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ORIGINAL RESEARCH

Dermoscopy and Pathological Correlation in Different Grades of Actinic Keratosis and Squamous Cell Carcinoma

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Background: Squamous Cell Carcinoma (SCC) is a common skin malignancy arising from keratinocytes and can develop from Actinic Keratosis (AK). Establishing reliable criteria for early differentiation of AK grades and SCC is essential for timely intervention and regular examination.

Purpose: This study investigates clinical and dermoscopic criteria for AK and SCC grades, exploring the pathological basis of features to aid clinicians in assessing disease status and guiding treatment.

Patients and Methods: Clinical and dermoscopic images of AK and SCC patients were assessed by three independent researchers. Key dermoscopic features were identified and correlated with pathological findings.

Results: A total of 106 AK cases (36 AK I, 24 AK II, 46 AK III; 33 PRO I, 40 PRO II, 33 PRO III) and 33 SCC cases were included. Clinical positive predictors for SCC included solitary lesions ($P = 0.020$), ulcerated crusts ($P < 0.001$), and yellow opaque scales ($P = 0.012$). Dermoscopic positive predictors for SCC were hairpin vessels (OR 5.644), white structureless areas (OR 3.538) and ulceration (OR 7.311). Negative predictors included strawberry pattern (OR 0.052) and linear vessels (OR 0.088). Dermoscopy also demonstrated potential in distinguishing between different grades of AK and SCC, particularly in high-grade AK and SCC. High-grade AK (AK III and PRO III) exhibited yellowish-white opaque scales, enlarged follicular openings. while SCC lesions demonstrated characteristic dermoscopic features including ulcerations (51.5%, 17/33) and erosions (66.7%, 22/33). Dermoscopic grading significantly correlated with both pathological grading systems ($P < 0.05$). Dermoscopic features such as pigmentation, white fine scaling, erosions, ulceration, white structureless areas, white lines, and vessel patterns were pathologically validated, corresponding to changes related to epidermal basal cells, along with increased inflammatory cell infiltration and fibroblast content in the dermis.

Conclusion: Dermoscopy offers a non-invasive and effective method for assessing lesion malignancy across various grades of AK and SCC, reflecting their pathological features and aiding clinical diagnosis while potentially reducing unnecessary biopsies.

Keywords: actinic keratosis, squamous cell carcinoma, dermatological imaging, tumor microenvironment

Introduction

Actinic keratosis (AK) is a common premalignant skin lesion characterized by disordered keratinocyte proliferation due to excessive ultraviolet (UV) exposure. A cross-sectional study reported that the prevalence of AK in China was 0.52%, and the yearly prevalence was 0.30–1.20%.[1] It is regarded as an early stage in the progression to Squamous Cell Carcinoma (SCC), with studies indicating a transformation rate up to 0.075% per lesion per year, and the risk of up to 0.53% per lesion in patients with a history of keratinocyte carcinoma.[2,3] Each AK lesion has the potential to progress to SCC after a prolonged period of time, and making early detection and intervention is crucial for preventing malignant transformation.[3]

Histopathological examination is the gold standard for grading both AK and SCC. AK is categorized by both histological grade, based on epidermal atypical keratinocyte extension (AK I-III: AK I, mild; AK II, moderate; AK

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III, severe), and underlying basal growth pattern (PRO I-III: PRO I, crowding; PRO II, budding; PRO III, papillary sprouting) along the basement membrane zone.[4,5] SCC is graded from well-differentiated to poorly-differentiated, based on the degree of keratinization, cellular pleomorphism, and invasive depth. Although high-grade AK and early-stage SCC may exhibit similar clinical presentations, they differ significantly in terms of treatment strategies and prognosis, underscoring the importance of accurate differentiation. However, since AK commonly occurs on sun-exposed areas like the face and often presents as multiple lesions, performing biopsies for every lesion would impose unnecessary economic and physical burdens on patients.

As a simple and noninvasive imaging modality, dermoscopy has become an increasingly valuable tool in dermatological diagnostics. In addition to its magnification capabilities, dermoscopy utilizes light filtration to enhance visualization depth, enabling detailed examination of the epidermis, the dermo-epidermal junction, and the papillary dermis. Modern dermoscopy devices are often equipped with both polarized and nonpolarized light modes, offering versatility in clinical use and enhanced accuracy.[6–8] In clinical practice, dermoscopy can improve the diagnostic accuracy of suspected AK and SCC lesions, while reducing unnecessary skin biopsies. The classic dermoscopic features of AK is red pseudonetwork. The presence of glomerular vessels, diffuse yellow opaque scales, and microerosions may suggest the possibility of SCC; furthermore, the appearance of hairpin vessels, linear-irregular vessels, targetoid hair follicles, white structureless areas, a central mass of keratin, and ulceration collectively indicates a more advanced stage of malignant progression within the lesion.[9–11] However, few studies have analyzed and summarized the dermoscopic features of SCC and various grades of AK as defined by the two different histopathological classification systems, particularly in Asian populations.

This study aims to investigate the clinical and dermoscopic criteria for different histopathological grades of AK and SCC, seeking to establish correlations between dermoscopic features and histopathological patterns. After identifying specific dermoscopic characteristics, we further provide pathological evidence supporting the use of dermoscopy in differentiating between between different grades of AK and SCC, ultimately enabling more accurate non-invasive diagnosis and appropriate treatment selection.

Materials and Methods

Study Design

A retrospective cohort study was conducted at Peking University Third Hospital, analyzing patients diagnosed with AK and SCC between January 2016 and December 2023. The inclusion criteria encompassed patients with lesions on sun-exposed areas (primarily face and neck) who underwent both dermoscopic examination and histopathological confirmation of AK or SCC. Exclusion criteria included incomplete clinical documentation and declined participation. Ultimately, 139 patients were included in the study, comprising 106 cases of AK and 33 cases of SCC (Table 1). All cases underwent independent evaluation by three experienced physicians, each performing clinical assessment, dermoscopic image evaluation, and histopathological assessment. Cases with concordant diagnoses were confirmed directly. In cases of disagreement, consensus was reached through discussion and majority voting. All enrolled patients provided written informed consent prior to participation. This study protocol was reviewed and approved by the Institutional Review

Table 1 Demographic and Clinical Characteristics Between AK and SCC

		AK (n = 106)	SCC (n = 33)	z/χ^2	*P*
Age, Year, M (Q_1, Q_3)		72.00 (63.00, 80.00)	72.00 (66.00, 80.50)	0.181	0.857
Disease Duration, Year, M (Q_1, Q_3)		2.00 (1.00, 5.00)	1.00 (0.25, 3.00)	−2.478	0.013
Sex	Male	34 (32.1%)	15 (45.5%)	1.974	0.160
	Female	72 (67.9%)	18 (54.5%)		
Numbers of lesions	Solitary	67 (63.2%)	28 (84.8%)	5.448	0.020
	Multiple	39 (36.8%)	5 (15.2%)		
Clinical features	Ulceration	22 (20.8%)	18 (54.5%)	14.020	<0.001
	Yellow Opaque Scales	61 (57.5%)	27 (81.8%)	6.382	0.012

