

Dermoscopic characteristics of nodular squamous cell carcinoma and keratoacanthoma

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ABSTRACT **Background:** Nodular squamous cell carcinoma (SCC) and keratoacanthoma (KA) may mimic a variety of other benign and malignant non-pigmented nodules.

Objectives: To analyze the dermoscopic characteristics of nodular SCC and KA.

Patients/Methods: Retrospective analysis of 50 nodular SCCs and 8 KAs collected from a tertiary dermatology referral center and a private dermatology practice in Melbourne, Australia, between 1 September 2009 and 1 October 2012. All lesions were nodules; defined as firm, elevated, round, palpable tumors with a diameter of 5 mm or more. Clinical and dermoscopic images were evaluated by two examiners in consensus.

Results: Signs of keratinization were frequently observed and included keratin crust/scale (90% of SCCs, 100% of KAs), central keratin mass (32% of SCCs, 88% of KAs), white structureless areas (66% of SCCs, 50% of KAs), white circles (32% of SCCs, 38% of KAs) and white keratin pearls (14% of SCCs, 12% of KAs). Hemorrhage was present in 72% of SCCs and 88% of KAs and preferentially occurred centrally and in areas of keratinization. For nodular SCCs and KAs, we observed glomerular vessels (42% and 25% respectively), linear irregular vessels (36% and 25% respectively), atypical vessels (30% and 38% respectively) and hairpin vessels (30% and 25% respectively).

Conclusions: Hemorrhage, keratinization and vascular features (glomerular, hairpin and linear irregular morphologies) are useful in diagnosing both nodular SCC and KA. Further research on the comparative dermoscopic characteristics of a range of amelanotic nodules is important in order to improve diagnosis of these clinically challenging tumors.

Introduction

Squamous cell carcinoma (SCC) is the second most common cutaneous malignancy after basal cell carcinoma (BCC), with

an increasing incidence worldwide [1,2]. It may present in a variety of morphologies, including as a keratinizing nodule, which may be clinically indistinguishable from keratoacanthoma (KA). Although traditionally diagnosed clinically,

nodular SCC and KA may mimic a variety of other benign and malignant nodules. In the context of a new or growing non-pigmented nodule, the differential diagnosis may include nodular BCC, hypertrophic intraepidermal carcinoma, atypical fibroxanthoma, Merkel cell carcinoma and nodular or desmoplastic melanoma. The differing prognostic and therapeutic implications of each of these diagnoses make their distinction important. However, misdiagnosis is common, and a recent study found that misdiagnosed nodular melanoma was mistaken for nodular SCC in 38% of cases [3].

Dermoscopy is an important in-vivo, non-invasive diagnostic technique that permits visualization of morphological features not visible with the naked eye. It greatly enhances the diagnostic accuracy for pigmented skin lesions [4-6]. Recent studies have shown that it also aids in the diagnosis of non-pigmented keratinizing skin lesions, including actinic keratosis and Bowen's disease [7-15]. However, relatively few studies have reported on the dermoscopic features of non-pigmented invasive SCC and keratoacanthoma and better understanding of their presenting dermoscopic features may help in differentiating them from other nodules [16-18].

As non-pigmented nodules are a commonly encountered clinical diagnostic dilemma, this study sets out to describe the dermoscopic features of nodular SCC and KA.

Materials and methods

Between 1 September 2009 and 1 October 2012, clinical and dermoscopic images for a series of 50 nodular SCCs and 8 KAs were collected from a single tertiary dermatology referral center and a single private dermatology practice (J.W.K.) in Melbourne, Australia. Data were obtained from the medical records for all cases including age at diagnosis, sex, nodule diameter, site and tumor differentiation. Institutional ethics committee approval was obtained.

All lesions were excised and histopathology was reviewed to confirm the diagnosis. The diagnosis of KA was based on histopathological architecture and pattern of cell differentiation [19]. All lesions were nodules; defined as firm, elevated, round, palpable tumors with a diameter of 5 mm or more [20].

Digital dermoscopic images were captured with a dermatoscope (DermLite DL3 dermatoscope, Heine, Herrsching, Germany) mounted on a digital camera (Cyber-shot DSC-W290, Sony Corporation, Tokyo, Japan). Tenfold magnification was used. Alcohol gel was used for immersion and precautions were taken to reduce compression artifact. Lesions were excluded if the image quality was unsatisfactory.

