
None	24 (53.3%)	13 (26.0%)
Perifollicular	7 (15.6%)	0 (0%)
Other	14 (31.1%)	37 (74.0%)
Dotted/glomerular vessels	14 (31.1%)	35 (70.0%)
Linear vessels	12 (26.7%)	27 (54.0%)
If linear vessels		
Branched	2 (4.4%)	8 (16.0%)
Not branched	10 (22.2%)	19 (38.0%)
Hairpin vessels	2 (4.4%)	21 (42.0%)
Serpentine/corkscrew vessels	0 (0%)	5 (10.0%)
White halos surrounding vessels	6 (13.3%)	21 (42.0%)
Scales	42 (93.3%)	39 (78.0%)
White	25 (55.6%)	23 (46.0%)
Yellow	4 (8.9%)	2 (4.0%)
Both	13 (28.9%)	14 (28.0%)
White and wide follicles	17 (37.8%)	12 (24.0%)
Rosettes	12 (26.7%)	5 (10.0%)
Background erythema	35 (77.8%)	20 (40.0%)
Ulceration/bleeding	8 (17.8%)	27 (54.0%)
Erosion	11 (40.7%)	10 (34.5)
Blood spots	12 (26.7%)	20 (40.04%)
White circles surrounding follicles	7 (15.6%)	20 (40.0%)
White structureless areas	7 (15.6%)	29 (58.0%)
Dermatoscopic pigmentation	10 (22.2%)	4 (8.0%)

Table II. Univariate and multivariate analyses identifying clinical and dermatoscopic predictors of squamous cell carcinoma

	Univariate			Multivariate		
Variables	OR	*P* value	95% CI	OR	*P* value	95% CI
Head and neck location	5.28	.045	1.04-26.85			
Elevated vs flat	2.98	.017	1.21-7.31			
Dotted/glomerular vessels	5.16	<.001	2.15-12.38	3.828	.016	1.279-11.457
Linear vessels	3.22	.008	1.36-7.66			
Hairpin vessels	15.56	<.001	3.39-71.51	12.116	.003	2.284-64.264
White halos surrounding vessels	4.70	.007	1.68-13.14			
Ulceration/bleeding	5.42	<.001	2.11-13.97			
White circles surrounding follicles	3.61	.010	1.35-9.69			
White structureless areas	7.49	<.001	2.80-20.02	3.582	.035	1.096-11.698
Monomorphous vessels	0.20	.006	0.06-0.63			
Background erythema	0.19	<.001	0.07-0.47	0.218	.012	0.066-0.718
Rosettes	0.30	.041	0.09-0.95			
Scales	0.25	.046	0.06-0.97			

CI, Confidence interval; *OR*, odds ratio.

background, erosions, and white and wide follicles. When present, the vessels were more commonly monomorphous, consisting mainly of dotted/glomerular or linear vessels. Rosettes were found in approximately 30% of our AK cases (Supplemental Fig 1).