Board of Peking University Third Hospital (approval number: LM2023247). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Clinical Assessment

Clinical data were systematically collected, including demographic characteristics (age and sex), disease history (duration and progression), lesion distribution (solitary or multiple, defined as one or more than one lesion, respectively), and anatomical locations. Detailed clinical manifestations were documented, encompassing erythema, ulceration, yellow opaque scales, and pigmentation. All lesions were graded according to Olsen's classification: grade I reflects slightly palpable AK, more easily felt than seen; grade II reflects moderately thick AK, easy to see and feel; and grade III reflects very thick AK.[12]

Dermoscopic Evaluation

Dermoscopic evaluation was performed based on previously established criteria, including vascular patterns (none/ monomorphous/polymorphous), vessel morphology (dotted, glomerular, linear [branched/linear-irregular/linear], hairpin, and corkscrew), red pseudonetwork (none/uniform/irregular), erythema, strawberry pattern, white fine scales, yellow opaque scales, keratin masses, erosions, ulceration, white structureless areas, yellow structureless areas, rosettes, dermatoscopic pigmentation, and enlarged follicular openings filled with keratotic plugs.[13,14]

The dermoscopic grading system for AK lesions was applied according to established criteria.[15] Grade 1 lesions were characterized by palpable elevation with red pseudonetwork and discrete white scales. Grade 2 lesions presented as moderately thick lesions with erythematous background, white to yellow keratotic material, and partially confluent enlarged follicular openings. Grade 3 lesions manifested as thick hyperkeratotic lesions with enlarged follicular openings containing keratotic plugs on a white to yellow scaly background.

Histopathological Evaluation

Histopathological confirmation was obtained through skin biopsies, examined for hyperkeratosis, parakeratosis, follicular plugging, acantholysis, liquefaction of basal cells, basal layer pigmentation and inflammatory cellular infiltrate (small focal/focal/ lichenoid). 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, with intact basement membrane. Histology of SCC consisted of nests of neoplastic keratinocytes invading the dermis. AK lesions were further classified according to two established grading systems. The first system evaluated the vertical extent of keratinocyte atypia within the epidermis, categorized as AK I (mild; atypical keratinocytes confined to the lower third of the epidermis), AK II (moderate; atypical keratinocytes involving the lower two-thirds of the epidermis), and AK III (severe; full-thickness epidermal atypia). Based on the basal growth pattern at the dermal-epidermal junction, lesions were further classified using the PRO grading system: PRO I (crowding; characterized by crowded atypical keratinocytes at the basal layer), PRO II (budding; distinguished by hemispherical buds of atypical cells protruding into the upper papillary dermis), and PRO III (papillary sprouting; marked by spiky proliferations of atypical keratinocytes extending into the upper dermis).[4,5,16]

Immunofluorescence Study of Vimentin and CK14

The investigation of Vimentin and CK14 was performed using an immunofluorescence technique. Paraffin sections of AK and SCC tissues were obtained from the tissue repository. After deparaffinization and rehydration, microwave heating was performed in a Tris-ethylenediaminetetraacetic acid (EDTA) buffer (pH 9.0). Indirect immunofluorescence was carried out using Vimentin (ab92547, 1:200 dilution, Abcam, USA) and CK14 (ab119695, 1:200 dilution, Abcam, USA) as the primary antibody, and goat anti-rabbit IgG (Alexa Fluor 594) (ab150080, 1:200 dilution, Abcam, USA) as the secondary antibody. The sections were viewed under CaseViewer (3DHISTECH, Hungary). A fixed area of the dermis beneath the tumor cells was selected, and the Integrated Density (IntDen) of this region was measured to represent the intensity of vimentin expression in the tissue.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics version 26 (IBM, USA). Continuous variables were presented as mean ± standard deviation for normally distributed data, or median (interquartile range [IQR]) for non-normally distributed data. The independent samples *t*-test was used for normally distributed continuous variables, while the Mann–Whitney *U*-test was applied for non-normally distributed data. Categorical variables were expressed as numbers (percentages) and analyzed using chi-square test or Fisher's exact test as appropriate. The associations between ordinal variables were evaluated using Spearman's rank correlation coefficient. To assess the relationship between dermoscopic features and SCC risk, multivariable logistic regression analysis was conducted to calculate odds ratios (ORs). The correlations among dermoscopic grading, histopathological grading, and imaging features were determined using Spearman's rank correlation coefficient, with correlation strength categorized as strong (≥ 0.7), moderate (> 0.4 to < 0.7), or weak (≤ 0.4). Statistical significance was set at $P < 0.05$ (two-tailed).

Results

Clinical Characteristics Between AK and SCC

Of the 139 enrolled patients, there were 49 males (35.3%) and 90 females (64.7%), with a male-to-female ratio of 0.54:1. Patient age ranged from 35 to 96 years, with a median age of 72 years. Disease duration varied from 0.02 to 28 years, with a median duration of 2.00 years (IQR: 1.00, 5.00) for AK, and 1.00 years (IQR: 0.25, 3.00) for SCC, confirming the more aggressive and rapid progression of SCC ($P < 0.05$). Histopathological examination confirmed 106 cases of AK and 33 cases of SCC. The anatomical distribution differed between groups: AK lesions predominantly occurred on the cheeks (42.5%, 45/106) and nose (25.5%, 27/106), whereas SCC lesions were primarily observed on the temples (30.3%, 10/33), followed by equal distribution on the scalp and cheeks (15.2%, 5/33 each). Comparative analysis revealed no statistically significant differences in sex, or age between AK and SCC cohorts (Table 1). Compared to AK, SCC was more likely to present as a solitary lesion ($P = 0.020$), ulceration ($P < 0.001$), and yellow opaque scales ($P = 0.012$).

Dermoscopic Features of AK and SCC

Analysis of dermoscopic features between AK and SCC (Table 2) identified several distinctive characteristics were identified. AK predominantly exhibited monomorphous vascular patterns, while SCC showed a higher prevalence of

