ONLINE FIRST

Dermoscopic Evaluation of Nodular Melanoma

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Importance: Nodular melanoma (NM) is a rapidly progressing potentially lethal skin tumor for which early diagnosis is critical.

Objective: To determine the dermoscopy features of NM.

Design: Eighty-three cases of NM, 134 of invasive non-NM, 115 of nodular benign melanocytic tumors, and 135 of nodular nonmelanocytic tumors were scored for dermoscopy features using modified and previously described methods. Lesions were separated into amelanotic/hypomelanotic or pigmented to assess outcomes.

Setting: Predominantly hospital-based clinics from 5 continents.

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

Results: Nodular melanoma occurred more frequently as amelanotic/hypomelanotic (37.3%) than did invasive non-NM (7.5%). Pigmented NM had a more frequent (compared with invasive non-NM; in descending order of odds ratio) symmetrical pigmentation pattern (5.8% vs 0.8%), large-diameter vessels, areas of homogeneous blue pigmentation, symmetrical shape, predominant peripheral vessels, blue-white veil, pink color, black color, and milky red/pink areas. Pigmented NM less frequently displayed an atypical broadened network, pigment network or pseudonetwork, multiple blue-gray dots, scarlike depigmentation, irregularly distributed and sized brown dots and globules, tan color, irregularly shaped depigmentation, and irregularly distributed and sized dots and globules of any color. The most important positive correlating features of pigmented NM vs nodular nonmelanoma were peripheral black dots/globules, multiple brown dots, irregular black dots/globules, blue-white veil, homogeneous blue pigmentation, 5 to 6 colors, and black color. A model to classify a lesion as melanocytic gave a high sensitivity (>98.0%) for both nodular pigmented and nonnodular pigmented melanoma but a lower sensitivity for amelanotic/hypomelanotic NM (84%). A method for diagnosing amelanotic/hypomelanotic malignant lesions (including basal cell carcinoma) gave a 93% sensitivity and 70% specificity for NM.

Conclusions and Relevance: When a progressively growing, symmetrically patterned melanocytic nodule is identified, NM needs to be excluded.

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NODULAR MELANOMA (NM) is defined as an invasive melanoma that lacks significant intraepidermal tumor cells beyond the margins of the dermal invasive component.[1] Although NM constitutes only 9% to 15% of invasive melanoma, it is overrepresented as a cause of lethal melanoma. Nodular melanoma is the most frequent subtype of thick, rapidly growing melanomas (reviewed by Chamberlain and Ng[2] and Kelly et al[3]), is frequently not diagnosed until it is at a locally advanced stage, and therefore is associated with a relatively poor prognosis. The lesions present clinically as firm papules or nodules, with more frequent ulceration and less color variegation than other invasive melanomas. Nodular melanoma lesions are more frequently light colored than the other common melanoma subtypes. For

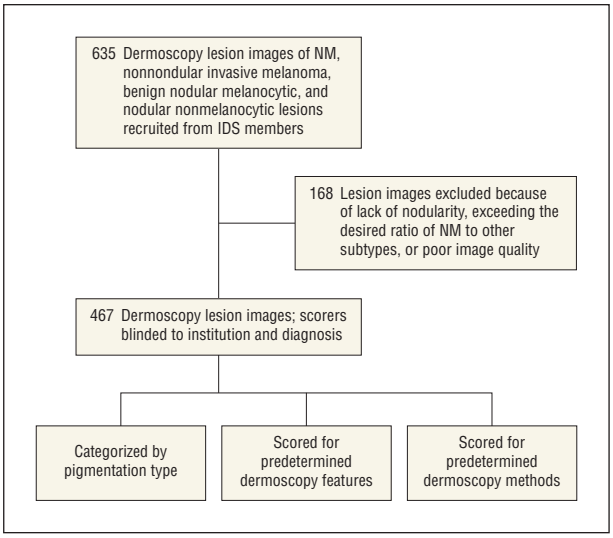

Figure 1. Flowchart of included lesions. IDS indicates International Dermoscopy Society; NM, nodular melanoma.

this reason, the well-known ABCD rule (*a*symmetry, *b*order irregularity, *c*olor variability, and *d*iameter >6 mm) for clinical diagnosis for NM is less useful, and an EFG pneumonic of *e*levation, *f*irm consistency, and progressive *g*rowth to describe their clinical presentation is more apt.[3] In Australia, NM lesions are more commonly found in sun-damaged skin of the head and neck region of elderly men.[2]

Unlike the extensive literature on the dermoscopy of melanoma in general, there is a relative paucity of dermoscopy literature on the subtype NM,[4-6] with many observations grouped with those of other invasive melanomas[7] or small case series.[8,9] In this study, we documented the dermoscopy features of a large series of NM; we describe that here and validate criteria used for their dermoscopic diagnosis.

