

Dermoscopic Evaluation of Amelanotic and Hypomelanotic Melanoma

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Objective: To determine the predictive dermoscopic features of amelanotic and hypomelanotic melanoma.

Design: A total of 105 melanomas (median Breslow thickness, 0.76 mm), 170 benign melanocytic lesions, and 222 nonmelanocytic lesions lacking significant pigment (amelanotic, partially pigmented, and light colored) were imaged using glass-plate dermoscopy devices and scored for 99 dermoscopic features. Diagnostic models were derived from and tested on independent randomly selected lesions.

Setting: Predominantly hospital-based clinics from 5 continents.

Main Outcome Measures: Sensitivity, specificity, and odds ratios for individual features and models for the diagnosis of melanoma and malignancy.

Results: The most significant negative predictors of melanoma were having multiple (>3) milialike cysts (odds ratio, 0.09; 95% confidence interval, 0.01-0.64), comma vessels with a regular distribution (0.10; 0.01-0.70),

comma vessels as the predominant vessel type (0.16; 0.05-0.52), symmetrical pigmentation pattern (0.18; 0.09-0.39), irregular blue-gray globules (0.20; 0.05-0.87), and multiple blue-gray globules (0.28; 0.10-0.81). The most significant positive predictors were having a blue-white veil (odds ratio, 13; 95% confidence interval, 3.9-40.0), scarlike depigmentation (4.4; 2.4-8.0), multiple blue-gray dots (3.5; 1.9-6.4), irregularly shaped depigmentation (3.3; 2.0-5.3), irregular brown dots/globules (3.2; 1.8-5.6), 5 to 6 colors (3.2; 1.6-6.3), and predominant central vessels (3.1; 1.6-6.0). A simple model distinguishing melanomas from all nonmelanomas had a sensitivity of 70% and a specificity of 56% in the test set. A model distinguishing all malignant lesions from benign lesions had a sensitivity of 96% and a specificity of 37%.

Conclusion: Although the diagnostic accuracy of dermoscopy for melanoma lacking significant pigment is inferior to that of more pigmented lesions, features distinguishing the former from benign lesions can be visualized on dermoscopic evaluation.

Arch Dermatol. 2008;144(9):1120-1127

PURE AMELANOTIC PRIMARY melanoma of the skin is rare, with the largest series suggesting an incidence of less than 2% of melanomas (although this figure is inflated because amelanotic metastases were included in the study).¹ Because evidence of melanin is usually found

ization of pigment not seen with the naked eye, a dermoscopic definition of lesions lacking significant pigment would be most useful and is presented in our study.

*For editorial comment
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in amelanotic melanoma histopathologically,² the difficulty in diagnosing these lesions lies with the clinician and not the pathologist, and a precise clinical definition of melanoma lacking significant pigment would be most useful. Furthermore, since dermoscopic evaluation allows the visual-

Although dermoscopic evaluation has been shown to improve the accuracy of pigmented melanoma diagnosis compared with naked eye examination,³ less literature is found regarding melanomas lacking significant pigment.⁴⁻⁸ Still, dermoscopic evaluation has been shown to be superior to naked eye examination for the diagnosis of amelanotic or hypomelanotic melanoma.⁴ To assess the diagnos-

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Table 1. Lesion Pigmentation Categories^a

| Lesion Pigmentation | Benign | | Nonmelanocytic |
|---------------------|----------------------|-----------------------|----------------------|
| | Melanoma | Melanocytic | |
| Amelanotic | 15 | 36 | 80 |
| Partially pigmented | 51 (16) ^b | 40 (16) ^b | 92 (36) ^b |
| Light colored | 55 (16) ^b | 110 (16) ^b | 86 (36) ^b |
| Total | 105 | 170 | 222 |

^aA total of 497 lesions met morphological and pigmentation criteria (see the "Methods" section for a list of inclusion criteria).

^bNumber in parentheses indicates lesions that had both partially pigmented and light-colored characteristics.

tic significance of dermoscopic features in these lesions, a large series of melanomas as well as nonmelanocytic and benign melanocytic lesions lacking significant pigment was examined.

METHODS

INCLUSION AND EXCLUSION CRITERIA

We selected 3 morphological dermoscopic variants of lesions lacking significant pigment. The first type, amelanotic lesions, have no melanin pigmentation (ie, tan, dark brown, blue, gray, or black) upon dermoscopic inspection. Tan pigmentation is defined as light brown pigmentation that is darker than the surrounding skin. In addition, 2 subgroups of hypomelanotic lesions were defined. On dermoscopic evaluation, partially pigmented lesions have a melanin pigmentation area of less than 25% of the total surface area. Light-colored (slightly pigmented) lesions have only tan, light blue, or light gray pigmentation that may occupy more than 25% of the total surface area; no dark brown, deep blue, or black pigmentation is found.

Lesions were excluded because of poor image quality or because they did not fit within any of the defined pigmentation categories. All lesion images used in the study were taken retrospectively from photographic libraries at various institutions, and patients gave verbal or written consent for their use.