Table 2 Multivariate Analysis of Disease Grades Between AK and SCC

	AK							SCC (n = 33)	χ^2	*P*
	AK I (n = 36)	AK II (n = 24)	AK III (n = 46)	PRO I (n = 33)	PRO II (n = 40)	PRO III (n = 33)	Total (n = 106)			
Vascular patterns									10.104	0.006
None	2(5.6%)	3(12.5%)	3(6.5%)	3(9.1%)	2(5.0%)	3(9.1%)	8(7.5%)	2(6.1%)		
Monomorphous	30(83.3%)	11(45.8%)	25(54.3%)	26(78.8%)	22(55.0%)	18(54.5%)	66(62.3%)	11(33.3%)		
Polymorphous	4(11.1%)	10(41.7%)	18(39.1%)	4(12.1%)	16(40.0%)	12(36.4%)	32(30.2%)	20(60.6%)		
Vessel morphology										
Dotted	11(30.6%)	4(16.7%)	11(23.9%)	15(45.5%)	6(15.0%)	5(15.2%)	26(24.5%)	2(6.1%)	5.336	0.021
Glomerular	4(11.1%)	4(16.7%)	12(26.1%)	5(15.2%)	9(22.5%)	6(18.2%)	20(18.9%)	13(39.4%)	5.856	0.016
Branched	2(5.6%)	7(29.2%)	12(26.1%)	3(9.1%)	8(20.0%)	10(30.3%)	21(19.8%)	12(36.4%)	3.808	0.051
Linear-irregular	11(30.6%)	9(37.5%)	22(47.8%)	7(21.2%)	20(50.0%)	15(45.5%)	42(39.6%)	15(45.5%)	0.354	0.552
Linear	15(41.7%)	6(25.0%)	13(28.3%)	16(48.5%)	9(22.5%)	9(27.3%)	34(32.1%)	4(12.1%)	5.044	0.025
Hairpin	2(5.6%)	0(0.0%)	5(10.9%)	0(0.0%)	4(10.0%)	3(9.1%)	7(6.6%)	9(27.3%)	10.555	0.001
Corkscrew	5(13.9%)	2(8.3%)	5(10.9%)	3(9.1%)	4(10.0%)	5(15.2%)	12(11.3%)	3(9.1%)	0.130	0.718
Red pseudonetwork									20.777	<0.001
None	13(36.1%)	6(25.0%)	31(67.4%)	11(33.3%)	17(42.5%)	22(66.7%)	50(47.2%)	30(90.9%)		
Uniform	19(52.8%)	5(20.8%)	9(19.6%)	17(51.5%)	12(30.0%)	4(12.1%)	33(31.1%)	0(0.0%)		
Irregular	4(11.1%)	13(54.2%)	6(13.0%)	5(15.2%)	11(27.5%)	7(21.2%)	23(21.7%)	3(9.1%)		

(*Continued*)

Table 2 (Continued).

	AK							SCC (n = 33)	χ²	P
	AK I (n = 36)	AK II (n = 24)	AK III (n = 46)	PRO I (n = 33)	PRO II (n = 40)	PRO III (n = 33)	Total (n = 106)			
Strawberry pattern	16(44.4%)	14(58.3%)	22(47.8%)	16(48.5%)	22(55.0%)	14(42.4%)	52(49.1%)	3(9.1%)	16.810	<0.001
Enlarged follicular openings with keratotic plugs	8(22.2%)	12(50.0%)	28(60.9%)	14(42.4%)	17(42.5%)	17(51.5%)	48(45.3%)	9(27.3%)	3.374	0.066
White fine scales	16(44.4%)	6(25.0%)	7(15.2%)	13(39.4%)	11(27.5%)	5(15.2%)	29(27.4%)	2(6.1%)	6.588	0.010
Yellow opaque scales	25(69.4%)	15(62.5%)	35(76.1%)	23(69.7%)	23(57.5%)	29(87.9%)	75(70.8%)	27(81.8%)	1.577	0.209
Erosions	8(22.2%)	4(16.7%)	12(26.1%)	5(15.2%)	9(22.5%)	10(30.3%)	24(22.6%)	22(66.7%)	22.029	<0.001
Ulceration	4(11.1%)	5(20.8%)	8(17.4%)	5(15.2%)	3(7.5%)	9(27.3%)	17(16.0%)	17(51.5%)	17.142	<0.001
White lines	11(30.6%)	11(45.8%)	9(19.6%)	8(24.2%)	12(30.0%)	11(33.3%)	31(29.2%)	13(39.4%)	1.198	0.274
White structureless areas	4(11.1%)	7(29.2%)	30(65.2%)	10(30.3%)	13(32.5%)	18(54.5%)	41(38.7%)	27(81.8%)	11.207	0.001
Yellow structureless areas	7(19.4%)	7(29.2%)	20(43.5%)	7(21.2%)	12(30.0%)	15(45.5%)	34(32.1%)	13(39.4%)	0.602	0.438
Dermatoscopic pigmentation	30(83.3%)	21(87.5%)	43(93.5%)	31(93.9%)	36(90.0%)	27(81.8%)	94(88.7%)	26(78.8%)	2.086	0.149

polymorphous patterns (P = 0.006). Specifically, dotted (P = 0.021) and linear vessels (P = 0.025) were more prevalent in AK, whereas glomerular (P = 0.016), hairpin (P = 0.001) and branched vessels (P = 0.051) were more frequently observed in SCC. The red pseudonetwork (P < 0.001), strawberry pattern (P < 0.001), and white fine scales (P = 0.010) were notably more prevalent in AK than in SCC. In contrast, AK showed lower frequencies of erosions (22.6% vs 66.7%, P < 0.001), ulceration (16.0% vs 51.5%, P < 0.001), and white structureless areas (38.7% vs 81.8%, P = 0.001) compared to SCC. Other features showed no statistically significant differences (P > 0.05) (Table 2).

Further, the logistic multivariate analysis of dermoscopic features showed significant differences in strawberry pattern, linear vessels, hairpin vessels, white structureless areas and ulceration (Figure 1). Other dermoscopic features did not show significant differences. Specifically, the strawberry pattern and linear vessels as protective factors were more frequently observed in AK lesions, while hairpin vessels, white structureless areas and ulceration as risk factors were predominantly found in SCC (Figure 1).

Dermoscopic Features of AK at Different Stages and SCC

Dermoscopic features were analyzed comparing SCC with AK using two distinct classification systems. Analysis of AK based on histological grades (I-III) demonstrated specific morphological patterns in relation to SCC. In AK grade I lesions, characteristic features comprised a uniform red pseudonetwork (52.8%, 19/36), white fine scales (44.4%, 16/36), monomorphous vessels (83.3%, 30/36), and centrally distributed vasculature (16.7%, 6/36). AK grade II lesions predominantly exhibited an irregular red pseudonetwork (54.2%, 13/24) as their distinctive dermoscopic feature. For AK

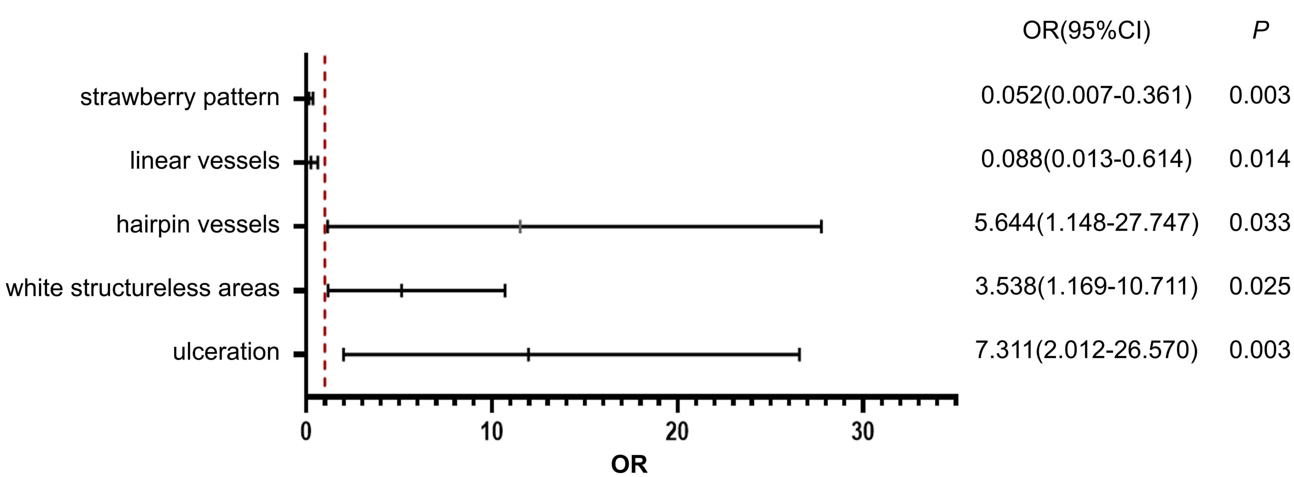

Figure 1 Multivariate analysis of histopathological grades in AK and SCC.