METHODS

IMAGE ACQUISITION AND INCLUSION AND EXCLUSION CRITERIA

Digital dermoscopic images of lesions taken with glass plate/liquid nonpolarized or cross-polarized photographic devices were obtained from members of the International Dermoscopy Society from 5 continents. A request was made for images of all NMs satisfying the inclusion criteria and for a random selection of nonnodular invasive primary melanoma, benign nodular melanocytic lesions, and nodular nonmelanocytic lesions at a desired ratio of NM to other subgroups of 1:2.

All lesions obtained were excised and histopathologic examination was performed except for some benign melanocytic nevi that showed no change over time compared with baseline photographs. Nodular melanoma was defined as an invasive melanoma without an in situ (junctional) component beyond 3 rete ridges of the dermal invasive component.[1] The histologic sections of all NM lesions were reviewed by a second pathologist either at the institution of origin or by one of us (R.A.S.). Lesions were included as "nodular" melanoma only when the second review confirmed the diagnosis according to the histologic definition used. Both nodular benign melanocytic lesions and nodular nonmelanocytic lesions were identified by the clinical appearance of a solitary nodule and confirmed using dermoscopic examination.

Table 1. Frequency of Diagnosis

Diagnosis	Frequency, No.
Invasive melanoma	217
Nodular melanoma	83
Superficial spreading melanoma	133
Lentigo maligna melanoma	1
Benign melanocytic lesions	115
Common nevi	87
Spitz nevi	12
Blue nevi	15
Deep penetrating nevi	1
Nonmelanocytic lesions	135
Basal cell carcinoma	62
Seborrheic keratosis	34
Hemangioma	11
Dermatofibroma	11
Other	17

Images received were included, attempting to maintain the desired ratio of 1:2 for nodular malignant melanoma (MM) to other subtypes within individual centers (M.A.), and confirmed as morphologically nodular and correctly categorized according to their histopathologic examination reports (P.G. and M.A.). These dermoscopic images were reviewed (S.W.M.), blinded to diagnosis and institution of origin, categorized by their pigmentation type as previously reported,[7] and excluded if the image quality was poor. Amelanotic lesions were defined as having no melanin pigmentation (ie, tan, dark brown, blue, gray, or black) on dermoscopic examination. Tan pigmentation is defined as light brown pigmentation that is darker than the surrounding skin. Two 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. All lesions not categorized as amelanotic or hypomelanotic by these definitions were defined as "pigmented." The flowchart of included lesions is shown in **Figure 1**.

The study consisted of 467 lesions; of these, 83 were NM, 134 were invasive non-NM, 115 were nodular benign melanocytic tumors, and 135 were nodular nonmelanocytic tumors. **Table 1** reports the frequency of each diagnosis, and **Table 2** lists the frequency of each major diagnostic category as a function of the overall dermoscopic pigmentation type.

All lesion images used in the study were obtained retrospectively from photographic libraries at various institutions, and participants provided verbal or written consent for their use. Formal ethics approval for the study was obtained at the coordinating center (Sydney Melanoma Diagnostic Centre, Australia). When relevant, institutional review board approval or waiver at the individual external sites was sought.

