ORIGINAL ARTICLE

Accuracy of dermoscopic criteria for the differential diagnosis between irritated seborrheic keratosis and squamous cell carcinoma

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Background: Even with the addition of dermoscopy, a significant morphologic overlap exists between irritated seborrheic keratosis (ISK) and squamous cell carcinoma (SCC).

Objective: The aim of this study was to investigate the dermoscopic criteria that could serve as potent predictors for the differential diagnosis between ISK and SCC.

Methods: Dermoscopic images of histopathologically diagnosed ISKs and SCCs were evaluated by 3 independent investigators for the presence of predefined criteria.

Results: A total of 104 SCCs and 61 ISKs were included. The main dermoscopic predictors of SCC were dotted vessels (odds ratio [OR], 10.4), branched linear vessels (OR, 5.30), white structureless areas (OR, 6.78), white circles surrounding follicles (OR, 23.45), a diffuse irregular (OR, 2.55) or peripheral (OR, 2.8) vessel arrangement, and a central scale arrangement (OR, 3.35). Dermoscopic predictors of ISK were hairpin vessels (OR, 0.38), a diffuse regular vessel arrangement (OR, 0.39 and OR, 0.36), and white halos surrounding vessels covering more than 10% of the lesion (OR, 0.29 and OR, 0.12).

Limitations: First, the retrospective design of the study; second, the differential diagnosis included in the study was restricted to ISK and SCC.

Conclusions: We confirmed the significant morphologic overlap between ISK and SCC, but we also identified potent predictors for the differential diagnosis between these 2 entities. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2020.02.019.)

Key words: dermatoscopy; dermoscopy; differential diagnosis; irritated seborrheic keratosis; skin cancer; squamous cell carcinoma.

Irritated seborrheic keratosis (ISK) is a peculiar variant of seborrheic keratosis (SK), histopathologically characterized by inflammatory cell infiltration with a partly lichenoid aspect in the dermis and a downward proliferation of the epidermis.[1,2] In contrast to the vast majority of classic SKs, ISKs are often challenging to clinically recognize because they share common clinical and dermoscopic characteristics with other keratinizing tumors such as squamous cell carcinoma (SCC) and common

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wart. Often, ISK is clinically characterized by scale, crust, and erosions, making the differential diagnosis from SCC virtually impossible.[1,3] This phenomenon was highlighted in a recent study by Chen et al,[4] who investigated the frequency of clinically misclassified cases that were initially diagnosed as SKs/ISKs but proved to be malignancies after histologic examination.

Dermoscopy is known to improve the clinical recognition of benign and malignant skin tumors. The dermoscopic characteristics of SK have been thoroughly investigated in previous studies and include milia-like cysts, comedo-like openings, fingerprint-like structures, fat fingers, cerebriform appearance, and sharp demarcation or moth-eaten borders.[3,5-8] As a result, the vast majority of SKs can be easily recognized based on their clinical and dermoscopic features. Unusual dermoscopic patterns of SKs have also been described. Squillace et al[9] evaluated a series of difficult-to-diagnose SKs that were excised to rule out malignancies and identified 10 unusual patterns. Among them, nonpigmented patterns, such as bowenoid, hairpin, and keratoacanthoma-like, were reported, all mimicking SCC.

Evidence on the dermoscopic findings of ISK is scarce and, in the few reported cases, ISK seems to lack the aforementioned dermoscopic criteria that typify SK. Therefore, the question of whether dermoscopy might enhance the clinical discrimination between ISK and SCC remains to be elucidated.

Indeed, screening the database of our center, we identified a clear clinical gap in the diagnosis of ISK, because most of the histopathologically diagnosed ISKs had been clinically assessed as SCCs, whereas histopathologically diagnosed SCCs that had been clinically assessed as ISKs were also found. Given that dermoscopy is routinely applied for the evaluation of all skin tumors in our center, the high number of inversely diagnosed ISKs and SCCs in our database further highlights the morphologic overlap between ISK and SCC and the lack of adequate dermoscopic discriminators.