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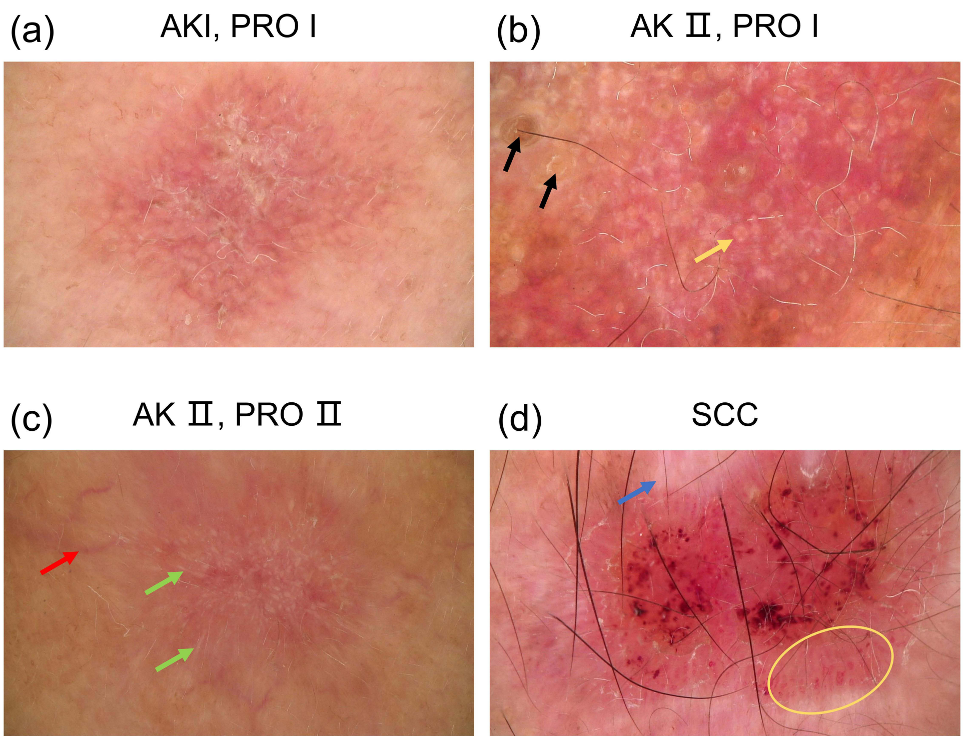

Figure 2 (**a**) Dermatoscopic image of actinic keratosis. AKI, PRO I. red pseudonetwork, white fine scales, linear vessels are seen; (**b**) Dermatoscopic image of actinic keratosis. AK II, PRO I. rosettes (yellow arrow), strawberry pattern and enlarged follicular openings with keratotic plugs (black arrow) are seen; (**c**)Dermatoscopic image of actinic keratosis. AK II, PRO II. Linear-irregular vessels(red arrow) and white lines (green arrow)are seen; (**d**) Dermatoscopic image of invasive squamous cell carcinoma. Radial arranged hairpin and linear-irregular vessels (yellow circle), ulcerations white structureless areas(blue arrow) were seen.

grade III, the predominant dermoscopic characteristics included enlarged follicular openings with keratotic plugs (60.9%, 28/46). The presence of white structureless areas under dermoscopy may suggest AK III (65.2%, 30/46) or SCC (81.8%, 27/33). SCC lesions demonstrated characteristic dermoscopic features including ulcerations (51.5%, 17/33) and erosions (66.7%, 22/33).

Further analysis of AK based on the basal growth pattern classification (PRO I-III), revealed characteristic dermoscopic features distinguishing from SCC. AK PRO grade I lesions predominantly exhibited monomorphous vascular patterns (78.8%, 26/33), with vessels displaying either linear (48.5%, 16/33) or dotted (45.5%, 15/33) morphology, while other dermoscopic features did not demonstrate significant specificity. For PRO II lesions, no distinctive dermoscopic features were identified. Yellow opaque scales emerged as a predominant feature in both PRO III (87.9%, 29/33) and SCC (81.8%, 27/33). SCC lesions were characterized by ulcerations (51.5%, 17/33), erosions (66.7%, 22/33), and white structureless areas (81.8%, 27/33) (Figure 2). Generally, as the grade of the lesion increases, the vascular pattern observed under dermoscopy gradually becomes more polymorphic (Table 3).

Table 3 Correlation Between Pathological Grading and Dermoscopic Vascular Patterns

Pathological Grading		**Vascular Patterns**			χ^2	***P***
		None	**Monomorphous**	**Polymorphous**		
AK Grading	I (n = 36)	2 (5.6%)	30 (83.3%)	4 (11.1%)	11.001	0.001
	II (n = 24)	3 (12.5%)	11 (45.8%)	10 (41.7%)		
	III (n = 46)	3 (6.5%)	25 (54.3%)	18 (39.1%)		
	SCC (n = 33)	2 (6.1%)	11 (33.3%)	20 (60.6%)		

(*Continued*)

Table 3 (Continued).

Pathological Grading		Vascular Patterns			χ^2	*P*
		None	Monomorphous	Polymorphous		
PRO Grading	I(n = 33) II (n = 40) III (n = 33) SCC (n = 33)	3 (9.1%) 2 (5.0%) 3 (9.1%) 2 (6.1%)	26 (78.8%) 22 (55.0%) 18 (54.5%) 11 (33.3%)	4 (12.1%) 16 (40.0%) 12 (36.4%) 20 (60.6%)	9.719	0.002

Correlation Between Clinical, Dermoscopic, and Histopathological Grades in AK

Using Spearman's rank correlation analysis, we evaluated the correlations between clinical (Olsen), dermoscopic, and pathological grading systems (including histological AK grading and PRO grading) of AK to assess their consistency. The Olsen classification showed a moderate correlation with dermoscopic grading (r_s = 0.478, P ≤ 0.01). Olsen grading showed a weak correlation with AK grading (r_s = 0.217, P = 0.026), but no significant correlation with PRO grading (r_s = 0.153, P = 0.118). Dermoscopic grading showed a weak correlation with AK grading (r_s = 0.281, P = 0.004) and PRO grading (r_s = 0.223, P = 0.022). A weak correlation was observed between different pathological grading systems (r_s = 0.396, P ≤ 0.01). Further comparison of the consistency between Olsen, dermoscopic, and pathological grading revealed that dermoscopic grading was more consistent with pathological grading than Olsen grading (Table 4, Figure 3).