IMAGE ACQUISITION

Digital dermoscopic images taken with glass plate/liquid photographic devices were obtained from members of the International Dermoscopy Society from 5 continents. A request was made for images of all melanomas satisfying the inclusion criteria, and a random selection of melanocytic and nonmelanocytic lesions also lacking significant pigment was made (nonmelanoma to melanoma ratio, 3:1). For all lesions, the diagnosis was histopathologically confirmed, except for some nevi that showed no changes following consecutive digital monitoring. To assess adequate image quality and assign the pigmentation category, lesions were examined by one of us (S.W.M.) blinded to the diagnosis or referring center. All images were adjusted to $\times 10$ magnification to approximate handheld dermoscopy devices. A total of 497 lesions, including 105 melanomas (median Breslow thickness, 0.76 mm), were included in the study. **Table 1** shows the frequency of lesions within each pigmentation category and **Table 2**, the frequency of lesion diagnoses.

DERMOSCOPIC FEATURES

The features included in the study were determined by consensus of the members of the International Dermoscopy Soci-

Table 2. Diagnosis Frequency

| Diagnosis | No. of Lesions |
|------------------------------|----------------|
| Melanoma | |
| Total^a | 105 |
| Superficial spreading | 80 |
| Nodular | 7 |
| Lentigo maligna | 3 |
| In situ arising within nevus | 13 |
| Acral invasive | 1 |
| Acral in situ | 1 |
| Benign melanocytic | |
| Total | 170 |
| Ephelis ^b | 1 |
| Lentigo ^b | 2 |
| Nevus | |
| Uncertain classification | 14 |
| Junctional/compound | 27 |
| Dermal | 47 |
| Spitz | 11 |
| Clark/dysplastic | 25 |
| Monitored unchanged | 43 |
| Nonmelanocytic | |
| Total | 222 |
| Basal cell carcinoma | 126 |
| Dermatofibroma | 17 |
| Hemangioma | 8 |
| Seborrheic keratosis | 22 |
| Lichen planuslike keratosis | 2 |
| Actinic keratosis | 8 |
| Bowen disease | 7 |
| Squamous cell carcinoma | 4 |
| Keratoacanthoma | 1 |
| Other | 27 |

^aThe median Breslow thickness for all melanomas was 0.76 mm (range, 0-8 mm) and for invasive melanomas was 1.00 mm (range, 0.19-8 mm).

^bEphelis and lentigo are not melanocytic lesions, but they are included in this category because they mimic melanocytic lesions on dermoscopic examination.

ety. These features were either based on the existing literature or on clinicians' anecdotal experience. Before scoring, clinicians were given a morphological tutorial to define all vascular and newly described features. This tutorial is available at the International Dermoscopy Society Web site: <http://dermoscopy-ids.org/studies> (click on "Amelanotic melanoma study"). Twelve clinicians (J.K., M.A.P., A.M., R.B., J.M., S.P., G.A., I.Z., H.S.R., M.O., H.C., and V.A.-S.) blinded to the lesion diagnoses and experienced in dermoscopic evaluation scored 99 individual morphological features in approximately equal sample sizes. All clinicians scored 55 preselected lesions with a variety of vascular features to assess interobserver concordance for vascular structures. One feature, light brown structureless areas, was chosen after scoring was completed and was subsequently scored by one of us (S.W.M.). The eTable (<http://www.archdermatol.com>) includes the 99 criteria with 21 items identified in the disease-specific groups for melanocytic, seborrheic keratosis, BCC (basal cell carcinoma), and vascular criteria. Precise morphological definitions of these features can be found elsewhere.⁹⁻¹⁵

First-step dermoscopic analysis to define a melanocytic lesion¹⁶ occurred if 1 or more of pigment network/pseudonetwork, aggregated globules (not multiple blue-gray globules), streaks (pseudopods/radial streaming), homogeneous blue pigmentation, or a parallel pattern (on volar sites) were present. If these were absent and the lesion lacked features of seborrheic keratosis (>3 milialike cysts, comedolike openings [ir-

Table 3. Second-Step Methods for the Diagnosis of Melanoma

| Method | Sensitivity, % | Specificity, % | | |
|---------------------------------|----------------|-----------------|---------------------|------------------------|
| | | All Nonmelanoma | Melanocytic Lesions | Nonmelanocytic Lesions |
| Menzies et al ¹⁷ | 54 | 76 | 71 | 79 |
| 7-Point checklist ¹⁸ | 41 | 83 | 78 | 87 |
| 3-Point checklist ¹⁹ | 50 | 71 | 71 | 71 |

regular crypts], light brown fingerprintlike areas, or fissures/ridges), BCC (arborizing vessels, leaflike areas, large blue-gray ovoid nests, multiple blue-gray globules, spoke wheel areas, or ulceration), vascular lesions (red-blue lacunes or red-blue to red-black homogeneous areas), or dermatofibroma (central white patch), then the lesion was also classified by default as melanocytic. Second-step analysis used the feature-based Menzies method, 7-point checklist, and 3-point checklist, as described elsewhere.¹⁷⁻¹⁹ The ABCD method of Stolz et al was not included because it is not, in general, a feature-based system.¹¹