CAPSULE SUMMARY

- The dermoscopic criteria of seborrheic keratosis and squamous cell carcinoma have been extensively reported in the literature. However, scarce evidence exists on the dermoscopic morphology of irritated seborrheic keratosis. Even with the addition of dermoscopy, a significant morphologic overlap exists between these 2 tumors.
- Dotted vessels, branched linear vessels, white structureless areas, white circles surrounding follicles, peripheral arrangement of vessels, and central scale distribution predict the diagnosis of squamous cell carcinoma. Hairpin vessels in a diffuse regular arrangement and multiple white perivascular halos predict the diagnosis of irritated seborrheic keratosis.

The aim of the present study was to investigate the dermoscopic criteria that could serve as potent predictors for the differential diagnosis between ISK and SCC, to help clinicians address the morphologic overlap between the 2 tumors.

METHODS

This was a retrospective study conducted at 2 referral centers for skin cancer diagnosis and management in Thessaloniki, Greece. Inclusion criteria were a definite histopathologic diagnosis of ISK or SCC and the availability of high-quality dermoscopic images of the tumors before biopsy. Routinely in our center, all tumors scheduled for biopsy or excision are clinically and dermoscopically documented. The age and sex of each patient and the anatomic site of tumor development were recorded.

The dermoscopic images had been captured with Dermlite Foto System (3Gen, San Juan Capistrano, CA) at 10-fold magnification. Three independent investigators with experience in dermoscopy, blinded for histopathologic diagnosis, evaluated all dermoscopic images for the presence of predefined criteria. The evaluators were asked to assess the presence or absence of each criterion and also to quantify the presence of each criterion as covering less than 10% of the lesion, 10% to 50% of the lesion, or more than 50% of the lesion. The selection of dermoscopic features that were included in the analysis was based on previously published literature on the dermoscopy of SK and SCC and was decided by consensus among the study authors.

We also used an external data set of images retrieved from the International Skin Imaging Collaboration archive (www.isic-archive.com). The external data set consisted of 30 ISKs and 31 SCCs. Three independent readers with experience in dermoscopy, blinded for histopathologic diagnosis and different from those involved in the first analysis, were asked to evaluate the 61 images of the external data set at 2 different time points. First, they were simply asked to classify the tumors as ISK or SCC. After a washout period of 2 weeks, they were

Abbreviations used:

ISK: irritated seborrheic keratosis
SCC: squamous cell carcinoma
SK: seborrheic keratosis

provided with the results of the univariate and multivariate analysis, and they were asked to again classify the 61 tumors of the external data set as ISK or SCC, this time also taking into account the novel findings of the statistical analysis.

Statistical analysis

All separate dermoscopic variables were included in the analysis. Crude and adjusted odds ratios and corresponding 95% confidence intervals were calculated by univariate and conditional multivariate logistic regression, respectively. The alpha level was set at .05, and an alpha level of .20 was used as the cutoff for variable removal in the automated model selection for multivariate logistic regression.

For the variables that proved to be not statistically significant in the univariate analysis, we further investigated if they were statistically significant after their quantification (subgroup analysis). All analyses were performed with SPSS 24.0 (IBM, Armonk, NY).

The diagnostic accuracy of the 3 readers at both time points was assessed by means of sensitivity, specificity, positive predictive value, and negative predictive value for SCC diagnosis.

RESULTS

Overall, 165 tumors from 165 patients with a definite histopathologic diagnosis were included in the study. Of them, 104 tumors were diagnosed as SCC and 61 as ISK. The study population consisted of 116 men and 49 women. The mean age of patients in the SCC and ISK groups was 76.2 and 64.8 years, respectively.

The most frequent anatomic site of involvement in the SCC group was the head/neck area (53/104, 51.0%), whereas ISKs were almost equally distributed on all anatomic sites.

The analytic results of dermoscopic analysis are shown in Table I. The interobserver agreement for dermoscopic variables was moderate to substantial, with kappa values ranging from 0.48 to 0.74.