Clinical and dermoscopic images were reviewed retrospectively. An initial meeting was held where a sample of 15 cases was scored and the literature reviewed to establish a

consensus on the criteria and consistency of reporting. All clinical and dermoscopic images were then evaluated by two examiners in consensus (Y.P. and M.J.L.) who were aware of the histopathologic diagnosis.

Vessel morphology was defined as glomerular, dotted/pin-point, linear irregular, hairpin, comma or corkscrew according to criteria described by Menzies et al [21]. Atypical vessels were defined as those vessels not fitting into any characteristic morphology. The pattern of vessel arrangement was then scored as radial, branched, clustered, centered, serpiginous, reticular or linear according to the criteria of Kittler et al [22]. We evaluated for the presence of keratin crust/scale, central keratin mass, collarette, white circles, white pearls, white lines, white structureless areas and hemorrhage. Dermoscopic colors were scored as white, yellow, pink, red, purple, blue, tan, brown, gray, blue or black. Finally, we assessed for the presence of pigmented structures and blue-gray veil. Dermoscopic features of nodular SCC and KA were compared. The Fisher exact test was used and analysis was performed using Stata (StataCorp 2011, Stata Statistical Software: Release 12, College Station, Texas).

Results

Fifty cases of nodular SCC and 8 cases of KA were collected. Of the nodular SCCs, 54% were well differentiated, 38% were moderately differentiated and 6% were poorly differentiated. The median diameter was 8 mm (range 6-28 mm) for nodular SCCs and 9 mm (range 6-16 mm) for KAs.

Keratin crust/scale was observed in the vast majority of cases (90% of SCCs and 100% of KAs) (Table 1).

A central keratin mass was present in 32% of nodular SCCs and 88% of KAs. White structures were common, in decreasing frequency we observed; white structureless areas (66% of SCCs and 50% of KAs), white circles (32% of SCCs and 38% of KAs) and white keratin pearls (14% of SCCs and 12% of KAs). We observed that the keratin pearls were often clustered, forming a mosaic pattern of indented round foci of keratin. Hemorrhage was observed in 72% of SCCs and 88% of KAs and tended to be present centrally in areas of keratinization. Collarette surrounded 12% of SCCs and 25% of KAs.

The vascular pattern was polymorphic in 50% of nodular SCCs and 38% of KAs. Vessels were not seen in 4% of SCCs. Glomerular vessels were the most common vessel type and were observed in 42% of SCCs and 25% of KAs. For nodular SCCs and KAs, we also commonly observed linear irregular vessels (36% and 25% respectively), atypical vessels (30% and 38% respectively) and hairpin vessels (30% and 25% respectively); 71% of hairpin vessels were positioned peripherally with a radial arrangement.

TABLE 1. Clinical and dermoscopic features of nodular squamous cell carcinoma and keratoacanthoma

Features		Nodular squamous cell carcinoma (n=50)	Keratoacanthoma (n=8)	p
Age, median (range), y		79 (53-103)	72 (58-88)	0.70
Male:Female ratio		1.50	1.67	1
Site				
	Head and neck	17 (34%)	2 (25%)	0.90
	Trunk	4 (8%)	1 (12%)	
	Upper extremity	13 (26%)	2 (25%)	
	Lower extremity	16 (32%)	3 (38%)	
Keratinization				
	Keratin crust/scale	45 (90%)	8 (100%)	0.60
	Central keratin mass	16 (32%)	7 (88%)	<0.01
	Collarette	6 (12%)	2 (25%)	0.58
	White circles	16 (32%)	3 (38%)	1
	White keratin pearls	7 (14%)	1 (12%)	1
	White structureless areas	33 (66%)	4 (50%)	0.44
	White lines	3 (6%)	0 (0%)	1
Hemorrhage		36 (72%)	7 (88%)	0.44
Vascular pattern				
	Monomorphic	23 (46%)	5 (62%)	0.61
	Polymorphic	25 (50%)	3 (38%)	
	Vessels absent	2 (4%)	0 (0%)	
Vessel morphology				
	Dotted/pinpoint	7 (14%)	0 (0%)	0.58
	Glomerular	21 (42%)	2 (25%)	0.56
	Linear irregular	18 (36%)	2 (25%)	0.7
	Hairpin	15 (30%)	2 (25%)	1
	Atypical	15 (30%)	3 (38%)	0.69
	Vessels absent	2 (4%)	0 (0%)	1
Vessel arrangement				
	No specific arrangement	33 (66%)	3 (38%)	0.26
	Radial	7 (14%)	2 (25%)	
	Branched	8 (16%)	3 (38%)	
	Vessels absent	2 (4%)	0 (0%)	
Pigmented structures		0 (0%)	0 (0%)	1
Blue-gray veil		0 (0%)	0 (0%)	1