Pathological Evidence Supporting Dermoscopic Features

We further analyzed the relationship between various pathological features and lesion grades of AK and SCC. First, the pathological features of the epidermis were analyzed. Both AK pathological grading systems showed a positive correlation with parakeratosis, acantholysis, and liquefaction of basal cells (P < 0.05), and a negative correlation with basal layer pigmentation (P < 0.05). The correlation between these pathological features and dermoscopic characteristics was further analyzed. Acantholysis and liquefaction of basal cells were found to be associated with erosion, ulceration, and vascular patterns (Table 5).

Besides, our analysis of the correlation between lesion thickness and dermoscopic features revealed that the presence of a white structureless areas (P = 0.001) and polymorphic vascular patterns (P = 0.010) indicated a greater lesion thickness, while no significant correlation was found between other dermoscopic features and lesion thickness.

Table 4 Consistency Analysis of Olsen Grading, Dermoscopic Grading, and Histopathological Grading

	Grade I	Grade II	Grade III	r_s	*P*
AK Grading (n = 109) PRO Grading (n = 109)	36 (34.0%) 33 (31.1%)	24 (22.6%) 40 (37.7%)	46 (43.4%) 33 (31.1%)		
	Concordance between Olsen grading and histopathological grading				
Olsen classfication (n = 109) AK Grading PRO Grading	52 (49.1%) 40.4% (21/52) 36.5% (19/52)	35 (33.0%) 20.0% (7/35) 34.3% (12/35)	19 (17.9%) 63.2% (12/19) 36.8% (7/19)	 0.217 0.153	 0.026 0.118
	Concordance between Dermoscopic classification and histopathological grading				
Dermoscopic classification (n = 109) AK Grading PRO Grading	13 (12.3%) 69.2% (9/13) 53.8% (7/13)	46 (43.4%) 37.0% (17/46) 50.0% (23/46)	47 (44.3%) 53.2% (25/47) 44.7% (21/47)	 0.281 0.223	 0.004 0.022

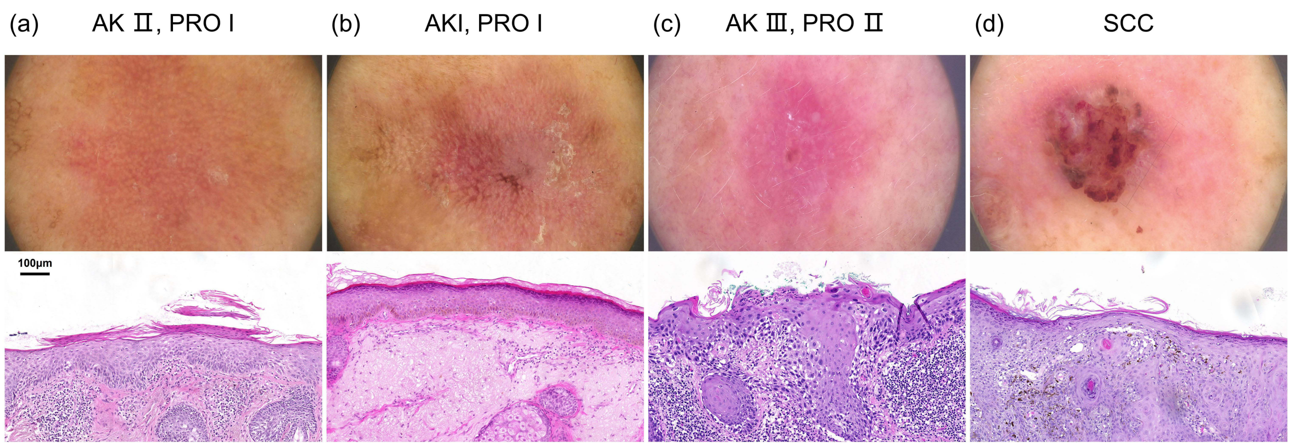

Figure 3 Clinicopathological Correlations and Corresponding Dermoscopic Features. (**a**) Pathologically, parakeratosis is observed, which may be observed dermoscopically as white fine scales; (**b**) Pathologically, basal layer pigmentation is present, which may be seen on dermoscopy as pigmentation; (**c**) Pathologically, liquefaction of basal cells and acantholysis are observed, which may correspond to the dermoscopic finding of central microerosion in the lesion; (**d**) Pathologically, acantholysis is present, which may corresponds to the dermoscopic features of ulceration and polymorphous vascular pattern.

We also analyzed the expression of keratin-14 (CK-14) in lesions to explore the relationship between different pathological features, dermoscopic characteristics, and the differentiation capacity of the lesions. The results indicated that CK-14 expression gradually increased from normal tissue to AK and then to SCC, with statistically significant differences observed among the groups ($P < 0.05$). However, no significant statistical differences in CK-14 expression were found among the different grades of AK lesions (Figure 4). A correlation analysis between CK-14 expression and dermoscopic features was conducted, but no statistically significant indicators were identified.

Table 5 Correlation Between Epidermal Pathological Features and Dermoscopic Features

Dermoscopic Features		**Pathological Features**		χ^2	***P***
Basal Layer Pigmentation					
		No	Yes		
Dermatoscopic Pigmentation	No (n = 19)	18 (94.7%)	1 (5.3%)	8.671	0.003
	Yes (n = 120)	72 (60.0%)	48 (40.0%)		
Parakeratosis					
		No	Yes		
White Fine Scales	No (n = 108)	33 (30.6%)	75 (69.4%)	4.679	0.031
	Yes (n = 31)	16 (51.6%)	15 (48.4%)		
Acantholysis					
		No	Yes		
Ulceration	No (n = 105)	82 (78.1%)	23 (21.9%)	4.883	0.027
	Yes (n = 34)	20 (58.8%)	14 (41.2%)		
Erosions	No (n = 93)	74 (79.6%)	19 (20.4%)	5.510	0.019
	Yes (n = 46)	28 (60.9%)	18 (39.1%)		
Vascular Patterns	No (n = 10)	7 (70.0%)	3 (30.0%)	6.598	0.037
	Monomorphous (n = 77)	63 (81.8%)	14 (18.2%)		
	Polymorphous (n = 52)	32 (61.5%)	20 (38.5%)		

(*Continued*)

Table 5 (Continued).

