STUDY

Surface Microscopy of Pigmented Basal Cell Carcinoma

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Objectives: To describe the relevant morphologic features and to create a simple diagnostic method for pigmented basal cell carcinoma (BCC) using in vivo cutaneous surface microscopy (ie, dermoscopy, dermatoscopy, or oil epiluminescence microscopy).

Design: Pigmented skin lesions were photographed in vivo using immersion oil (surface microscopy). All pigmented skin lesions were excised and reviewed for histological diagnosis. Photographs of 142 pigmented BCCs, 142 invasive melanomas, and 142 benign pigmented skin lesions were randomly divided into 2 equally sized training and test sets. Images from the training set were scored for 45 surface microscopy features. From this a model was derived and tested on the independent test set.

Setting: All patients were recruited from the primary case and referral centers of the Sydney Melanoma Unit, Sydney, Australia, and the Skin and Cancer Unit, Skin and Cancer Associates, Plantation, Fla.

Patients: A random sample (selected from a larger database) of patients whose lesions were excised.

Main Outcome Measures: Sensitivity and specificity of the model for diagnosis of pigmented BCCs.

Results: The following model was created. For a pigmented BCC to be diagnosed it must not have the negative feature of a pigment network and must have 1 or more of the following 6 positive features: large gray-blue ovoid nests, multiple gray-blue globules, maple leaflike areas, spoke wheel areas, ulceration, and arborizing "treelike" telangiectasia. On an independent test set the model had a sensitivity of 97% for the diagnosis of pigmented BCCs and a specificity of 93% for the invasive melanoma set and 92% for the benign pigmented skin lesion set.

Conclusion: A robust surface microscopy method is described that allows the diagnosis of pigmented BCCs from invasive melanomas and benign pigmented skin lesions.

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A PROPORTION of basal cell carcinomas (BCCs) contain pigment. In the largest histological series the incidence ranges from 6.7% to 8.5% of BCCs, but a racial predilection probably exists.[1,2] Most of the BCCs' histological patterns can have pigmented varieties; however, morphoeic and infiltrative subtypes are uncommonly pigmented. Histologically, melanin can be found in the tumor mass and surrounding dermis. Within the tumor mass melanocytes are often hyperplastic and melanosomes are often confined to the melanocytes. However, they may be taken up by surrounding malignant epithelial cells.[3,4] Melanin is preferably seen in the superficial component of the tumor.[1] In dermis, melanin is found primarily in melanophages, but small amounts may be lying free. Finally, hyperplastic melanocytes may be found in the overlying epidermis.[1]

Because of their growth patterns and asymmetry of pigmentation, pigmented BCCs are included in the differential diagnosis of invasive melanoma. They may also be confused with other benign pigmented skin lesions (PSLs).

In vivo "cutaneous surface microscopy," "dermoscopy," "dermatoscopy," and "epiluminescence microscopy" are terms that describe the same process of examination of skin lesions with an incident light magnification system using oil at the skin-microscope interface. Many studies have shown that surface microscopy can improve the diagnostic accuracy of PSLs including melanoma.[5-12]

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SUBJECTS AND METHODS

Pigmented skin lesions were photographed in vivo using immersion oil and a camera (Dermaphot; Heine Ltd, Herrsching, Germany) at the Sydney Melanoma Unit, Sydney, Australia, or at the Skin and Cancer Unit, Skin and Cancer Associates, Plantation, Fla. Here, PSLs are photographed prior to excision, and subsequently catalogued following review for histological diagnosis by a research assistant who was not a study participant. The study included 142 pigmented BCCs, 142 invasive melanomas, and 142 randomly selected clinically atypical benign nonmelanoma lesions chosen from the larger photographic library (**Table 1**). Most of the nonmelanomas were considered atypical by the clinician, thus leading to the decision to perform a biopsy. The large set was divided into training and test sets by randomization, resulting in 71 BCCs, 71 melanomas, and 71 benign PSLs in each set. The surface microscopy images were studied on a viewer (Kodak Ektagraphic Viewer, model 575AF; Eastman Kodak Co, Rochester, NY).