STATISTICAL ANALYSIS

SPSS statistical software, version 14 (SPSS Inc, Chicago, Illinois), was used to analyze the data. Two-tailed tests with a significance level of 5% were used throughout. To develop and test the performance of potential predictive scores based on morphological features, a random sample of 80% of lesions was assigned to a training set and the remaining 20% to a test set. Initially, all features were entered as candidate variables in a multiple logistic regression analysis with backward stepwise variable selection to identify the independent predictors of melanoma in the training set. The resulting best-fitting model involved a linear predictor, which included 18 features, far too many for practical implementation in a clinical setting. One of us (S.W.M.) had previously developed clinically useful scores for diagnosing melanoma and pigmented BCC by considering features with high specificity and low sensitivity.^{17,20} The possible positive features for diagnosing melanoma lacking significant pigment in the training set were therefore restricted to those with high specificity (>80%) for which distribution differed significantly between the melanoma group and each of the nonmelanocytic and benign melanocytic groups. In addition, low sensitivity features (≤1%) for melanoma were included for model development. Using all features as candidate variables, multiple logistic regression analysis with backward stepwise variable selection was also used to identify the independent predictors of malignant lesions from benign lesions in the training set.

The area under the receiver operating characteristic curve and its standard error were used to quantify the global discriminatory power of a potential diagnostic score and to assist in determining a suitable cutoff point on the basis of performance in the training set. The sensitivity and specificity of the resulting classifications were then assessed in the independent test set.

RESULTS

INTEROBSERVER AGREEMENT

Interobserver concordance about the 9 main vascular features, expressed as the median percentage of clinicians who agreed with the presence or absence of the feature per lesion, was assessed for 55 preselected lesions that exhibited a variety of vascular structures. Agreement was

high for arborizing vessels (median, 100%; interquartile range, 91%-100%), comma vessels (82%; 73%-91%), dotted vessels (82%; 73%-100%), hairpin vessels (91%; 82%-100%), vessels with white or yellow pigmented halo (91%; 82%-100%), milky red/pink areas (82%; 64%-91%), milky red globules (91%; 73%-100%), and nontumor vessels (91%; 82%-100%). In contrast, linear irregular vessels had a median agreement per lesion of 73% (interquartile range, 64%-91%), and only 42% (95% confidence interval, 30%-55%) of lesions showed more than 80% agreement for the presence or absence of linear irregular vessels.

TWO-STEP DERMOSCOPIC ANALYSIS

The standard first-step procedure,¹⁶ which describes the dermoscopic features distinguishing melanocytic from nonmelanocytic lesions, was applied to the melanoma set. However, only 75 of 105 melanomas lacking significant pigment (71.4%) were correctly classified as melanocytic using this method. Furthermore, the 3 second-step methods for distinguishing benign melanocytic lesions from melanoma showed poor sensitivity (range, 41%-54%) (**Table 3**).

DERMOSCOPIC FEATURES OF MELANOMAS VS NONMELANOMAS

Based on our aforementioned analysis, current dermoscopic algorithms developed using more heavily pigmented lesions were not reliable for correctly classifying a melanoma lacking significant pigment. Therefore, an analysis of the sensitivity and specificity of features for the diagnosis of melanoma compared with all non-melanomas was performed (**Table 4**).

The most significant negative predictors of melanoma, in order of lowest odds ratio for melanoma, were having multiple (>3) milialike cysts (**Figure 1**), comma vessels as the predominant vessel type (Figure 1), symmetrical pigmentation pattern, blue-gray globules that were irregular in size and/or distribution, multiple blue-gray globules, arborizing small diameter vessels, and symmetrical shape. Of these features, only symmetrical pigmentation pattern and symmetrical lesion shape were significant negative predictors for melanoma compared with the melanocytic and nonmelanocytic nonmelanoma lesions. The presence of multiple milialike cysts, regularly distributed comma vessels, and comma vessels as the most predominant vessel type did not differ significantly in frequency between melanoma and nonmelanocytic lesions, whereas the presence of blue-gray globules (present or irregular), small diameter arborizing vessels, and arborizing vessels