For nodular SCCs and KAs, the primary dermoscopic color was pink (62% and 75% respectively), white/yellow (32% and 25% respectively) and red (6% of SCCs). Mul-

tipple colors were present in all lesions, with 41% having 5 or 6 colors. Pigmented structures or blue-gray veil were not seen.

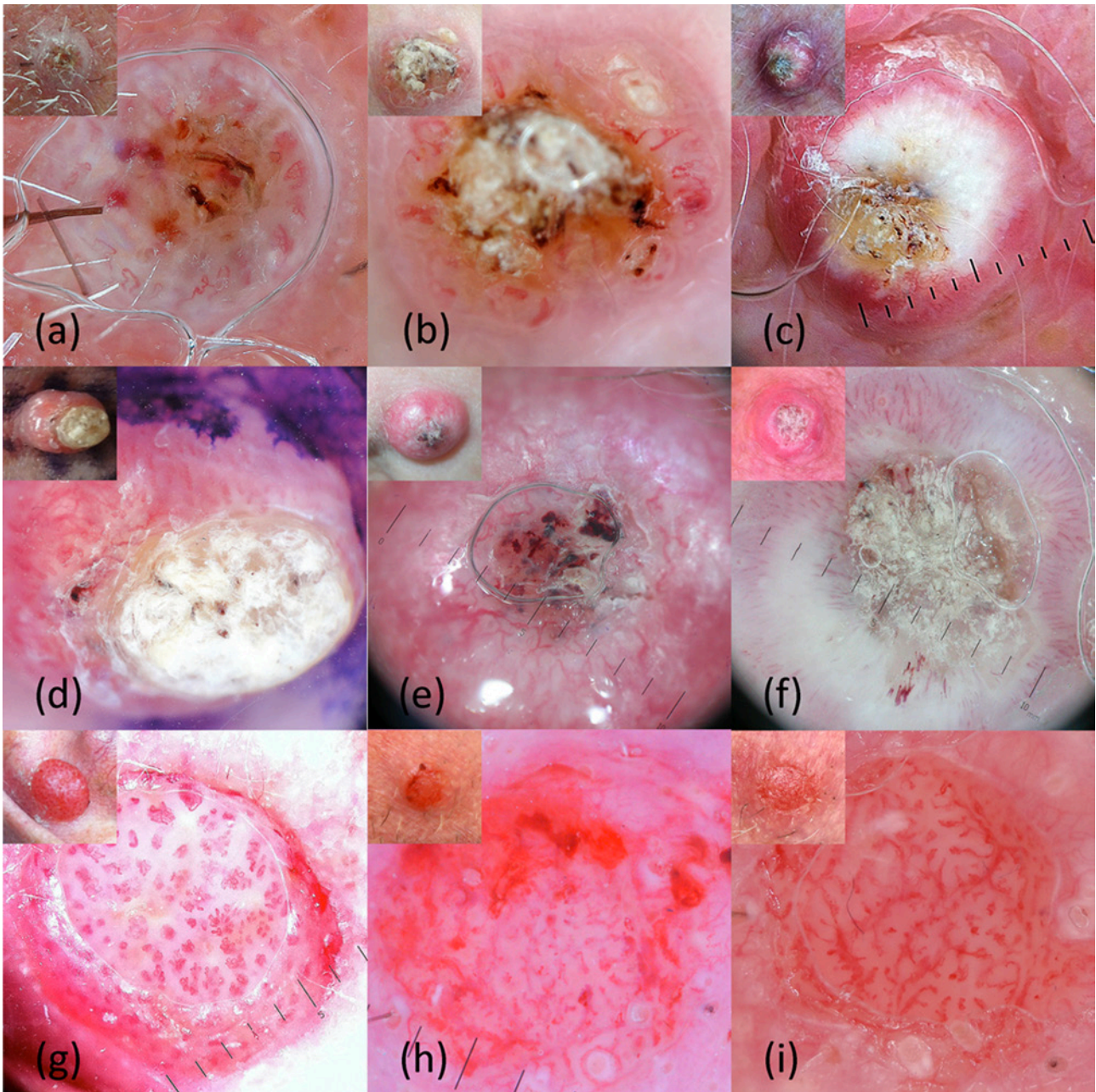


Figure 1. Clinical and dermoscopic images of 6 nodular squamous cell carcinomas (lesions A-C and G-I) and 3 keratoacanthomas (lesions D-F). Lesions A-F are clinically keratinizing nodules which exhibit central keratin mass surrounded by radially oriented hairpin vessels (A,B,F) and/or linear irregular vessels (A,B,D,E). White structureless areas (C,F) and hemorrhagic areas (A,E,F) are also seen. Lesions G-I lack obvious clinical clues of keratinization, however dermoscopy reveals white circles (H,I), hemorrhage (H), coiled glomerular vessels (G,H) and branched linear irregular vessels (I). [Copyright: ©2014 Lin et al.]

Discussion

In this study we have identified useful clues that may aid in the diagnosis of nodular SCC and KA. Dermoscopic signs of keratinization were present in the vast majority of nodular SCCs and in all KAs (Figure 1). The frequent observation of keratin scale, central keratin mass, white structureless areas, white circles, white keratin pearls and hemorrhage in our series is comparable to two recent studies (Table 2) [16,17]. The results of our study support the notion that dermoscopic features of keratin are the most useful features in identifying nodular SCC and KA [17].

A common therapeutic dilemma with nodular SCC is distinguishing it from KA. The results of our study show considerable similarity and overlap in the dermoscopic appearance of nodular SCC and KA. For clinicians who encounter a growing keratinizing nodule that is clinically suspicious for either SCC or KA, it appears