In the first phase of the study, images of the training set were reported without knowledge of the histological diagnosis by two of us (S.W.M. and K.W.) for 45 surface microscopy features (**Table 2**). Most of these features have been described elsewhere.[14,15] All morphologic features observed in this study are easily identifiable with a handheld ×10 surface microscope (eg, Dermatoscope, Heine Ltd; or Episcope, Welch Allyn Inc, Skaneateles Falls, NY).

In the training set the difference between the proportions of pigmented BCCs and non-BCCs identified with each feature was analyzed in a series of χ^2 tests of independences. A decision-wise error rate of $P<.05$ was used to determine the statistical significance of each test. Because multiple tests were performed, the experiment-wise error rate was not controlled, and the type I error rate was clearly inflated. This strategy was justified by the potential clinical benefit of identifying new predictors of BCC. We believe that, in this context, rejecting a real effect (type II error) was of greater concern than accepting a chance difference (type I error).

The sensitivity for diagnosis of pigmented BCC is equal to the number of scored positive BCCs divided by the total number of BCCs (expressed as a percentage). The specificity for the diagnosis is equal to the number of scored negative non-BCCs divided by the total number of non-BCCs (expressed as a percentage).

From the training set data a simple model suitable for use by the clinician for diagnosing pigmented BCC were constructed on principles described previously.[16] Here, features were selected for low sensitivity (negative features) and high specificity for the invasive melanoma and benign PSL sets (positive features). Models were optimized to achieve adequate sensitivity for diagnosis while achieving high specificity using the benign PSL set and moderate to high specificity using the invasive melanoma set. In the second phase of the study the single optimal model derived from the training set was scored on the independent test set, without knowledge of the diagnosis of each lesion.

Many surface microscopy features of pigmented BCCs have been described.[6,13,14] However, formal statistical evaluation of such features has been reported on only one occasion, and on a small sample of lesions.[15] For this reason we analyzed the morphologic features of a large set of 142 pigmented BCCs and produced a simple surface microscopy method for diagnosis that would allow differentiation from melanomas and benign pigmented tumors.

RESULTS

Forty-five surface microscopy features were scored on each lesion from the training set by 2 of us (S.W.M. and K.W.). The following features were found with a significantly different frequency in pigmented BCCs compared with invasive melanomas and benign PSLs when analyzed separately (Table 2). Ulceration, areas of extensive (>50% and >75%) amelanotic regions, large gray-blue ovoid nests, blue globules, multiple gray-blue globules, maple leaflike areas, spoke wheel areas, and telangiectasia with arborization, large diameter or kinking were all significantly increased in BCCs. A pigment network, dark brown color, and extensive (>75%) pigmentation were significantly decreased in BCCs.

Using the sensitivity and specificity results (Table 2) an optimized simple model for the diagnosis of pigmented BCC suitable for clinical use was formed (see "Subjects and Methods" section). Here, for a pigmented BCC to be diagnosed, it must not have the negative feature of a pigment network and must have 1 or more of the following 6 positive features (**Table 3**).

The 6 positive features are defined as follows. Spoke wheel areas are well-circumscribed radial projections, usually tan but sometimes blue or gray, meeting at an often darker (dark brown, black, or blue) central axis (**Figure 1**). Large gray-blue ovoid nests are well-circumscribed, confluent or near confluent pigmented

Table 1. Diagnosis Frequency of Pigmented Lesions

Diagnosis	Training Set, No. (%)	Test Set, No. (%)
Pigmented basal cell carcinoma	**71 (100)**	**71 (100)**
Invasive melanoma*	**71 (100)**	**71 (100)**
Benign pigmented skin lesions	**71 (100)**	**71 (100)**
Ephelis	0	1 (1)
Solar lentigo	4 (6)	3 (4)
Common nevus	15 (21)	19 (27)
Dysplastic nevus	34 (48)	38 (54)
Blue nevus	3 (4)	2 (3)
Spitz nevus	4 (6)	0
Seborrheic keratosis	9 (13)	5 (7)
Dermatofibroma	0	1 (1)
Hemangioma	0	1 (1)
Other	2 (3)	1 (1)