As shown in Table I, most tumors in both groups displayed polymorphous vessels (68.3% of SCCs and 67.2% of ISKs). The most frequent morphologic types of vessels in SCC were hairpin (52/104, 50.0%), linear (42/104, 40.4%), and dotted (41/104, 39.4%). Moreover, if linear vessels were present, they were mainly branched (34/42, 81.0%). The most frequent morphologic types of vessels in ISKs were hairpin (46/61, 75.4%), followed by serpentine (26/61, 42.6%) and glomerular vessels (19/61, 31.1%). Concerning vessel arrangement, SCCs more

Table I. Frequency of dermoscopic criteria according to diagnosis

Dermoscopic variables	Squamous cell carcinoma (n = 104), n (%)	Irritated seborrheic keratosis (n = 61), n (%)
Morphology of vessels		
No vessels	3 (2.8)	5 (8.2)
Monomorphous	30 (28.8)	15 (24.6)
Polymorphous	71 (68.3)	41 (67.2)
Dotted	41 (39.4)	7 (11.5)
Glomerular	30 (28.8)	19 (31.1)
Lacunes	0 (0)	0 (0)
Serpentine	36 (34.6)	26 (42.6)
Linear	42 (40.4)	16 (26.2)
If linear:		
Branched	34/42 (81.0)	7/16 (43.8)
Not branched	8/42 (19.0)	9/16 (56.2)
Comma	12 (11.5)	11 (18.0)
Corkscrew	5 (4.8)	0 (0)
Hairpin	52 (50.0)	46 (75.4)
Vessel arrangement		
Diffuse regular	27 (26.0)	31 (50.8)
Diffuse irregular	20 (19.2)	9 (14.8)
Clustered	1 (1.0)	3 (4.9)
Peripheral	21 (20.2)	5 (8.2)
Central	0 (0)	1 (1.6)
Cannot be evaluated	34 (32.7)	12 (19.7)
Bleeding	47 (45.2)	36 (59.0)
Blood spots	52 (50)	39 (63.9)
Erosions	38 (36.5)	22 (36.1)
Ulceration	1 (1.0)	1 (1.6)
Structureless white areas	30 (28.8)	4 (6.6)
White halos surrounding vessels		
Absent	22 (21.2)	15 (24.6)
<10% of the surface	28 (26.9)	4 (6.6)
>10% of the surface	54 (51.9)	42 (68.9)
White circles surrounding follicles	28 (26.9)	1 (1.6)
Scale/keratin masses	93 (89.4)	49 (80.3)
Scale/keratin arrangement	93 (89.4)	49 (80.3)
Central	39 (37.5)	8 (13.1)
Peripheral	6 (5.8)	8 (13.1)
Diffuse	48 (46.2)	33 (54.1)
Predominant color		
White	18 (17.3)	0
Red	7 (6.7)	1 (1.6)
Yellow	5 (4.8)	3 (4.9)
Milia-like cysts	4 (3.8)	11 (18.0)
Comedo-like openings	0 (0)	0 (0)
Fingerprint-like structures	0 (0)	1 (1.6)
Cerebriform appearance	0 (0)	2 (3.3)

Table II. Univariate and multivariate analysis: dermoscopic predictors of squamous cell carcinoma versus irritated seborrheic keratosis

	Univariate			Multivariate		
Variables	**OR**	***P***	**CI**	**OR**	***P***	**CI**
Dotted vessels	5.02	**<.001**	2.08-12.10	10.41	**.001**	2.97-36.43
Hairpin vessels	0.33	**.002**	0.16-0.65	0.38	**.04**	0.15-0.98
Linear branched vessels	5.30	**.009**	1.51-18.58			
Vessel arrangement						
Diffuse irregular vs diffuse regular	2.55	**.05**	0.99-6.54	3.67	.05	0.99-13.62
Peripheral vs diffuse regular	2.80	**.03**	1.10-7.12	3.05	.105	0.78-11.88
White structureless areas	5.78	**.002**	1.92-17.34	6.78	**.01**	1.45-31.45
White circles	22.11	**.003**	2.98-166.5	23.45	**.008**	2.29-246.1
White halos surrounding vessels						
10%-50%	0.29	**.04**				
>50%	0.12	**<.001**				
Scale/keratin masses arrangement						
Central	3.35	**.007**	1.39-8.08	2.76	.11	0.80-3.54

Bold text indicates statistical significance.
CI, Confidence interval; *OR*, odds ratio.

commonly displayed diffuse regular (27/104, 26.0%), diffuse irregular (20/104, 19.2%), and peripheral distribution (21/104, 20.2%), whereas in ISKs the scale was mainly distributed in a diffuse regular arrangement (31/61, 50.8%).