Dermoscopic Features		**Pathological Features**		χ^2	***P***
Liquefaction of Basal Cells					
		No	Yes		
Ulceration	No (n = 105)	57 (54.3%)	48 (45.7%)	4.944	0.026
	Yes (n = 34)	11 (32.4%)	23 (67.6%)		
Rosettes	No (n = 110)	49 (44.5%)	61 (55.5%)	4.039	0.044
	Yes (n = 29)	19 (65.5%)	10 (34.5%)		
Erosions	No (n = 93)	55 (59.1%)	38 (40.9%)	11.744	0.001
	Yes (n = 46)	13 (28.3%)	33 (71.7%)		
Vascular Patterns	No (n = 10)	6 (60.0%)	4 (40.0%)	6.833	0.033
	Monomorphous (n = 77)	44 (57.1%)	33 (42.9%)		
	Polymorphous (n = 52)	18 (34.6%)	34 (65.4%)		
Linear Vessels	No (n = 101)	42 (41.6%)	59 (58.4%)	7.958	0.005
	Yes (n = 38)	26 (68.4%)	12 (31.6%)		
Hairpin Vessels	No (n = 123)	64 (52.0%)	59 (48.0%)	4.140	0.042
	Yes (n = 16)	4 (25.0%)	12 (75.0%)		

Additionally, the pathological features of the dermis were analyzed, including inflammatory cell infiltration and fibroblast content. No statistically significant correlation was observed between AK grading and dermal inflammatory infiltration, whereas PRO grading was positively correlated with the degree of inflammatory cell infiltration in the dermis (P = 0.044). Further, the extent of inflammatory cell infiltration in the dermis was significantly correlated with specific dermoscopic features, including erosions, white structureless areas and hairpin vessels (Table 6).

The fibroblast content was evaluated by immunofluorescence staining using the fibroblast marker Vimentin. Also, Vimentin expression can be indicative of increased migration and invasiveness of fibroblasts. The analysis of fluorescence intensity revealed that Vimentin expression in the papillary dermis was significantly higher in SCC compared to AK (P = 0.001) and normal tissue (P = 0.001), while its expression in the reticular dermis showed no significant statistical difference among the groups. However, Vimentin fluorescence intensity showed no statistically significant differences between AK and normal tissue, nor among the different histological grades of AK. Interestingly, the Vimentin expression level in the papillary dermis of AK PRO grade III lesions was significantly lower than that observed in SCC (P = 0.021), yet remained significantly higher than in normal tissue (P = 0.018) and in AK PRO grade I lesions (P = 0.026). Further correlation analysis between Vimentin expression intensity and dermoscopic features showed a significant association between Vimentin expression and the presence of the white lines (P = 0.047) (Figure 5).

Discussion

SCC is the second most common skin malignancy, which can arise from AK. A previous Ten-Year Follow-up study found that in addition to AK, older age, Caucasian race, male gender, and a history of basal cell carcinoma are risk factors for cutaneous SCC.[17] Previous studies have analyzed the dermoscopic features of AK and SCC, and proposed a dermoscopic grading system for AK.[18] But the study populations were predominantly Caucasian, the dermoscopic features and clinicopathological correlations of different grades of AK in the Asian population still warrant investigation. Furthermore, previous research has often analyzed AK as a whole, with fewer studies specifically comparing the dermoscopic features and corresponding pathological changes among different histopathological grades of AK.

Early diagnosis and appropriate grading of suspicious AK and SCC lesions are crucial in clinical practice. Roewert-Huber et al proposed a classical histological grading system for AK (AK I-III grading) based on the extent of epidermal involvement, primarily reflecting the classic progression pathway to malignancy.[5] However, recent studies have suggested that the malignant transformation of AK may not always follow this classic pathway. Even low-grade AK lesions (AK I) carry a risk of directly progressing to invasive SCC. This alternative malignant transformation pathway, known as

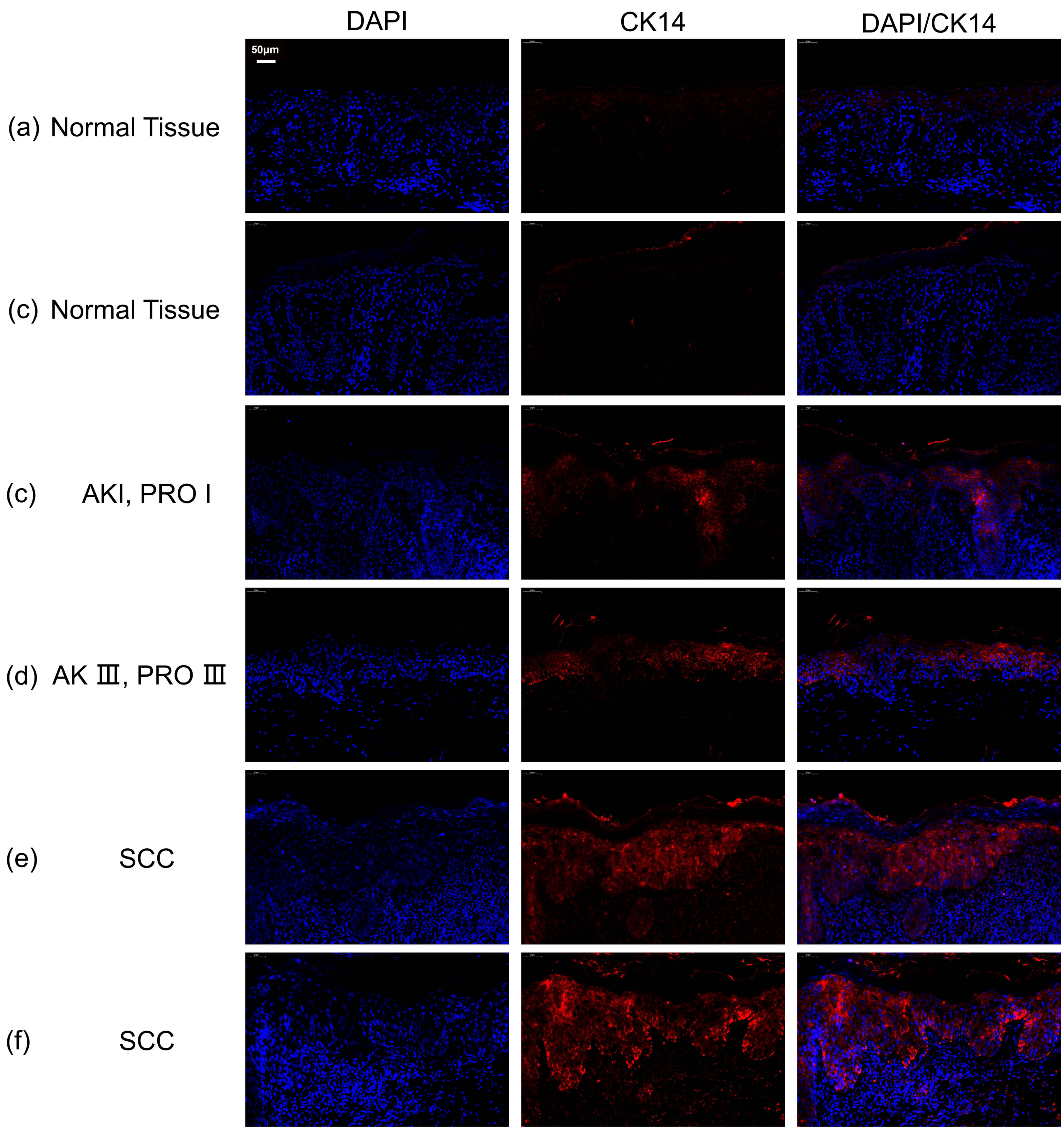

Figure 4 Immunofluorescence examination of CK-14 (red)/ nucleus (blue). Figures (**a**) and (**b**) represent typical cases of normal tissue, Figures (**c**) and (**d**) illustrate typical cases of AK, while Figures (**e**) and (**f**) depict typical cases of SCC.