**The median Breslow thickness was 0.74 mm for the training set and 0.67 mm for the test set.*

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Table 2. Sensitivity and Specificity Analysis of Surface Microscopy Features for the Diagnosis of Pigmented Basal Cell Carcinomas (BCCs)*

Feature	Sensitivity, %‡	Specificity, % (*P*)†	
		Invasive Melanoma§	Benign PSLs‖
Ulceration	27	87 (.03)	97 (<.001)
Colors present			
Blue	72	25 (NS)	69 (<.001)
Black	14	68 (.01)	93 (NS)
Gray	49	52 (NS)	55 (NS)
Tan	76	5.6 (.002)	15 (NS)
Dark brown	58	11 (<.001)	15 (<.001)
Red	83	20 (NS)	59 (<.001)
Solitary color	1.4	100 (NS)	97 (NS)
Multiple (5-6) colors	11	65 (.001)	94 (NS)
Pigmented area, %			
0-25	41	94 (<.001)	97 (<.001)
26-50	25	99 (<.001)	96 (<.001)
51-75	23	80 (NS)	80 (NS)
76-100	7.0	38 (<.001)	27 (<.001)
Milialike cysts	10	96 (NS)	92 (NS)
Asymmetry of pattern	100	0 (NS)	13 (.003)
Large gray-blue ovoid nests	55	97 (<.001)	99 (<.001)
Multiple gray-blue globules	27	97 (<.001)	97 (<.001)
Targetlike areas	7.0	99 (NS)	99 (NS)
Color of globules			
Brown	51	13 (<.001)	44 (NS)
Gray	21	87 (NS)	79 (NS)
Blue	49	79 (<.001)	83 (<.001)
Black	4.2	72 (<.001)	99 (NS)
Maple leaflike areas	17	100 (<.001)	100 (<.001)
Spoke wheel areas	10	100 (.007)	100 (.007)
Pigment network	2.8	41 (<.001)	45 (<.001)
Depigmentation	93	13 (NS)	48 (<.001)
Irregular depigmentation	69	20 (NS)	63 (<.001)
Scarlike depigmentation	5.6	59 (<.001)	93 (NS)
Telangiectasia	73	35 (NS)	65 (<.001)
Central	68	54 (.01)	72 (<.001)
Peripheral	58	63 (.01)	76 (<.001)
Arborizing (treelike) telangiectasia	52	77 (<.001)	92 (<.001)
Pinpoint	30	49 (.01)	75 (NS)
Hairpin	8.5	89 (NS)	94 (NS)
Large diameter	21	87 (.02)	94 (.007)
Kinking	66	65 (<.001)	85 (<.001)
Red-blue lacunes	4.2	100 (NS)	100 (NS)
Blue-white veil	15	49 (<.001)	94 (NS)
Pseudopods	1.4	87 (.009)	97 (NS)
Radial streaming	2.8	76 (<.001)	94 (NS)
Multiple brown dots	4.2	77 (<.001)	99 (NS)
Multiple blue-gray dots	24	61 (.047)	79 (NS)
Broadened pigment network	0	65 (<.001)	80 (<.001)
Peripheral black dots or globules	1.4	92 (NS)	100 (NS)
Graduated edge	46	83 (<.001)	59 (NS)

*Lesions in the training set (Table 1) were scored for 45 surface microscopy features. Features in boldface type were subsequently used to create the diagnostic model seen in Table 3. PSLs indicates pigmented skin lesions; NS, not significant.

†Statistical significance of each feature for a pigmented BCC vs a non-BCC was determined using the χ^2 test of independence; with $P<.05$ defining statistical significance (see "Subjects and Methods" section). The lowest P value defined is <.001.

‡Sensitivity of the feature for diagnosis of pigmented BCCs; equal to the number of scored positive BCCs for that feature divided by the total number of BCCs (expressed as a percentage).

§Specificity of the feature for diagnosis of pigmented BCC using the invasive melanoma set; equal to the number of melanomas lacking that feature divided by the total number of melanomas (expressed as a percentage).