As shown in Table I, both SCCs and ISKs more commonly exhibited scale (89.4% and 80.3%, respectively), white halos surrounding vessels (78.8% and 75.4%, respectively), blood spots (50.0% and 63.9%, respectively), bleeding (54.8% and 41.0%, respectively), and erosions (36.5% and 36.1%, respectively). Concerning the arrangement of scale and keratin, it was diffuse (46.2%) or central (37.5%) in SCCs, whereas in ISKs, a diffuse pattern predominated (54.1%). Moreover, we found white as the predominant color in most SCCs (60.0%), but yellow was found in most ISKs (75.0%).

The univariate analysis showed several dermoscopic predictors of SCC. Conditional backward elimination multivariate logistic regression was used to model the influence of dermoscopic criteria on SCC diagnosis (Table II). Based on these results, the main positive dermoscopic predictors of SCC were dotted vessels, white structureless areas, white circles surrounding follicles, diffuse irregular vessel arrangement, peripheral vessel arrangement, central scale arrangement, and linear branched vessels. In contrast, negative SCC predictors (therefore, positive ISK predictors) were hairpin vessels, diffuse regular arrangement of vessels, and white halos surrounding vessels in more than 10% of the lesion.

The results of the readers' evaluations of the external data set are shown in Table III. As shown in the table, the accuracy of diagnosis of all 3 readers improved when they considered the results of our analysis. The improvement was more remarkable in terms of sensitivity for SCC diagnosis, with a respective cost in specificity.

Table III. Results of the readers' evaluation on an external data set composed of 31 SCCs and 30 ISKs

Assessment of diagnostic accuracy	**Reader 1, %**	**Reader 2, %**	**Reader 3, %**
Correct diagnoses			
Before	73.8	57.4	75.4
After	82.0	63.9	78.7
Difference	+8.2	+6.5	+3.3
Sensitivity for SCC			
Before	58.1	45.2	74.2
After	87.1	93.5	90.3
Difference	+29.0	+48.3	+16.1
Specificity for SCC			
Before	90.0	70.0	76.7
After	76.7	33.3	66.7
Difference	−13.3	−36.7	−10.0
Positive predictive value			
Before	85.7	60.9	76.7
After	79.4	59.2	73.7
Difference	−6.3	−1.7	−3.0
Negative predictive value			
Before	67.5	55.3	74.2
After	85.2	83.3	87.0
Difference	+17.7	+28.0	+12.8

ISK, Irritated seborrheic keratosis; *SCC*, squamous cell carcinoma.

DISCUSSION

Our study confirms that ISKs usually lack the well-known dermoscopic characteristics of SKs and often display a rather atypical pattern, closely mimicking SCC. However, through a detailed morphologic