DERMOSCOPIC FEATURES

The features included in the study were determined by consensus of the members of the International Dermoscopy Society. Before scoring, clinicians were given a morphologic tutorial to define all vascular and more recently defined structures. The definitions of the features are as described previously.[7] Twelve scorers blinded to the lesion diagnosis scored 99 indi-

Table 2. Lesion Pigmentation Categories[a]

Diagnosis	No. (%)					
	Pigmented	Amelanotic	Partially Pigmented	Light-Colored	Partially Pigmented and Light-Colored	Total
NM	52 (62.7)	8 (9.6)	14 (16.9)	8 (9.6)	1 (1.2)	**83** (100.0)
Nonnodular invasive melanoma	124 (92.5)	3 (2.2)	5 (3.7)	2 (1.5)	0	**134** (100.0)
Nodular benign melanocytic lesion	75 (65.2)	11 (9.6)	7 (6.1)	22 (19.1)	0	**115** (100.0)
Nodular nonmelanocytic lesion	63 (46.7)	31 (23.0)	10 (7.4)	18 (13.3)	13 (9.6)	**135** (100.0)

Abbreviation: NM, nodular melanoma.

[a] A total of 467 study lesions were obtained (see the Methods section for the inclusion criteria). The pigmentation category of tumors differed significantly as a function of diagnosis ($P < .001$, Fisher exact test).

vidual features in each lesion of approximately equal sample sizes, as previously described.[7] Following the review of the article for publication, an additional feature (blue-black structures) was scored for all lesions by one observer (E.C.). First-step dermoscopic analysis to define a melanocytic lesion was scored separately (S.W.M.). This method[10] was extended to allow the diagnosis of amelanotic or hypomelanotic melanocytic lesions. Hence, in this study, the extended method defines a melanocytic lesion as diagnosed if 1 or more of pigment network or pseudonetwork, aggregated brown or black globules, streaks (pseudopods or radial streaming), homogeneous blue structureless pigmentation within the lesion, parallel pattern (on volar sites), pinpoint (small dotted) vessels, or comma vessels are found. In addition, if a lesion has no features of a nonmelanocytic lesion, it is also defaulted as melanocytic. Second-step analysis (to determine a diagnosis of melanoma) was scored separately on all lesions using the ABCD method (with a score >5.45 indicating melanoma)[11] (M.C.), the Menzies method[12] (S.W.M.), 7-point checklist (with a score ≥3 indicating melanoma)[13] (G.A. and I.Z.), 3-point checklist[14] (D.C.G and H.P.S.), CASH (*c*olor, *a*rchitecture, *s*ymmetry, and *h*omogeneity) score (with a score ≥8 indicating melanoma)[15] (F.J.M.), and a high-sensitivity model for amelanotic/hypomelanotic malignant lesions[7] (S.W.M.).

STATISTICAL ANALYSIS

Commercial statistical software was used to analyze the data (SPSS for Windows, version 18; SPSS Inc, and LogXact, version 6; Cytel Inc). The exact permutation methods available in the latter package were used when zero cell counts were observed. Two-tailed tests with a significance level of 5% were used throughout the analysis, and χ^2 tests (or Fisher exact test when appropriate) were used to test for association between the presence of a feature and lesion type. Odds ratios (ORs) and their 95% CIs were used to quantify the level of association. The sensitivity and specificity of each feature for the diagnosis of interest compared with other lesion types were expressed as percentages. The McNemar test was used to compare the predicted lesion status according to different diagnostic methods within various subgroups of patients.

RESULTS

GENERAL TUMOR CHARACTERISTICS

The diagnostic categories of the study lesions are summarized in Table 1. The median Breslow thickness of NM (2.7 mm) was significantly greater than that of the nonnodular invasive melanoma (0.7 mm) ($P < .001$, Mann-Whitney test). The pigmentation category of tumors (amelanotic, partial pigmented, light colored, and pigmented) differed significantly as a function of diagnosis ($P < .001$, Fisher exact test) (Table 2). In particular, NM was less frequently pigmented (62.7%) than nonnodular invasive melanoma (92.5%) but more pigmented than nodular nonmelanocytic lesions (46.7%) ($P < .001$, Fisher exact test). For this reason, when comparing the 4 broad diagnostic categories of tumors, analyses were always stratified according to pigmentation type.

DERMOSCOPIC FEATURES OF PIGMENTED NODULAR VS NONNODULAR INVASIVE MELANOMA

When analyzing only pigmented tumors, NM was more frequently (compared with nonnodular invasive melanoma; in descending order of OR) found to have a symmetrical pigmentation pattern (5.8% vs 0.8%), large-diameter vessels, areas of homogeneous blue pigmentation, symmetrical shape, predominant peripheral vessels, blue-white veil, pink color, black color, and milky red/pink areas (**Table 3**). Pigmented NM less frequently (in ascending order of OR compared with nonnodular invasive melanoma) displayed an atypical broadened network, pigment network or pseudonetwork, multiple blue-gray dots (granularity), scarlike depigmentation, irregularly distributed and sized brown dots and globules, tan color, irregularly shaped depigmentation, and irregularly distributed and sized dots and globules. Because of the limited sample size of nonpigmented non-NM (n = 10), a comparison between nonpigmented melanoma is not reported.