‖Specificity of the feature for diagnosis of pigmented BCC using the benign PSL set; equal to the number of benign PSLs lacking that feature divided by the total number of PSLs (expressed as a percentage).

ovoid or elongated areas, larger than globules, and not intimately connected to a pigmented tumor body (Figure 1 and **Figure 2**).[14] Arborizing telangiectasia (telangiectasia with ramification) are telangiectasia with distinct treelike branching (Figure 1, **Figure 3**, and **Figure 4**). They should be differentiated from hairpin loop telangiectasia. Multiple gray-blue globules (Figure 3 and Figure 4) should be differentiated from multiple gray-blue dots (melanophages). Maple leaflike areas are brown to gray-blue discrete bulbous extensions forming a leaflike pattern. They should be distinguished from pseudopods because maple leaf areas are discrete pigment nests (islands) never arising from a pigment network and usually not arising from an adjacent confluent pigmented area (**Figure 5**).[14,17] Ulceration, the absence of the epidermis often associated with congealed blood, when seen, should not be due to a well-described recent history of trauma (Figure 3).

The sensitivity and specificity of the above diagnostic model was determined on an independent test set of 71 pigmented BCCs, 71 invasive melanomas, and 71 atypical benign PSLs. The results gave a sensitivity of 97% for the diagnosis of pigmented BCC and a specificity of 93% for the invasive melanoma set and 92% for the benign PSL set. Figures 1 through 5 show various presentations of pigmented BCCs.

COMMENT

To our knowledge, only one study has statistically analyzed the surface microscopy features of pigmented BCCs.[15] In that study 25 BCCs were compared with 25 melanomas. Because the differential diagnosis of pigmented BCCs includes benign PSLs, we specifically analyzed the features of pigmented BCCs in comparison with invasive melanomas and benign PSLs. Our results supported this experimental design since many features were significantly different from BCCs in either invasive melanomas or benign PSLs, but far fewer were significant in both groups. We only used the latter features to create our diagnostic model.

A feature of the surface microscopy of a pigmented BCC is pigmentation confined to well-circumscribed morphologic areas. These highly spe-

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Table 3. Method of Diagnosis of Pigmented Basal Cell Carcinomas (BCCs)*

Negative feature (cannot be found)
Pigment network
Positive features (at least 1 feature found)
Ulceration
Large blue-gray ovoid nests
Multiple blue-gray globules
Maple leaflike areas
Spoke wheel areas
Aborizing (treelike) telangiectasia

**On a training set of 71 pigmented BCCs, 71 invasive melanomas, and 71 pigmented skin lesions, the method gave a sensitivity of 89% for the diagnosis of pigmented BCCs and a specificity of 85% for invasive melanomas and 93% for benign pigmented skin lesions. On an equal sample size independent test set, the method gave a sensitivity of 97% (95% confidence interval [CI], 90-100) for the diagnosis of pigmented BCC and a specificity of 93% (95% CI, 83-97) for invasive melanomas and 92% (95% CI, 83-97) for benign pigmented skin lesions. Combining both the training and test sets gave a sensitivity of 93% (95% CI, 87-97) and a specificity of 89% (95% CI, 82-93) for invasive melanomas and 92% (95% CI, 87-96) for benign pigmented skin lesions.*

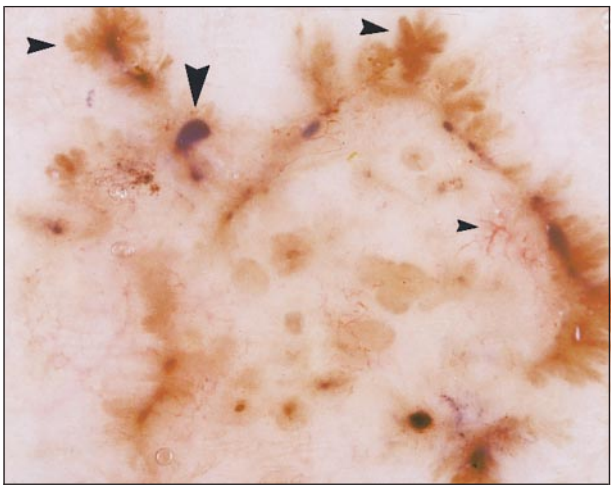

Figure 1. *This pigmented basal cell carcinoma has an absent pigment network (negative feature) and more than 1 of the following positive features described in the diagnostic model (Table 3)—large gray-blue ovoid nests (large arrowhead), spoke wheellike areas (medium-sized arrowheads) and arborizing (treelike) telangiectasia (small arrowhead). The spoke wheellike areas are differentiated from maple leaflike areas because, in the former, radial projections meet at a central axis.*