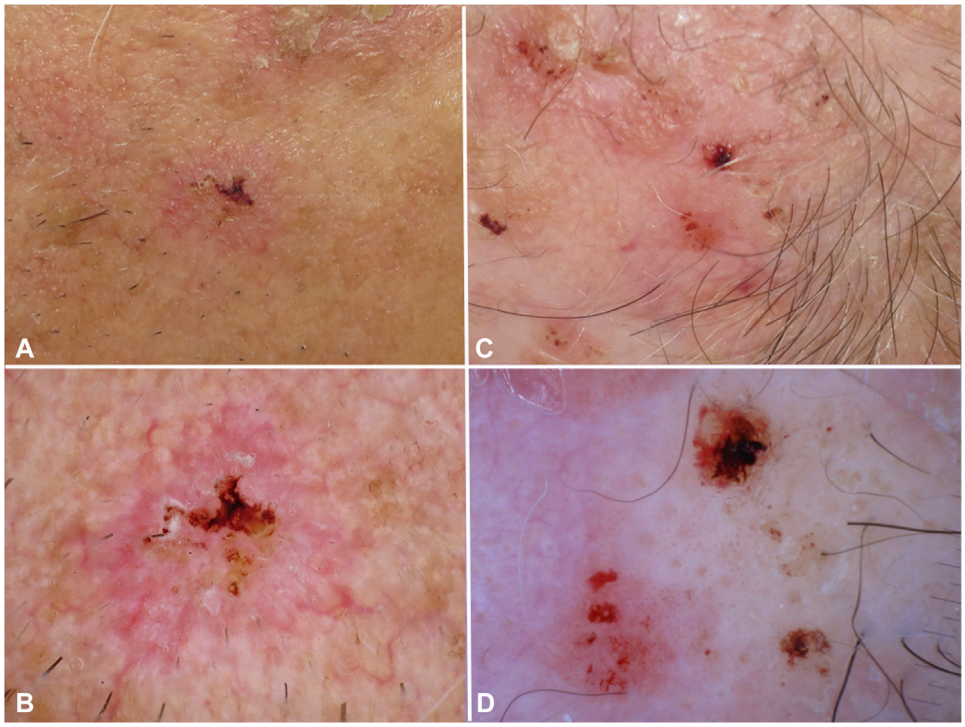

Fig 1. Actinic keratosis and squamous cell carcinoma. **A**, Clinical image of flat palpable scaly actinic keratosis on the face. **B**, Dermatoscopic image of the lesion typified by background erythema, scales, and erosions. **C**, Clinical image of a flat nonpigmented squamous cell carcinoma on the scalp. **D**, Dermatoscopic image displaying dotted/glomerular vessels and ulceration/bleeding.

In early SCCs, the vessels were predominantly polymorphous, mainly consisting of dotted/glomerular, linear, and hairpin. Moreover, early SCCs mainly displayed scales, white structureless areas, ulceration/bleeding, white halos surrounding vessels, erythema background, blood spots, and white circles surrounding follicles, findings in line with previous evidence.

Our analysis revealed 4 potent predictors for the differential diagnosis between AK and early SCC. White structureless areas represented the most potent dermatoscopic predictor of early SCC (3.5-fold; Supplemental Figs 2 and 3). Moreover, our results suggest that vessel morphology may provide valuable information for the discrimination of these 2 entities. Specifically, dotted vessels were present in more than 70.0% of the early SCCs and hairpin vessels were seen in about 40% of them (Fig 1 and Supplemental Fig 2). In the multivariate analysis, both of them proved to be potent predictors of early SCC, posing a 3.8-fold and 12.1-fold probability over AK, respectively. In contrast, background erythema was identified as a predictor of AK (4.7-fold higher odds; Fig 1 and Supplemental Fig 1). The presence of the 3 positive SCC predictors mentioned above and the absence of the 1 negative SCC predictor (positive AK predictor) yielded a diagnosis of SCC with a sensitivity of 84.0% and a specificity of 80.0%.

Our univariate model also suggested 3 additional SCC predictors, namely ulceration/bleeding, white halos surrounding vessels, and white circles surrounding follicles (Table II). Although the latter criteria did not retain their diagnostic significance in the multivariate analysis, they should be taken into consideration for the clinical differential diagnosis. The latter is also supported by previous evidence suggesting that the presence of white circles is a strong predictor of SCC[22,23,28-30] (Supplemental Fig 3). Moreover, ulceration accompanied by bleeding is a common finding in malignant tumors, histopathologically correlating to full loss of the epidermis and dermal invasion. Opposed to white circles, white perivascular halos are not considered specific for SCC and essentially represent a sign of keratinization. Correspondingly, rosettes, scales, and monomorphous vessels proved to be univariate dermatoscopic predictors of AK (Supplemental Fig 1 and Fig 1). In terms of clinical morphology and localization, elevated lesions located on the head and neck area were more likely to be early SCC.

The current study has some limitations. The retrospective evaluation of clinical and

dermatoscopic images is subject to recall and observation biases, which were addressed by involving 3 independent evaluators blinded to the clinical and histologic diagnosis. Because the differential diagnosis included in the study is restricted between AK and early SCC, the suggested accuracy of dermatoscopic criteria cannot be generalized, but refers only to the discrimination between these 2 entities.

CONCLUSION

In the present study, we were able to identify potent dermatoscopic predictors for the discrimination of AK and early SCC, which may better guide management decisions in everyday clinical practice.

Conflicts of interest

None disclosed.

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