Table 4. Univariate Analysis of Melanomas vs All Nonmelanomas^a

| Feature | Sensitivity, % ^b | Specificity, % ^c | Odds Ratio (95% Confidence Interval) | P Value ^d |
|--|-----------------------------|-----------------------------|---|----------------------|
| Negative | | | | |
| Multiple (>3) milialike cysts | 1.0 | 90.1 | 0.087 (0.012-0.64) | .003 |
| Comma vessels, regular distribution | 1.0 | 90.8 | 0.10 (0.01-0.70) | .004 |
| Comma vessels as the predominant vessel type | 2.9 | 84.4 | 0.16 (0.05-0.52) | .001 |
| Symmetrical pigmentation pattern | 7.6 | 68.9 | 0.18 (0.09-0.39) | <.001 |
| Blue-gray globules of irregular size and/or distribution | 1.9 | 91.3 | 0.20 (0.05-0.87) | .02 |
| Multiple blue-gray globules | 3.8 | 87.8 | 0.28 (0.10-0.81) | .01 |
| Arborizing small diameter vessels | 6.7 | 81.4 | 0.31 (0.14-0.70) | .003 |
| Symmetrical shape | 23.8 | 52.0 | 0.34 (0.21-0.55) | <.001 |
| Arborizing vessels as the predominant vessel type | 8.6 | 82.4 | 0.44 (0.21-0.91) | .02 |
| Positive | | | | |
| Blue-white veil | 11.4 | 99.0 | 13.0 (3.9-40.0) | <.001 ^e |
| Scarlike depigmentation | 22.9 | 93.6 | 4.4 (2.4-8.0) | <.001 |
| Multiple blue-gray dots (peppering) | 21.9 | 92.6 | 3.5 (1.9-6.4) | <.001 |
| Irregularly shaped depigmentation | 35.2 | 85.7 | 3.3 (2.0-5.3) | <.001 |
| Irregular brown dots/globules | 23.8 | 91.1 | 3.2 (1.8-5.6) | <.001 |
| 5-6 Colors | 15.2 | 94.6 | 3.2 (1.6-6.3) | .001 |
| Predominant central vessels | 16.2 | 94.1 | 3.1 (1.6-6.0) | .001 |
| Red-blue color | 27.6 | 88.3 | 2.9 (1.7-4.9) | <.001 |
| Peripheral light brown structureless areas >10% | 19.0 | 92.6 | 2.9 (1.6-5.5) | <.001 |
| Blue color | 19.0 | 92.3 | 2.8 (1.5-5.2) | .001 |
| Asymmetrical pigmentation pattern | 75.2 | 46.2 | 2.6 (1.6-4.2) | <.001 |
| Hairpin vessels | 21.0 | 90.6 | 2.5 (1.4-4.5) | .001 |
| Milky red pink areas | 50.5 | 71.2 | 2.5 (1.6-3.9) | <.001 |
| >1 Shade of pink | 32.4 | 82.9 | 2.3 (1.4-3.8) | .001 |
| Asymmetrical shape | 57.1 | 63.3 | 2.3 (1.5-3.5) | <.001 |
| Dotted and linear irregular vessels | 29.5 | 84.7 | 2.3 (1.4-3.8) | .001 |
| Linear irregular vessels as predominant vessel type | 34.3 | 79.8 | 2.1 (1.3-3.3) | .002 |
| Multifocal depigmentation | 27.6 | 84.4 | 2.1 (1.2-3.4) | .004 |
| Atypical network | 21.0 | 88.5 | 2.0 (1.2-3.6) | .01 |
| Vessels of irregular shape/size | 62.9 | 53.8 | 2.0 (1.3-3.1) | .002 |
| Milky red globules | 21.0 | 88.3 | 2.0 (1.1-3.5) | .02 |
| Dotted vessels as predominant vessel type | 33.3 | 79.8 | 2.0 (1.2-3.2) | .004 |
| Dots/globules of irregular size or distribution | 22.9 | 86.5 | 1.9 (1.1-3.3) | .02 |
| >1 Shade of tan/brown | 42.9 | 71.9 | 1.9 (1.2-3.0) | .004 |
| Streaks (pseudopods/radial streaming) | 4.8 | 98.7 | 3.9 (1.1-14.0) | .04 ^d |
| Central white striated patch | 4.8 | 98.7 | 3.9 (1.1-14.0) | .04 ^d |
| Gray color | 33.3 | 77.0 | 1.7 (1.1-2.7) | .03 |
| Linear irregular vessels | 40.0 | 70.9 | 1.6 (1.0-2.5) | .03 |

^aThose features in bold type are significant with the same odds ratio trend in both melanocytic and nonmelanocytic lesions compared with melanoma.

^bThe percentage of melanomas with that feature.

^cThe percentage of nonmelanomas without that feature.

^dPearson χ^2 test ($\leq .05$ indicates significance) unless otherwise indicated.

^eFisher exact test.

as the predominant vessel type did not differ significantly in frequency between melanoma and benign melanocytic lesions (data not shown).

The most positive predictors of melanoma were, in order, having a blue-white veil, scarlike depigmentation, multiple blue-gray dots, irregularly shaped depigmentation, brown dots or globules irregular in size or distribution, 5 to 6 colors, predominant central vessels, red-blue color, and peripheral light brown structureless areas of more than 10% of the area of the lesion. All these features were significant positive predictors of melanoma compared with benign melanocytic lesions and nonmelanocytic lesions.

Of vascular or vascular-related features, the most predictive for melanoma were, in order, having predominantly central vessels, hairpin vessels, milky red-pink areas, more than 1 shade of pink, a combination of dot-

ted and linear irregular vessels, and linear irregular vessels as the predominant vessel type. With the exception of hairpin vessels, for which the distribution did not differ significantly between melanoma and nonmelanocytic lesions (data not shown), all these vascular-related structures were significant positive predictors of melanoma compared with benign melanocytic lesions and nonmelanocytic lesions.

The distribution of the number of vessel types per lesion (0, 1, or ≥ 2) differed significantly between melanoma and nonmelanoma lesions (**Table 5**). A higher percentage of lesions with 2 or more vessels (ie, polymorphous vessels) was seen among melanomas than nonmelanomas. The odds ratio for melanoma was 2.1 (95% confidence interval, 1.02-4.2) for lesions with ≥ 2 vessels compared with those with no vessels; 11% of melanomas had no visible vessels.