that dermoscopy does not help to reliably distinguish between the two lesions. The exception to this was the presence of a central keratin mass, which was more common in KA than in SCC (88% vs. 32%, $p < 0.01$). However, this is not surprising given that the central keratin plug is part of the architectural criteria for the histopathologic

TABLE 2. Comparison of studies investigating dermoscopic features of squamous cell carcinoma and keratoacanthoma

	Present study		Rosendahl et al ¹⁶		Zalaudek et al ¹⁷	
	Nodular SCC (n=50)	KA (n=8)	SCC (n=60)	KA (n=43)	SCC (n=78)	KA (n=24)
Keratinization						
Keratin crust/scale	90%	100%	70.0%	79.1%	48.7%	41.6%
Central keratin mass	32%	88%	30.0%	51.2%	39.4%	58.3%
White circles	32%	38%	60.0%	25.6%	41.0% (targetoid hair follicles)	41.6% (targetoid hair follicles)
Keratin pearls	14%	12%	16.7% (white clods)	25.6% (white clods)	n/a	n/a
White structureless areas	66%	50%	40.0%	55.8%	42.3%	50.0%
White lines	6%	0%	n/a	n/a	n/a	n/a
Collarette	12%	25%	n/a	n/a	n/a	n/a
Vessel morphology						
Glomerular	42%	25%	75.0% (coils)	55.8% (coils)	14.1% (dotted/glomerular)	12.5% (dotted/glomerular)
Linear irregular	36%	25%	23.3% (serpentine)	32.6% (serpentine)	17.90%	70.8%
Hairpin	30%	25%	21.7% (looped)	11.6% (looped)	38.50%	37.5%
Dotted/pinpoint	14%	0%	3.3%	2.3%	14.1% (dotted/glomerular)	12.5% (dotted/glomerular)
Atypical	30%	38%	n/a	n/a	n/a	n/a
Vessels absent	4%	0%	13.3%	18.6%	n/a	n/a
Hemorrhage	72%	88%	41.7% (blood spots)	51.2% (blood spots)	29.5% (micro-erosions)	62.5% (micro-erosions)

n/a refers to criteria not described

diagnosis of KA. Rosendahl et al concluded from their data that dermoscopy did not improve the ability to confidently differentiate between SCC and KA [17]. Indeed, dermatopathologists continue to debate whether KA is a highly differentiated form of SCC or a benign involuting tumor [23].