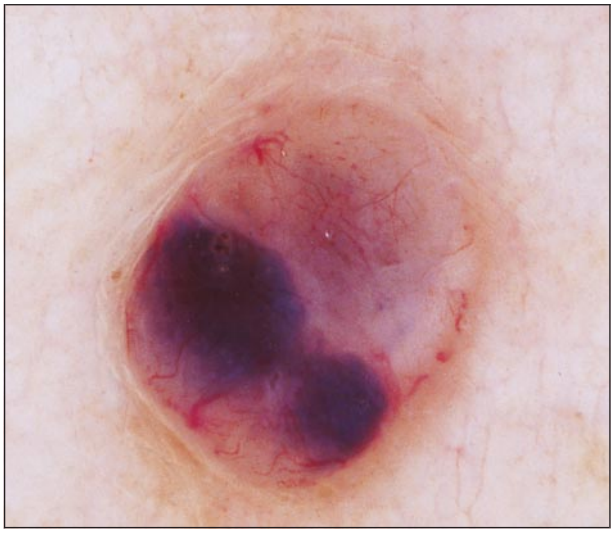

Figure 2. *The most common highly specific feature of pigmented basal cell carcinomas are large gray-blue ovoid nests.*

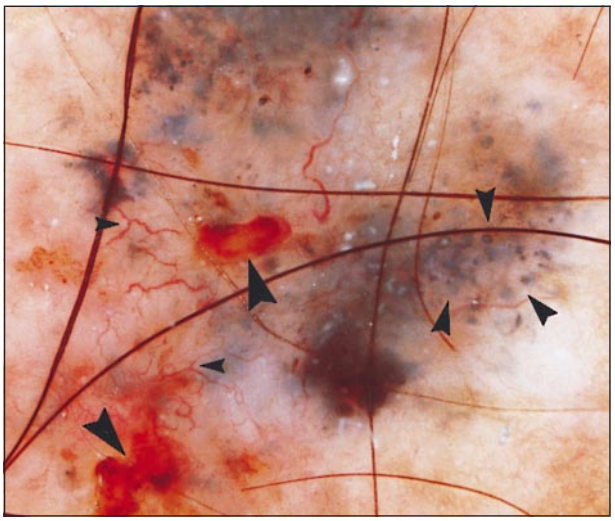

Figure 3. *This basal cell carcinoma has an absent pigment network and 3 positive features—ulceration (large arrowheads), multiple gray-blue globules (such as delineated by medium-sized arrowheads), and arborizing (treelike) telangiectasia (small arrowheads).*

cific areas are, in decreasing frequency, large gray-blue ovoid nests, multiple gray-blue globules, maple leaflike areas, and spoke wheel areas. These areas are often found on a background of hypomelanotic surface. While we have not analyzed the histopathological correlates of these structures, it is highly likely that these patterns are due to pigmented tumor islands, since most nontumor melanin in pigmented BCCs is seen in dermal melanophages[1] that have the characteristic surface microscopy pattern of multiple blue-gray dots.[14]

Pigmented BCCs often have large areas of hypomelanotic surface. In our series 66% of lesions had less than 50% of the area pigmented and only 7% of lesions had greater than 75% of their area pigmented. All colors can be found in pigmented BCCs, including black and dark brown. While these colors are due to melanin in the epidermis,[14] it is known that hyperplastic melanocytes can be found in the overlying epidermis of pigmented BCCs.[1]

As previously reported[15] telangiectasia with arborization (ramification), large diameter, or kinking were all significantly increased in BCCs. Arborization (treelike pattern) of telangiectasia gave the most robust diagnostic model, and was found in 52% of the pigmented BCCs. While in our series, none from 12 dermal nevi had arborizing telangiectasia (data not shown), occasionally irritated dermal nevi may have arborizing vessels. The negative diagnostic feature of a pigment network was not surprising, since this is the most diagnostic surface microscopy feature of epidermally derived melanocytic lesions. Finally, the tendency of BCCs to ulcerate early was confirmed in our study, with 27% of BCCs showing ulceration.