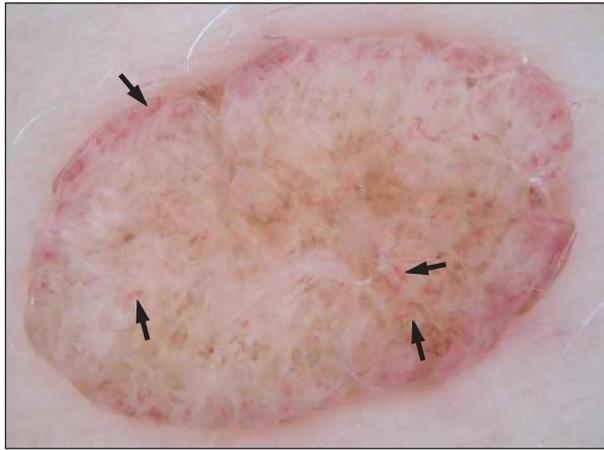


Figure 1. This lesion has 2 negative predictors of melanoma: regularly distributed comma vessels (arrows) (odds ratio, 0.10), which are often, as in this case, found predominantly at the periphery of the lesion, and comma vessels as the predominant vessel type (odds ratio, 0.16). The diagnosis was dermal nevus.

Table 5. Significance of Polymorphous Vessels

| No. of Vessels ^a | No. (%) of Lesions | |
|-----------------------------|--------------------|-------------|
| | Melanoma | Nonmelanoma |
| 0 | 11 (11) | 65 (17) |
| 1 | 33 (31) | 153 (39) |
| ≥2 ^b | 61 (58) | 174 (44) |

^aVessel types included arborizing, linear irregular, comma, hairpin, dotted, glomerular, and milky red globules.

^bThere was a significant increase in the number of polymorphous vessels (≥2) in melanomas vs nonmelanomas (χ^2 test; $P = .04$).

DERMOSCOPIC FEATURES OF THIN VS THICK MELANOMA

Comparison of thin (<0.75 mm) vs thick (>1 mm) melanomas showed that thin melanomas had an increased frequency of atypical network, network/pseudonetwork, more than 1 shade of tan or brown, graduated edge throughout the entire lesion, and dotted/pinpoint vessels as the predominant type. In contrast, thick melanomas had a greater frequency of hairpin vessels, peripheral vessels, large blue-gray ovoid nests, central vessels, ulceration, large diameter vessels, and pink color (**Table 6**).

MODEL DISTINGUISHING MELANOMA FROM NONMELANOMA

The multiple logistic regression analysis, which used as candidate variables those with high specificity (≥80%) or very low sensitivity (≤1%) for melanoma and whose distribution for the high specificity variables differed significantly between the melanoma group and each of the nonmelanocytic and benign melanocytic groups, identified 8 independent predictors of melanoma in the training set. A simple model suitable for distinguishing melanoma from all nonmelanoma (including malignant BCC, Bowen disease, and squamous cell carcinoma) was developed using these 8 features (**Table 7**). Here, a diag-

Table 6. Dermoscopic Features Distinguishing Thick vs Thin Melanomas

| Dermoscopic Feature | Lesion Thickness, ^a mm | | P Value ^b |
|--|-----------------------------------|-----------|----------------------|
| | <0.75 (n=44) | >1 (n=32) | |
| Hairpin vessels | 3 (6.8) | 13 (40.6) | <.001 |
| Atypical network | 17 (38.6) | 2 (6.3) | .001 |
| Pigment network/pseudonetwork | 20 (45.5) | 4 (12.5) | .002 |
| Peripheral vessels (at or near edge) | 13 (29.5) | 20 (62.5) | .004 |
| Large blue-gray ovoid nests | 0 | 5 (15.6) | .01 ^c |
| Central vessels | 11 (25) | 17 (53.1) | .01 |
| Ulceration | 2 (4.5) | 8 (25.0) | .01 ^c |
| >1 Shade of tan/brown | 25 (56.8) | 10 (31.3) | .03 |
| Large diameter vessels | 6 (13.6) | 11 (34.4) | .03 |
| Graduated edge (entire lesion) | 30 (68.2) | 14 (43.8) | .03 |
| Pink color | 24 (54.5) | 25 (78.1) | .03 |
| Dotted/pinpoint as predominant vessel type | 18 (40.9) | 6 (18.8) | .04 |

^aData are given as the number (percentage) of lesions.

^bPearson χ^2 test (≤.05 indicates significance) unless otherwise indicated.

^cFisher exact test.

Table 7. Simple Dermoscopic Model for the Diagnosis of Melanoma Lacking Significant Pigment^a

| |
|--|
| Negative feature (if present, nonmelanoma) |
| >3 Milialike cysts |
| Positive features (if any 1 present, then melanoma) |
| Irregularly sized or distributed brown dots/globules |
| Multiple blue/gray dots |
| Irregularly shaped depigmentation |
| Blue-white veil |
| >1 Shade of pink |
| Predominant central vessels |
| Dotted and linear irregular vessels |

^aIn the training set, sensitivity was 75% and specificity was 66% for the diagnosis of melanoma (area under the receiver operating characteristic curve, 0.74; SE, 0.03). In the independent test set, sensitivity was 70% and specificity was 56% (area under the receiver operating characteristic curve, 0.69; SE, 0.07).

nosis of melanoma is made if the lesion does not have the negative feature of multiple (>3) milialike cysts and has 1 or more of 7 positive features. In the training set, the sensitivity was 75% and specificity 66% for the diagnosis of melanoma. In the independent test set, the sensitivity was 70% and specificity 56%. **Figure 2** shows an example of a lesion evaluated using the model.