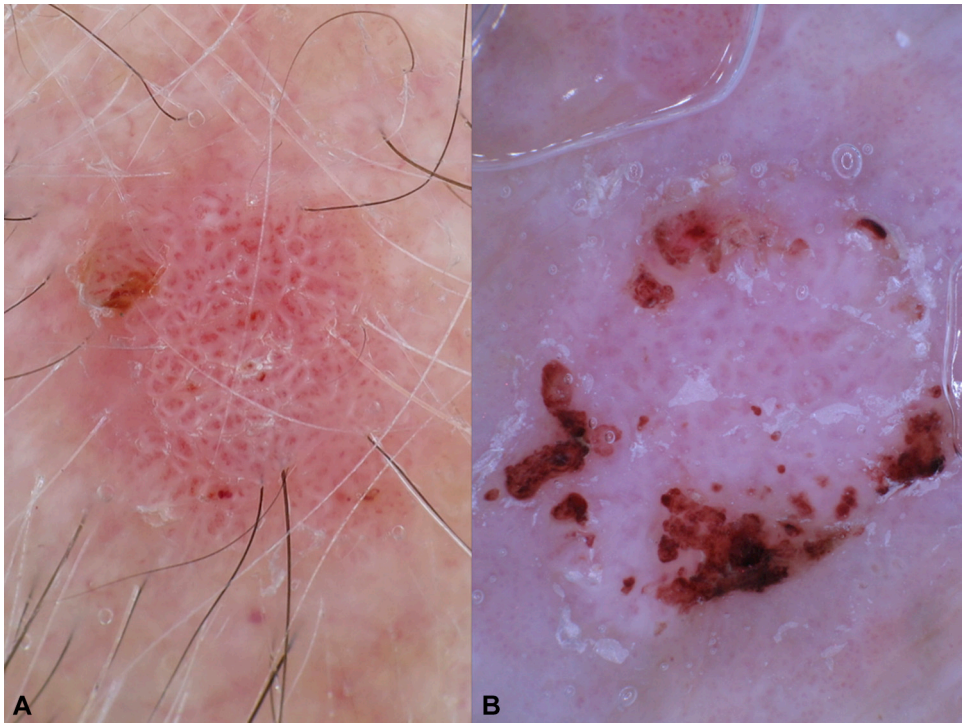

Fig 1. Squamous cell carcinoma (SCC). Dermoscopic images of (**A**) a nonpigmented SCC displaying polymorphous vessels consisting mainly of dotted and glomerular vessels and (**B**) a nonpigmented SCC typified by dotted vessels. A few glomerular vessels and bleeding are additionally seen.

analysis, we identified potent predictors for the discrimination between the 2 tumors. Predictors of SCC include dotted vessels, branched linear vessels, white structureless areas, white circles surrounding follicles, a diffuse irregular or peripheral vessel arrangement, and a central scale arrangement. In contrast, hairpin vessels, a diffuse regular vessel arrangement and multiple white halos surrounding vessels predict the diagnosis of ISK.

All of our cases were nonpigmented. It has been previously reported that the presence of pigmentation is very useful when evaluating skin tumors, whereas nonpigmented tumors are much more difficult to assess.[10,11]

Our results suggest that the differential diagnosis between ISK and SCC cannot be based on the evaluation of the morphology of vascular structures, because both tumors usually display polymorphous vessels. In SCCs, they consisted mainly of hairpin, dotted, and linear vessels, whereas in ISKs, the vessels were more frequently hairpin, serpentine, and glomerular. The most useful finding concerning vessel morphology was that, when dotted vessels are present, the possibility of SCC is significantly higher (10.4-fold) (Fig 1). Additionally, if linear vessels were present, then the presence of branches favors the diagnosis of SCC. Our analysis suggested hairpin vessels as an ISK predictor (2.6-fold higher odds) (Fig 2), but we suggest that this result should be interpreted cautiously, because 50.0% of SCCs also displayed hairpin vessels.

Our study showed that the assessment of the distribution of vessels and scale in the tumor might provide particularly valuable information for the differential diagnosis between SCC and ISK. Specifically, we found that the vast majority of ISKs exhibit a diffuse scale (54.1%) and a diffuse regular vessel arrangement (50.8%). Both of them proved to be multivariate potent predictors of ISK, highlighting its rather symmetric dermoscopic morphology (Fig 2). In contrast, diffuse irregular and peripheral vessel arrangement were identified as SCC predictors. A central scale arrangement was also identified as a potent SCC predictor, and this finding in combination with the peripheral vessel arrangement probably corresponds to the keratoacanthoma type of SCC (Fig 3).[12]

We also found that ISK and SCC also share common nonvascular dermoscopic features, as shown in Table I. However, white structureless areas and white circles surrounding follicles were significantly more frequent in SCC than ISKs, and both represented potent SCC predictors (6.78- and 23.45-fold higher odds, respectively) (Fig 4). The latter is in