DERMOSCOPIC FEATURES OF NM VS NODULAR NONMELANOMA

Table 4 reports the univariable analysis of the significant dermoscopic features found in pigmented NM compared with all pigmented nodular nonmelanomas. The negative correlating features related to those found in nodular pigmented basal cell carcinoma (arborizing vessels, leaflike areas, large blue-gray ovoid nests, and multiple blue-gray globules), which were all absent in NM, were features found in seborrheic keratoses (millialike cysts, comedolike openings/irregular crypts) and features found in benign melanocytic lesions (regular size and distributed dots/globules, symmetrical pigmentation pattern). Regularly shaped and sized vessels were also a negative correlating feature of melanoma. The most

Table 3. Dermoscopic Features of Pigmented Nodular vs Pigmented Nonnodular Invasive Melanoma

Feature	Melanoma, %		*P* Value	OR (95% CI)
	Nodular	Nonnodular		
Positive features				
Symmetrical pigmentation pattern	5.8	0.8	.045	7.6 (0.8-75.6)
Large-diameter vessels[a]	5.8	0.8	.04	7.6 (0.8-75.6)
Homogeneous blue pigmentation within lesion	80.8	43.1	<.001	5.6 (2.6-12.1)
Symmetrical shape	32.7	11.3	.001	3.8 (1.7-8.5)
Predominant peripheral vessels	25.0	8.1	.02	3.8 (1.5-9.3)
Blue-white veil	84.6	62.6	.004	3.3 (1.4-7.6)
Pink color	48.1	29.0	.02	2.3 (1.2-4.4)
Black color	75.0	56.5	.02	2.3 (1.1-4.8)
Milky red/pink areas	34.6	19.4	.03	2.2 (1.1-4.5)
Negative features				
Atypical network (broadened and irregular)	3.8	32.5	<.001	0.08 (0.02-0.36)
Pigment network/pseudonetwork	11.5	58.5	<.001	0.09 (0.04-0.23)
Multiple blue-gray dots (granularity)	3.8	14.6	.04	0.23 (0.05-1.04)
Scarlike depigmentation	17.3	45.5	<.001	0.25 (0.11-0.56)
Irregular brown dots/globules	40.4	65.3	.002	0.36 (0.19-0.70)
Tan color	42.3	66.9	.002	0.36 (0.19-0.71)
Irregular shape depigmentation	15.4	33.1	.02	0.37 (0.16-0.85)
Irregular dots/globules of any color	42.3	59.7	.04	0.49 (0.26-0.95)

Abbreviation: OR, odds ratio.
[a] Linear (horizontal) vessels with a caliber diameter at least 3 times that of the neighboring thinnest-caliber (small-diameter) vessels.

important positive correlating features of NM were (in order of OR) peripheral black dots/globules, multiple brown dots, irregular black dots/globules, blue-white veil, pseudopods, homogeneous blue pigmentation, 5 to 6 colors, black color, irregular blotches (black, brown, or gray), irregularly sized and distributed dots/globules, blue-black structures, central black dots/globules, atypical vascular pattern (linear irregular or dotted vessels not clearly seen within regression structures), dark brown color, and milky red-pink areas.

Table 5 reports the univariable analysis of the significant dermoscopic features found in amelanotic/hypomelanotic NM compared with all amelanotic/hypomelanotic nodular nonmelanomas. The negative correlating features were symmetrical pigmentation pattern, which was significantly more frequent in both benign melanocytic and nonmelanocytic lesions compared with melanoma; arborizing vessels (presence, predominance, and small diameter); regular comma vessels; a single color; and symmetrical shape. The most important positive correlating features, in order of OR, were blue-white veil, atypical vascular pattern (linear irregular or dotted vessels not clearly seen within regression structures), homogeneous blue pigmentation, 5 to 6 colors, black color, central white patch, blue color, more than 1 shade of pink, predominant linear irregular vessels, irregular black dots/globules, milky red-pink areas, irregular depigmentation, black or brown globules, irregular blotches, milky red globules, irregular dots/globules, and hairpin vessels.