MODEL DISTINGUISHING ALL MALIGNANT FROM BENIGN LESIONS

Because the first model lacked high sensitivity for the diagnosis of melanoma, another model was developed to distinguish all malignant lesions (melanoma, BCC, Bowen disease, squamous cell carcinoma, and keratoacanthoma) from nonmalignant lesions. A clinically practical model suitable for distinguishing malignant from benign lesions was developed using the 12 independent predictor features (**Table 8**). For a lesion to be diag-

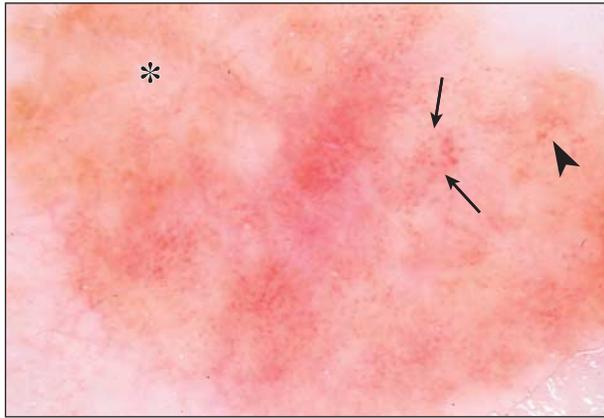


Figure 2. This light-colored lesion illustrates the positive dermoscopic features in the model distinguishing melanoma from nonmelanoma (Table 7): having predominant central vessels, more than 1 shade of pink, dotted (arrows) and linear (arrowhead) irregular vessels, and irregularly shaped depigmentation (asterisk). The diagnosis was in situ melanoma arising in a dysplastic nevus.

nosed as malignant using this model, the total number of positive features must equal or exceed the total number of negative features. In the independent test set, the sensitivity for the diagnosis of malignancy was 96% (95% for melanoma) and the specificity, 37%. To improve specificity, the cutoff point for the score can be increased. However, a significant reduction in sensitivity will result (Table 8). **Figure 3** shows an example of a lesion evaluated using the model.

COMMENT

Although dermoscopic evaluation has been shown to improve the diagnosis of melanoma lacking significant pigment, it is clear from these results that diagnostic accuracy is significantly diminished compared with significantly pigmented lesions. Whereas many dermoscopic methods achieve a sensitivity exceeding 90% and specificity exceeding 70% with predominantly pigmented lesions,¹⁶ the model described in our study of lesions lacking significant pigment had a sensitivity of 75% and specificity of 66% for melanoma. Although the sensitivity for melanoma could be increased to more than 90% when classifying all malignant vs nonmalignant lesions, this was at the expense of a very low specificity (37%). Furthermore, the first-step procedure developed primarily for pigmented lesions to distinguish melanocytic lesions from pigmented BCC, hemangioma, seborrheic keratoses, and dermatofibroma and standard second-step procedures to distinguish melanomas from benign melanocytic lesions were not effective discriminators for lesions lacking significant pigment.

Loss of pigmentation in lesions included in this study could be owing to either a true lack of significant melanin in tumor cells or to regression. Because of variation in reporting regression among different clinics, we could not stratify results based on the 2 different histopathological entities: regression vs amelanosis. It is noted that the dermoscopic features of scarlike depigmentation and multiple blue-gray dots (melanophages) were found in 23% and 22% of our melanomas, respectively, indicat-

Table 8. Dermoscopic Model for Distinguishing Malignant From Nonmalignant Lesions Lacking Significant Pigment^a

| | |
|--|--|
| Negative features (score -1 for each feature) | |
| Multiple (>3) miliumlike cysts | |
| Symmetrical pigmentation pattern | |
| Comma vessels in regular distribution | |
| Multiple brown dots | |
| Positive features (score +1 for each feature) | |
| Depigmentation | |
| Small diameter arborizing vessels | |
| Leaflike areas | |
| Ulceration | |
| Irregular size or distributed blue-gray globules | |
| Gray color | |
| Large-diameter vessels | |

^a In this model, the area under the receiver operating characteristic (ROC) curve was 0.85 (SE, 0.02) for the training set and 0.79 (SE, 0.04) in the test set. Two thresholds for malignant neoplasm can be used, depending on the preferred sensitivity and specificity results:

High sensitivity model: A nonnegative total score (≥ 0) is necessary for a diagnosis of malignant neoplasm. In the training set, sensitivity was 97% and specificity was 41% for the diagnosis of malignant neoplasm; sensitivity for the diagnosis of melanoma was 98%. In the independent test set, sensitivity for the diagnosis of malignant neoplasm was 96% and the specificity, 37%; sensitivity for the diagnosis of melanoma was 95%.