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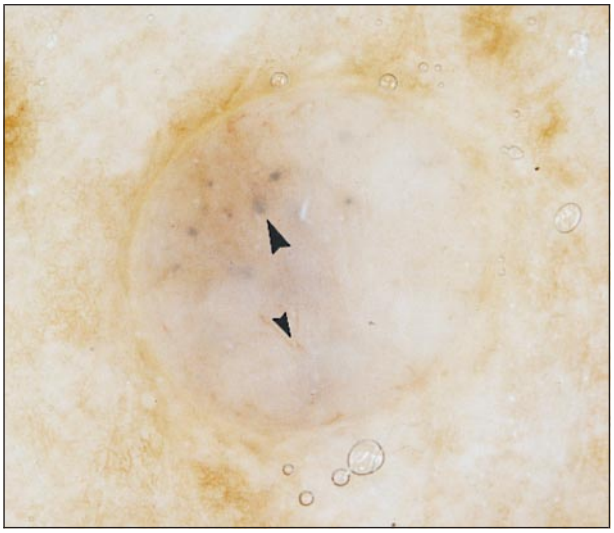

Figure 4. *A common presentation of pigmented basal cell carcinomas is large areas of amelanotic tumor with small areas of pigmentation. In our series 41% of pigmented basal cell carcinomas have less than 25% of their surface pigmented. Here the diagnosis is made by the absent pigment network and the presence of 2 positive features—multiple gray-blue globules (large arrowhead) and arborizing (treelike) telangiectasia (small arrowhead).*

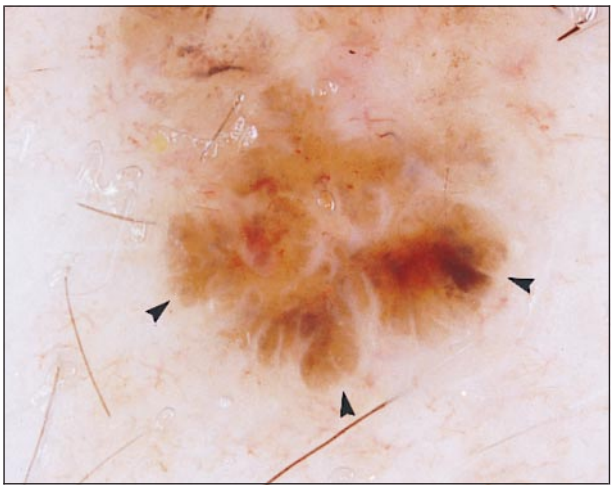

Figure 5. *This pigmented basal cell carcinoma has extensive areas of maple leaflike areas at the edge of the lesion (arrowheads).*

Interobserver agreement is an important issue in surface microscopy. Interobserver errors are less problematic when features are scored as present or absent (rather than grading) and when features are well defined.[18,19] While we did not formally test the interobserver error of our method, the model provides stringent morphologic definitions for each feature and uses only present or absent scoring criteria. Furthermore, the final diagnosis for each lesion was agreed on by 2 observers (S.W.M. and K.W.).

In conclusion, from a large series of pigmented BCCs, we have reported a simple surface microscopy method that allows their diagnosis from invasive melanomas and benign PSLs. On an independent test set the model gave a sensitivity of 97% for the diagnosis of pigmented BCCs and a specificity of 93% for the invasive melanoma set and 92% for the benign PSL set. Combining test and training set results gave a sensitivity of 93% for the diagnosis of pigmented BCCs and specificity of 89% for invasive melanomas and 92% for benign PSLs.

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