There were no significant differences between the frequency of ulceration in NM vs nonnodular invasive melanoma or nodular nonmelanomas; however, ulceration was significantly decreased in NMs (14.5% [12 of 83 lesions]) compared with nodular basal cell carcinomas (35.5% [22 of 62]) ($P = .003$, χ^2).

TWO-STEP PROCEDURE FOR DIAGNOSIS OF NM

We tested a revised first-step procedure (see the Methods section, Dermoscopic Features subsection) to classify a lesion as melanocytic vs nonmelanocytic (**Table 6**). The method had a high sensitivity (>98%) for correctly classifying nodular pigmented and nonnodular pigmented melanoma as melanocytic lesions. However, there was a significant decrease in the sensitivity for amelanotic/hypomelanotic NM (84%) and non-NM (50%) compared with their pigmented counterparts.

We tested previously described second-step methods for the diagnosis of melanoma for pigmented melanocytic lesions (**Table 7**). When comparing the sensitivity for the diagnosis of NM vs non-NM within individual methods, we found significantly decreased sensitivity for NM with the 7-point checklist ($P = .02$), a borderline but nonsignificant decrease with the Menzies method ($P = .06$), but no significant difference within the other methods (ABCD, $P = .92$; CASH, $P = .42$; and 3-point, $P = .62$). The highest sensitivity for pigmented NM was 92.3% (Menzies method), although this was at the expense of a relatively lower specificity compared with most other methods. **Figure 2** shows typical examples of pigmented NM lesions that were confirmed with all diagnostic methods. **Figure 3** shows examples of pigmented NM lesions that were misclassified with most methods. The hallmark of the latter was the symmetrical pigment pattern, which is more frequently found in pigmented nodular (5.8%) vs nonnodular (0.8%) invasive melanoma.

We assessed the high-sensitivity method described for the diagnosis of amelanotic/hypomelanotic malignant lesions[7] on all amelanotic/hypomelanotic lesions. In the model with melanoma diagnosed with a score of 1 or more, the sensitivity for the diagnosis of NM was 93%

Table 4. Univariable Analysis of Pigmented NM vs All Pigmented Nodular Nonmelanoma