the "differentiation pathway", is often considered more aggressive, and Schmitz et al proposed a new grading system (PRO I-III grading system) to reflect this pathway.[4,19,20] But our study found that the clinical Olsen grading system showed a weak correlation with AK grading and no significant correlation with PRO grading. Previous studies have confirmed that dermoscopy offers high specificity and sensitivity for diagnosing AK, with the correlation between dermoscopic features and pathological grading confirmed.[9,21] In this research, we further analyzed the dermoscopic features associated with different grades of AK and SCC. Dermoscopic grading was moderately correlated with both AK

Table 6 Correlation Between Inflammatory Cell Infiltration in Dermis and Dermoscopic Features

		Inflammatory Cellular Infiltrate				χ^2	*P*
		None	Small Focal	Focal	Lichenoid		
Erosions	No (n = 93)	9 (9.7%)	30 (32.3%)	24 (25.8%)	30 (32.3%)	5.067	0.024
	Yes (n = 46)	3 (6.5%)	9 (19.6%)	9 (19.6%)	25 (54.3%)		
White structureless areas	No (n = 71)	7 (9.9%)	28 (39.4%)	16 (22.5%)	20 (28.2%)	9.008	0.003
	Yes (n = 68)	5 (7.4%)	11 (16.2%)	17 (25.0%)	35 (51.5%)		
Hairpin Vessels	No (n = 123)	12 (9.8%)	37 (30.1%)	28 (22.8%)	46 (37.4%)	4.321	0.038
	Yes (n = 16)	0 (0.0%)	2 (12.5%)	5 (31.2%)	9 (56.2%)		

and PRO grading, and its consistency with pathological grading was generally better than that of the clinical Olsen grading system. These results highlight the importance of dermoscopy as a valuable tool for the diagnosis and assessment of AK and SCC.

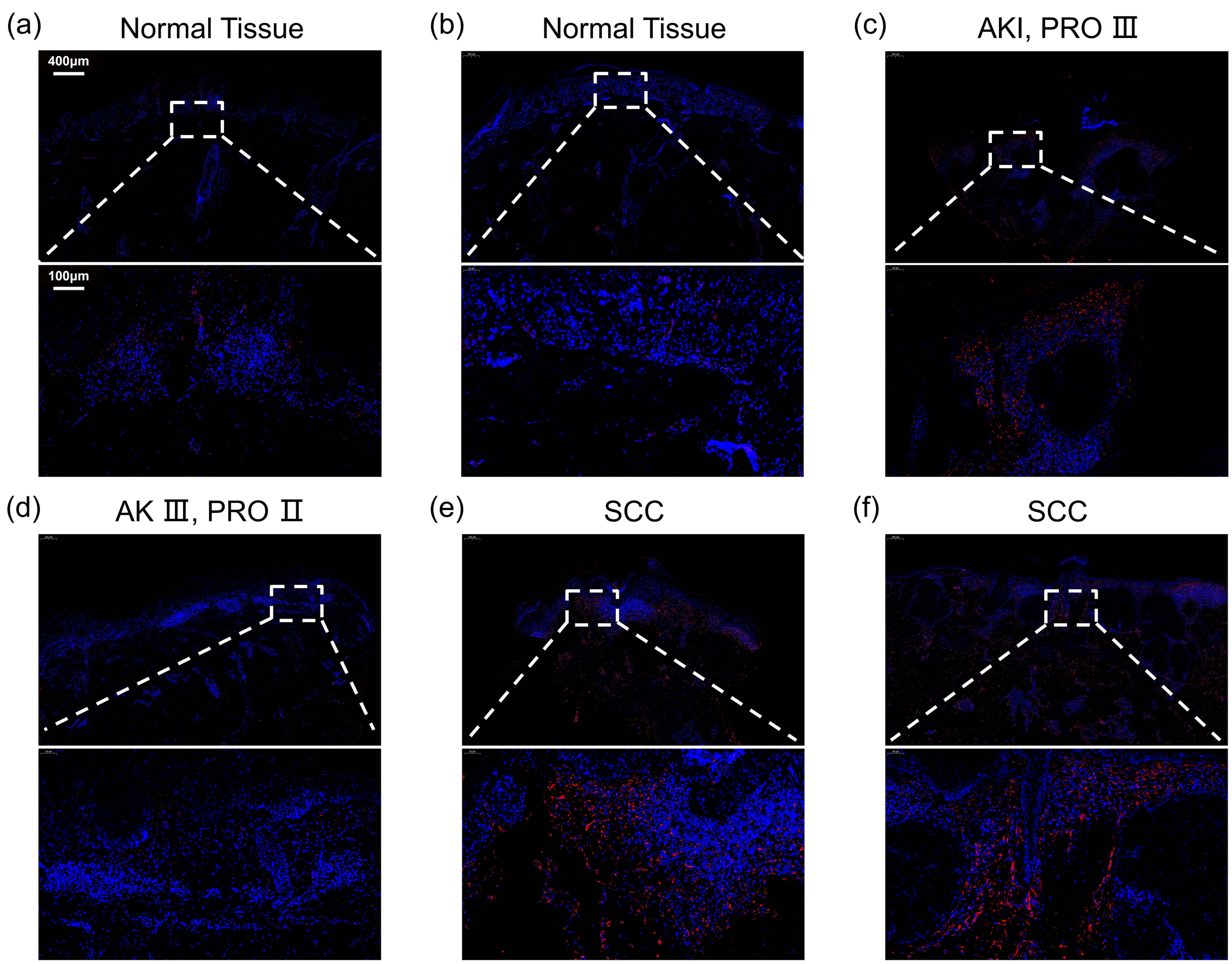

Figure 5 Immunofluorescence examination of Vimentin (red)/ nucleus (blue). Figures (**a**) and (**b**) represent typical cases of normal tissue, Figures (**c**) and (**d**) illustrate typical cases of AK, and Figures (**e**) and (**f**) depict typical cases of SCC.

In addition to previously reported dermoscopic features that are related to grading, such as red pseudonetwork structure, enlarged follicular openings filled with keratotic plugs, and yellow structureless areas, we also identified other dermoscopic features that can provide insights into the malignancy of lesions, especially in helping us differentiate between high-grade AK and SCC.[11,14,18] Specific vascular patterns were significantly associated with different degrees of lesion malignancy, hairpin vessels function as positive predictors for SCC. Furthermore, a significant correlation exists between the two AK pathological grades and vascular patterns, where polymorphic vascular patterns indicate higher-grade lesions. These findings highlight the crucial diagnostic value of vascular patterns in the evaluation of AK and SCC. Multivariate analysis indicated that the white structureless areas is a positive predictive factor for SCC. These areas demonstrated a progressive increase in frequency corresponding to lesion grade severity (AK I: 11.1%, AK II: 29.2%, AK III: 65.5%, SCC: 81.8%). While no statistically significant difference was observed in the frequency of white structureless areas between AK III and SCC, a significant difference was detected between PRO III and SCC. Additionally, a significant correlation was found between lesion thickness and the presence of white structureless areas. These findings are consistent with previous literature, indicating that white structureless areas correspond histopathologically to aggregates of neoplastic squamous cells exhibiting keratinization.[11] In addition, the highest frequency of enlarged follicular openings filled with keratotic plugs was observed in AK III lesions (P = 0.003). This may be attributed to the neoplastic keratinocytes in SCC disrupting the normal epidermal structure, along with the development of ulceration, erosion, and keratinous corpora, which consequently leads to a reduction of follicular keratin plugs.