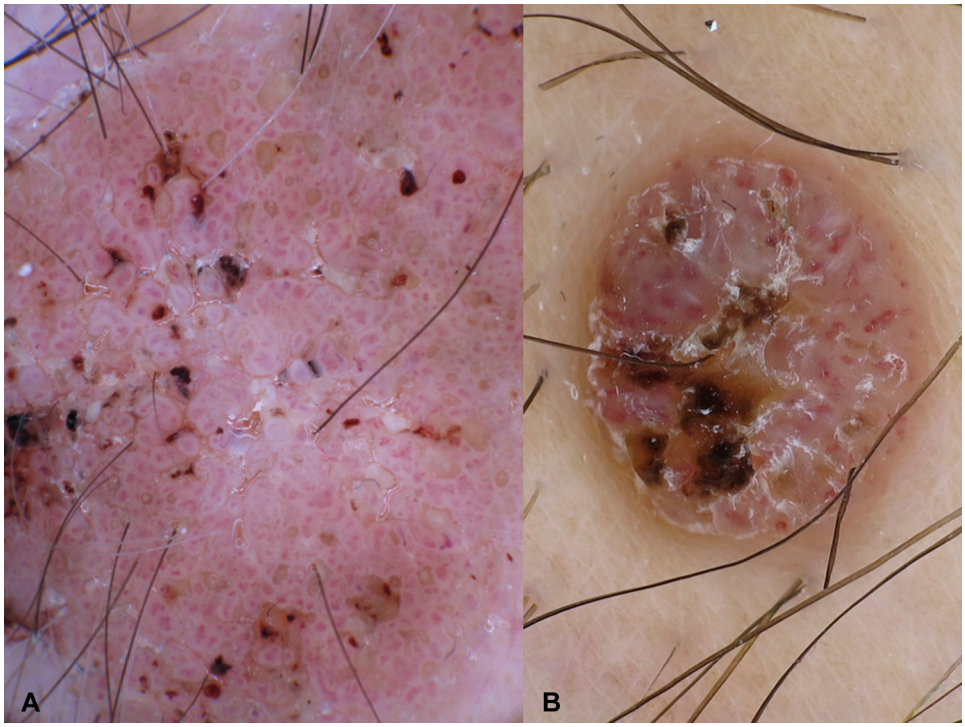

Fig 2. Irritated seborrheic keratosis. **A** and **B**, irritated seborrheic keratoses dermoscopically typified by hairpin vessels surrounded by multiple white halos in a diffuse regular arrangement. Erosions and scale are also seen.

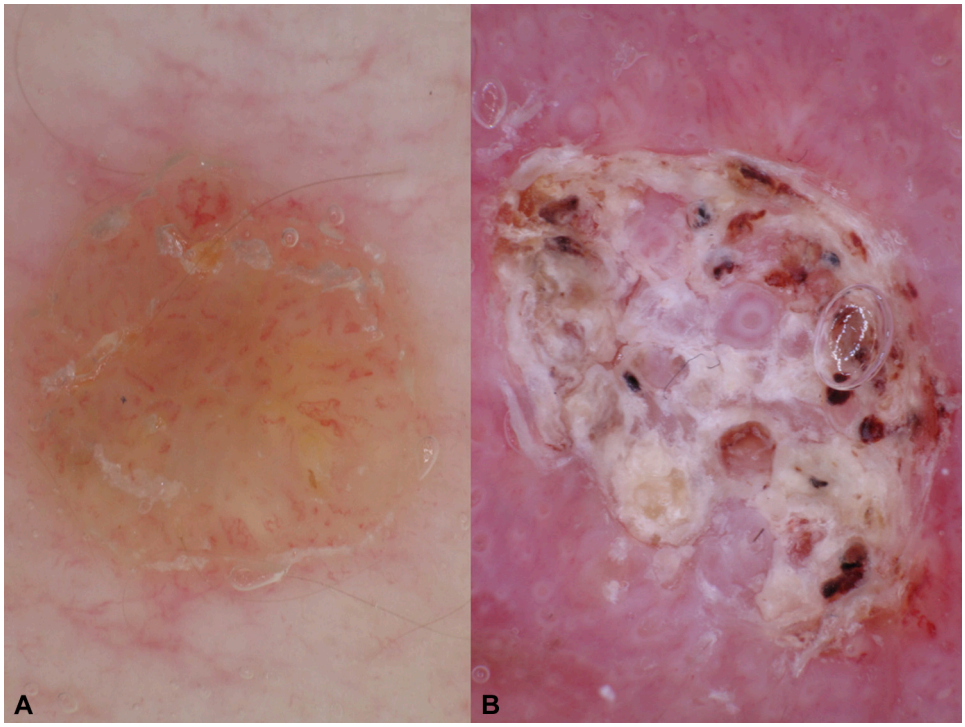

Fig 3. **A**, Irritated seborrheic keratosis (ISK). **B**, Squamous cell carcinoma (SCC). Dermoscopic images of (**A**) an ISK exhibiting mainly hairpin vessels in a diffuse regular arrangement and diffuse scale and (**B**) an SCC typified by central keratin masses, white circles surrounding follicles, and a few white perivascular halos.