Higher specificity model: A positive total score (≥ 1) is necessary for a diagnosis of malignant neoplasm. In the training set, sensitivity was 77% and specificity was 79% for the diagnosis of malignant neoplasm; sensitivity for the diagnosis of melanoma was 69%. In the independent test set, sensitivity for the diagnosis of malignant neoplasm was 79% and the specificity, 65%; sensitivity for the diagnosis of melanoma was 80%.

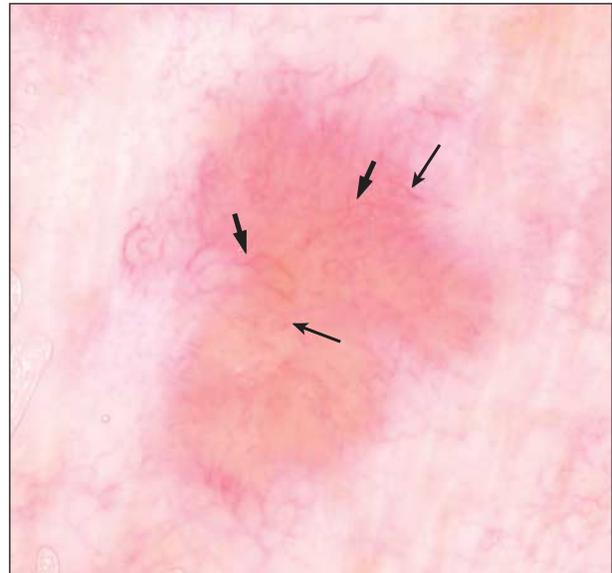


Figure 3. This 6 × 5-mm raised yellow lesion has small-diameter arborizing (thick arrows) and linear irregular vessels (thin arrows). Using the model distinguishing all malignant from all benign lesions (Table 8), a score of +1 indicates the need for excision or biopsy. Diagnosis is melanoma, 0.8 mm, Clark level 4.

ing regression in these lesions. It is probable that certain dermoscopic features are preferentially found in melanomas displaying true amelanosis vs regression.

The importance of vascular structures for the diagnosis of lesions lacking pigment is clear from this study. Two of 8 features described in the model distinguishing melanomas from nonmelanomas and 3 of 11 features in

the model distinguishing malignant from benign lesions were vascular structures. Furthermore, of the 7 most significant variables indicative of melanoma or nonmelanoma in a univariate analysis (all with an odds ratio exceeding 4 for the diagnosis of melanoma or nonmelanoma), 2 were vascular structures (ie, comma vessels regularly distributed and comma vessels as the predominant vessel type). Nevertheless, vascular structures failed to reach the level of significant positive predictors of melanoma compared with other classically described nonvascular structures. In this regard, the only vascular structure exceeding an odds ratio of 3 for melanoma, when distinguishing melanomas from all nonmelanomas, was the feature of predominant central vessels. Most other vascular structures positively predicting melanoma had odds ratios ranging from 2 to 2.5.

Vascular structures previously reported to be significant features of melanoma were confirmed by the results of our larger series. In 2 previous series,^{4,21} linear irregular vessels have been found to be an important vascular predictor of melanoma. However, in our study, they were not significantly different in melanomas vs benign melanocytic lesions. In our series, a more significant finding was having linear irregular vessels as the predominant vessel type. This was significantly different in melanomas compared with benign melanocytic and nonmelanocytic lesions, with a sensitivity of 34% and specificity of 80% for melanoma overall (odds ratio, 2.1). However, as noted by Pizzichetta et al,⁴ the combination of linear irregular and dotted vessels was diagnostically more important and was significantly different among benign melanocytic and nonmelanocytic lesions compared with melanomas, with a 30% sensitivity and 85% specificity overall (odds ratio, 2.3 for melanoma).

Milky red globules and areas^{4,21,22} were also confirmed to be predictors of melanoma in our study. Dotted/pinpoint vessels, indicative of melanocytic tumors rather than melanoma,²¹ were not significantly different among the melanoma vs the benign melanocytic lesion group. The rarity of comma vessels in melanomas seen in our series is consistent with observations made by others; in previous reports, none of 150 predominantly pigmented melanomas²¹ and none of 44 amelanotic/hypomelanotic melanomas had these vessels.⁴ Comma vessels are found in 66% of dermal or congenital nevi, with a very high positive predictive value of 94% for comma vessels in these lesions, as previously reported.²¹ Finally, the absence of multiple gray-blue globules in pigmented melanomas²¹ and amelanotic/hypomelanotic melanomas,⁴ in contrast to their presence in pigmented BCC, was reconfirmed in our study.

Although a large series of nonmelanoma lesions was included in this study, no pyogenic granulomas were found. Recently, the dermoscopic features of a series of these lesions have been reported, and common features include reddish homogeneous areas, white collarette, "white rail" lines that intersect the lesion, and ulceration.²³

This study was morphologically based. It did not include clinical information, such as age, sex, location, ugly duckling sign, and evolution, in formulating the diagnostic methods. However, such information may improve diagnostic accuracy for these lesions in clinical practice.