The tumor microenvironment (TME), primarily composed of immune cells and stromal cells (predominantly fibroblasts), plays a pivotal modulating role in tumor proliferation and invasion. Within this complex ecosystem, immune cells orchestrate inflammatory responses that fundamentally reshape tumor cell phenotype through various molecular mechanisms.[21–23] By analyzing the pathological features of lesions at different grades, we observed that the degree of inflammatory infiltrate was positively correlated with PRO grading. A similar trend was also observed in AK grading, although no significant statistical differences were found between the groups. In our dermoscopic analysis, the evolution of vascular patterns from monomorphous to polymorphous configurations, may reflect these underlying inflammatory processes, suggesting that dermoscopy might serve as a non-invasive tool for assessing the inflammatory status of the TME, potentially offering insights into disease progression and therapeutic response.

Fibroblasts play another critical role in the TME, remodeling the surrounding extracellular matrix (ECM) and secreting various tumorigenic factors.[24] Previous studies in melanoma have demonstrated that shiny white streaks observed under dermoscopy may indicate papillary dermal fibrosis.[25] Inspired by this, we analyzed dermal fibroblasts in AK and SCC and sought to investigate the correlation between their quantity and dermoscopic features. The intermediate filament protein Vimentin is a widely used phenotypic marker for fibroblasts and myofibroblasts.[26] Our analysis revealed significantly elevated Vimentin expression in the papillary dermis of SCC compared to AK and normal tissue, indicating an expansion of the fibroblast population during malignant progression. Comparative analysis of fibroblast content between advanced AK and SCC revealed that while fibroblast numbers were significantly higher in SCC compared to AK III and PRO III lesions, the fibroblast content in PRO III lesions was notably elevated compared to lower-grade AK and normal tissue. High Vimentin expression showed significant correlation with white streaks observed under dermoscopy. This finding suggests that the white lines areas observed under dermoscopy may represent a visual manifestation of increased stromal fibroblast density, potentially serving as a dermoscopic marker for disease progression. This observation aligns with current understanding of cancer-associated fibroblasts (CAFs) in tumor progression, and suggests that dermoscopy might offer a non-invasive window into the dynamic changes of CAFs.[24,27] However, the pathological features corresponding to the white structures observed under dermoscopy have not yet been fully determined. For instance, white structureless areas may be associated with an increase in keratin within the epidermis, while the white halos around hair follicles may suggest keratinocyte keratinization, white streaks are thought to be related to dermal fibrosis or hyperkeratosis[11,14,25,28] Therefore, larger sample studies may be needed to further clarify the dermoscopic features that could indicate dermal fibrosis.

It is noteworthy that, based on the previously mentioned changes in fibroblast proliferation and dermal inflammatory cell infiltration, we hypothesize that the impact of dysplastic keratinocytes proliferating and infiltrating solely within the epidermis (as assessed by AK grading) is limited. In contrast, the PRO grading system appears to be more closely associated with alterations in the dermal microenvironment. These findings suggesting that the differentiation pathway represented by the basal growth pattern of neoplastic squamous cells may drive tumor progression and enhance invasive potential by remodeling the tumor microenvironment, thereby providing a more accurate assessment of lesion malignancy. Regarding the two commonly used histological grading systems for AK (AK Grading and PRO Grading), previous studies have analyzed their prognostic value and found that SCC, particularly invasive SCC, may be more closely associated with PRO III lesions rather than AK III lesions.[29,30] Some researchers have hypothesized that dysplastic keratinocytes with low invasive potential cannot disrupt the basement membrane and primarily grow upward, confining lesions to the epidermis, in contrast, those with high invasive potential can invade downward directly.[30] However, our study found that CK-14 expression in the epidermis of AK was significantly higher than in normal tissue but lower than in SCC. Notably, there were no significant differences in CK14 expression among different grades of AK. CK-14 is an early keratinization differentiation marker. Previous studies have confirmed its high expression in SCC, promoting tumor progression by influencing the differentiation of keratinocytes.[31] Therefore, the expression trend of CK-14 in different grades of AK and SCC suggests that the differentiation capacity of dysplastic keratinocytes may not vary significantly across these grades. On the other hand, some previous studies have highlighted the heterogeneity in gene expression within AK lesions, indicating that those with gene expression patterns resembling tumors may possess higher malignant potential, the upregulated differentially expressed genes in these lesions are linked to inflammatory responses that promote tumor progression through innate immunity activation.[32] In our study, as previously mentioned, PRO grading was significantly associated with changes in the dermal layer of the lesions, including alterations in vascular patterns, proliferation of fibroblasts in the dermal papillae, and infiltration of inflammatory cells. In contrast, such correlations were not significant in classic AK grading. Therefore, we hypothesize that PRO III lesions may remodel the underlying dermis, creating a tumor microenvironment conducive to tumor proliferation and metastasis, thereby promoting the progression of the lesions. Consequently, PRO grading may hold value in assessing the malignant potential of AK. However, further analyses of gene expression and proteomics in different grades of AK and SCC tissue are necessary to validate these conclusions and explore the underlying molecular mechanisms.

Conclusion

Dermoscopy provides a non-invasive and effective tool for evaluating lesion malignancy from different grades of AK to SCC. It aids in the assessment and monitoring of disease progression through its potential to evaluate inflammatory responses and CAFs non-invasively. This capability assists clinicians in determining optimal biopsy timing and developing tailored treatment strategies, ultimately reducing unnecessary economic and psychological burdens on patients.

Abbreviations

AK, Actinic Keratosis; SCC, Squamous Cell Carcinoma; iSCC, Invasive Squamous Cell Carcinoma; PRO, Pattern of basal growth; TME, Tumor Microenvironment; CAFs, Cancer-Associated Fibroblasts; ECM, Extracellular Matrix; ALA-PDT, 5-Aminolaevulinic Acid Photodynamic Therapy; EMT, Epithelial-Mesenchymal Transition; IntDen, Integrated Density; OR, Odds Ratio; IQR, Interquartile Range; SPSS, Statistical Package for the Social Sciences; EDTA, Ethylenediaminetetraacetic Acid; Tris, Tris(hydroxymethyl)aminomethane; IgG, Immunoglobulin G; DAPI, 4',6-Diamidino-2-Phenylindole; UV, Ultraviolet; rs, Spearman's rank correlation coefficient; P, P-value.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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