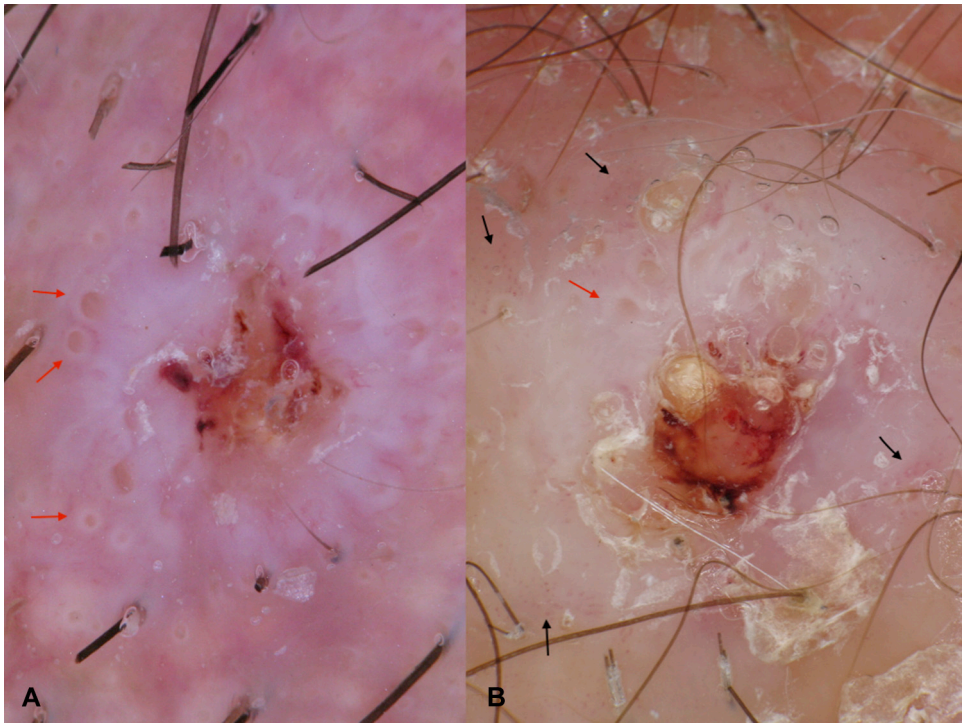

Fig 4. Squamous cell carcinoma (SCC). Dermoscopic images of (**A**) an SCC displaying white structureless areas and a few white circles (red arrows) and (**B**) an SCC exhibiting white structureless areas, a white circle (red arrow), and a few dotted vessels (black arrows).

line with previous evidence suggesting white circles as a strong indicator of SCC.[13-16] Therefore, the detection of white structureless areas or white circles surrounding follicles should prompt clinicians to seek histopathologic confirmation.

Both SCCs and ISKs commonly displayed white halos surrounding vessels (78.8% and 75.4%, respectively). This is not surprising because it has already been described that white halos surrounding vessels represent a sign of keratinization and can be found in several keratinizing tumors. However, our analysis showed that the quantification of this criterion might be particularly useful for the discrimination between SCC and ISK. Specifically, the presence of white halos surrounding vessels in more than 10% of the lesion represented an ISK predictor, whereas white halos surrounding vessels in less than 10% of the lesion were more frequently observed in SCC (Fig 3). Kitamura et al[17] reported the dermoscopic features in a series of 10 ISKs and suggested "small pinkish round structures on a whitish background" as a specific feature of ISK, possibly corresponding to dilated vessels in the dermal papillae surrounded by acanthotic tumor cells (p e94). In our opinion, this feature is a simply another term to describe the white halos surrounding the vessels and, therefore, is consistent with our findings.

The results of the independent readers' evaluations showed that their diagnostic accuracy was improved after they considered the results of the main analysis. Although the number of the readers was very small, the fact that the evaluation was performed on an external data set of images supports the reproducibility of our findings and indicates that the predictors extracted by our analysis might enhance clinicians to better differentiate between ISK and SCC and, especially, improve their ability to recognize SCC, which is clinically much more relevant.

Our study has several limitations. First, the retrospective design is subject to recall and observation biases, which was addressed by involving 3 independent evaluators blinded to the clinical and histologic diagnosis. Second, the differential diagnosis included in the study was restricted to ISK and SCC. Thus, the suggested accuracy of dermoscopic criteria cannot be generalized but refers only to the differential diagnosis between these 2 entities.

In conclusion, in the present study, we confirmed the significant morphologic overlap between ISK and SCC, but we also identified potent predictors for the differential diagnosis between these 2 entities that may enhance the clinical diagnosis in everyday practice. Further studies in larger samples are required to assess the validity of our results.

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