In addition, our study included selection biases. Lesions were recruited from multiple centers retrospectively and, in many cases, may not have been from consecutive patients at each institution. More important, because the study was not prospective, hypomelanotic lesions that were not photographed, leading to missing data, may suggest a morphological bias in our collection of cases. Furthermore, the skin phototype was not recorded for lesions, which may influence dermoscopic features such as the type and quantity of blood vessels. Finally, it is important to realize that this study consisted of glass plate dermoscopic images at a magnification consistent with $\times 10$ handheld dermoscopes. Although compression of vessels may be reduced by application of ultrasonography gel, there was no doubt that significant compression occurred with many lesions imaged. Indeed, this is the reality with such devices in the clinical setting. Many of the vascular-related features scored in this study would have varied depending on the pressure applied to the skin. In this regard, our study showed that 11% of melanomas had no visible vessels. This is consistent with the previous report of 9% in amelanotic/hypomelanotic melanoma in a study by Pizzichetta et al.⁴ More significant vascular detail may be found using cross-polarized noncontact dermoscopy devices²⁴ or by increasing magnification. Future planned studies will help determine whether such devices will allow description of greater discriminating features of malignancy in lesions lacking significant pigment.

Accepted for Publication: December 12, 2007.

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Additional Information: The eTable is available at <http://www.archdermatol.com>.

Financial Disclosure: None reported.

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Archives Feature

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eTable. Scored Dermoscopy Features

Melanocytic criteria

- Pigment network/pseudonetwork
- Aggregated globules (not multiple blue-gray globules)
- Streaks (pseudopods/radial streaming)
- Homogeneous blue pigmentation
- Parallel pattern (on volar sites)

Seborrheic keratosis criteria

- Multiple (>3) milialike cysts
- 1-3 Milialike cysts
- Comedolike openings (irregular crypts)
- Light brown fingerprintlike areas
- Fissures/ridges

Basal cell carcinoma criteria

- Arborizing vessels
- Arborizing small diameter
- Arborizing large diameter
- Leaflike areas
- Large blue-gray ovoid nests
- Multiple blue-gray globules
- Spoke wheel areas
- Ulceration

Vascular lesion criteria

- Red-blue lacunes
- Red-blue to red-black homogeneous areas
- Vessels of the dermal plexus

Other criteria

- Central white striated patch
- Typical network (regular prominent or discrete)
- Atypical network (broadened and irregular, includes rhomboidal structures on face)
- Negative pigment network
- Regular dots/globules (regular size and distribution)
- Irregular dots/globules (irregular size and/or distribution)
- Regular black dots/globules
- Irregular black dots/globules
- Peripheral black dots/globules
- Central black dots/globules
- Regular brown dots/globules
- Irregular brown dots/globules
- Multiple brown dots
- Regular blue-gray globules
- Irregular blue-gray globules
- Multiple blue-gray dots (peppering)
- Irregular-shaped depigmentation
- Regular depigmentation (symmetrical distribution)
- Single focus depigmentation
- Multifocal depigmentation
- Diffuse depigmentation (throughout the lesion)
- Scarlike depigmentation
- Blue-white veil
- Tan
- >1 Shade of tan/brown
- Dark brown
- Red-blue
- Blue
- Gray
- Pink

eTable. Scored Dermoscopy Features (cont)

- >1 Shade of pink
- Black
- White
- Color count 1-6 (tan, dark brown, red, blue, gray, or black; excluding white)
- Sharply demarcated colors
- Blurred "out of focus" colors
- Follicular plugs
- Abrupt edge (any aspect)
- Graduated edge (entire lesion)
- Symmetrical pigmentation pattern
- Asymmetrical pigmentation pattern
- Symmetrical shape
- Asymmetrical shape
- Irregular blotch (irregular-shaped homogeneous area larger than 10% of the area)
- Regular blotch
- Regular vessels (uniform shape/size)
- Irregular vessels (irregular shape/size)
- Peripheral vessels (at or near the edge)
- Central vessels
- Predominantly peripheral vessels (all vessel types combined)
- Predominantly central vessels (all vessel types combined)
- Large-diameter vessels
- Linear-irregular or dotted vessels not clearly combined with regression structures
- Comma vessels of regular distribution
- Comma vessels of irregular distribution
- Hairpin vessels
- Peripheral hairpin vessels
- Central hairpin vessels
- Regular distribution of dotted/pinpoint vessels (not confined to the holes of pigment network)
- Irregular distribution of dotted/pinpoint vessels (not confined to the holes of pigment network)
- Linear irregular vessels
- Dotted and linear irregular vessels
- Radial (wreathlike or "crown") vessels
- Milky red-pink areas
- Glomerular vessels
- Milky red globules
- Some vessels surrounded by white halo or yellow pigment
- Most vessels surrounded by white halo or yellow pigment

Predominant vessel type (circle one only):

- Arborizing
- Comma
- Crown/radial
- Dotted/pinpoint vessels (not confined to the holes of the pigment network)
- Hairpin
- Linear irregular
- Vessels with white or yellow pigmented halo
- Glomerular
- Other features _____
- Light brown peripheral structureless areas occupy >10% of the lesion.

The morphological definitions are as described elsewhere (see references 9-15 in the published article). Examples of vascular and other definitions are found at the International Dermoscopy Society Web site: <http://dermoscopy-ids.org/studies> (click on "Amelanotic melanoma study").

(continued)