Another feature of keratinization not reported in other dermoscopic series of SCC or KA is collarette, which we found in 12% of nodular SCCs and 25% of KAs. This is compared with an incidence of collarette found in 74% of pyogenic granulomas, 11% for melanomas and 5% for basal

cell carcinomas [24]. Given that collarette is not uncommonly seen in rapidly growing nodules, it is probably not a useful distinguishing feature.

Vascular features are important clues in the diagnosis of non-pigmented nodules. Glomerular vessels, linear irregular vessels, radially oriented hairpin vessels and atypical vessels were commonly present in our series. These vessel types are often found in other keratinizing lesions, including actinic keratosis and Bowen's disease [16,17]. However, compared to actinic keratosis and Bowen's disease, invasive SCCs and

KAs developed a more polymorphic vascular pattern with an increased frequency of hairpin and linear irregular vessels.

When faced with a pink or red nodule, one of the most important diagnostic decisions to make is the distinction between a nodular SCC and a clinically non-pigmented nodular melanoma. Pigmented structures and blue-gray veil are important positive dermoscopic features that strongly favor the diagnosis of hypomelanotic nodular melanoma and these were both negative dermoscopic features in our series of nodular SCCs and KAs [25,26]. However, the diagnosis of truly amelanotic nodular melanoma becomes particularly challenging because it also lacks dermoscopic features of pigmentation.

Although none of the cases in our series contained pigmented structures, pigmented SCC is a recognized entity. The clinical and dermoscopic diagnosis of this rare tumor have been described in several case reports and the presence of keratin scale might be useful clue for the diagnosis [27-32].

Another common differential diagnosis of nodular SCC is nodular BCC. In our series, cases did not display the characteristic arborizing vessels associated with BCC [33,34]. Conversely, BCC rarely contains the glomerular, hairpin or linear irregular vessels, which were frequently observed in nodular SCC and KA.

Seborrheic keratosis may also be confused with nodular SCC. Dermoscopically, keratin and hairpin vessels are common to both, however, hairpin vessels have been found to be more predictive of seborrheic keratosis [33]. Seborrheic keratosis may also be pigmented and have milia-like cysts and comedo-like openings which aid diagnosis [35].

Merkel cell carcinoma is a rare tumor that may also mimic nodular SCC. Both are non-pigmented nodules that commonly contain linear irregular vessels [36,37]. However, other vascular features may help discriminate, with hairpin vessels favoring the diagnosis of SCC and arborizing vessels favoring the diagnosis of Merkel cell carcinoma. Hyperkeratosis is typically absent from Merkel cell carcinomas, which also tend to have a shinier cherry red appearance [38].

There were several limitations to this study. Firstly, the two examiners of images were not blinded to the diagnosis of SCC or KA. Secondly, we did not include nodules other than SCC and KA and the study was not designed to test the sensitivity nor specificity of dermoscopic criteria in differentiating nodular SCC and KA from other nodular lesions. Finally, the study was not designed to determine if dermoscopy alters the naked eye diagnosis of a nodular SCC or KA. For example, in Figure 1, lesions A-F appear as clinically keratinizing nodules, where the major differential diagnosis on naked eye examination would be SCC or KA and it is unlikely that dermoscopy would alter diagnosis in these cases. On the other hand, lesions G-I lack clinical clues of keratinization and it is here that dermoscopy may become useful in diagnosis. However,

the study was not designed to determine whether dermoscopy would alter the diagnosis.

Conclusion

Hemorrhage, keratinization, pink color and vascular structures (glomerular, hairpin and linear irregular morphologies) are useful dermoscopic features in diagnosing nodular SCC and KA. There is considerable similarity and overlap in the dermoscopic appearance of these lesions. Further research on the dermoscopic characteristics of a range of amelanotic nodules is important in order to improve the diagnosis of these clinically challenging tumors.

Prior presentation

This study was presented in part at the 8th World Congress of Melanoma, Hamburg, Germany, July 17-20, 2013.

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