Feature	Sensitivity, %[a]	Specificity, %[b]	*P* Value	OR (95% CI)
Negative				
Arborizing vessels	0	91.3	.04	0 (0 to 0.91)
Arborizing vessels, small diameter	0	92.8	.08	0 (0 to 1.15)
Leaflike areas	0	92.7	.08	0 (0 to 1.15)
Large blue-gray ovoid nests	0	89.9	.02	0 (0 to 0.75)
Multiple blue-gray globules	0	90.5	.03	0 (0 to 0.83)
Regular dots/globules (size and distribution; any color)	0	84.8	.002	0 (0 to 0.46)
Multiple (>3) milialike cysts	1.9	81.1	.003	0.08 (0.01 to 0.64)
Comedolike openings (irregular crypts)	1.9	81.2	.003	0.08 (0.01 to 0.64)
Regular vessels (uniform shape/size)[c]	1.9	83.3	.01	0.10 (0.01 to 0.75)
1-3 Milialike cysts	3.8	85.5	.04	0.23 (0.05 to 1.04)
Symmetrical pigmentation pattern	5.8	79.9	.02	0.25 (0.07 to 0.84)
Regular brown dots/globules	5.8	81.1	.03	0.27 (0.08 to 0.91)
Positive				
Peripheral black dots/globules[c]	17.3	99.3	<.001	28.43 (3.5 to 229.1)
Multiple brown dots[c]	7.7	100.0	.01	14.90 (1.8 to >100)
Irregular black dots/globules[c]	50.0	93.5	<.001	14.29 (6.0 to 34.0)
Blue-white veil[c]	84.6	69.8	<.001	12.68 (5.5 to 29.3)
Pseudopods	7.7	99.3	.01	11.34 (1.3 to 103.2)
Homogeneous blue pigmentation[c]	80.8	72.0	<.001	10.81 (4.9 to 23.7)
5-6 Colors[c,d]	57.7	87.7	<.001	9.74 (4.6 to 20.6)
Black color[c]	75.0	75.3	<.001	9.16 (4.4 to 19.2)
Irregular blotches (black, brown, or gray)	46.2	91.3	<.001	9.02 (4.0 to 20.2)
Irregular dots/globules (size and/or distribution; any color)[c]	59.6	84.1	<.001	7.80 (3.8 to 16.0)
Blue-black structures[c]	51.9	87.0	<.001	7.20 (3.4 to 15.0)
Central black dots/globules[c]	17.3	97.1	<.001	7.05 (2.1 to 24.1)
Atypical vascular pattern[c,e]	38.5	91.3	<.001	6.56 (2.9 to 14.8)
Dark brown color[c]	75.0	60.9	<.001	4.66 (2.3 to 9.5)
Milky red/pink areas	34.6	88.4	<.001	4.05 (1.9 to 8.8)
Streaks (pseudopods/radial streaming)	9.6	97.2	.05	3.62 (0.9 to 14.1)
Milky red globules	13.5	95.7	.03	3.44 (1.1 to 10.8)
Linear irregular vessels, predominant type	28.8	89.1	.002	3.32 (1.5 to 7.4)
Irregular brown dots/globules[c]	40.4	82.6	.001	3.22 (1.6 to 6.5)
Blue color	73.1	51.5	.002	2.88 (1.4 to 5.8)
Red-blue color	32.7	84.8	.01	2.70 (1.3 to 5.7)
Linear irregular vessels	28.8	86.2	.0	2.54 (1.2 to 5.5)
Blurred "out of focus" colors	69.2	50.7	.01	2.31 (1.2 to 4.6)
Abrupt edge (any aspect)[c]	63.5	56.5	.01	2.26 (1.2 to 4.4)
Asymmetrical shape	55.8	63.0	.02	2.15 (1.1 to 4.1)
Pink color	48.1	69.6	.02	2.12 (1.1 to 4.1)

Abbreviations: NM, nodular melanoma; OR, odds ratio.
[a] The percentage of NM lesions with that feature.
[b] The percentage of nonmelanoma lesions without that feature.
[c] Indicates features that are significant with the same OR trend (ie, either all >1 or all <1) in both benign melanocytic and nonmelanocytic lesions compared with melanoma.
[d] Colors scored are tan, dark brown, black, blue, gray, and red.
[e] Linear irregular or dotted vessels not clearly seen within regression structures.

and the score for nonnodular invasive melanoma was 90%. The specificity for benign nodular melanocytic lesions was 70%. When the threshold was reduced with melanoma diagnosed at a score of 0 or more, 100% sensitivity for the diagnosis of both nodular and non-NM was achieved but with a relatively low specificity of 52.5% for benign nodular melanocytic lesions. **Figure 4** shows examples of amelanotic/hypomelanotic NM.

COMMENT

Consistent with the literature,[16] in our series NM was more frequently amelanotic/hypomelanotic (37.3%) than was invasive non-NM (7.5%). Furthermore, our study depended on the clinician to image a lesion before excision. Nonpigmented NM may not be clinically suspected to be melanoma; hence, it is conceivable that images may be taken less frequently compared with the pigmented variety. As with other subtypes of melanoma, the dermoscopy features of hypomelanotic melanoma are very different from those of the pigmented variety. For this reason, the diagnostic approach for hypomelanotic and pigmented NM should be separate.

In our study, 5.8% of pigmented NM showed symmetry of pigmentation pattern across all axes. In contrast, only 0.8% of invasive pigmented non-NM showed symmetry of pattern. Our results are consistent with limited data previously published. In a series of 10 NM lesions, all showed an asymmetrical pigmentation pattern under dermoscopy examination.[6] In a study of thin and

Table 5. Univariable Analysis of Amelanotic/Hypomelanotic NM vs All Amelanotic/Hypomelanotic Nodular Nonmelanoma

Feature	Sensitivity, %[a]	Specificity, %[b]	*P* Value	OR (95% CI)
Negative				
Symmetrical pigmentation pattern[c]	3.2	69.2	.002	0.07 (0.01-0.57)
Arborizing vessels	3.2	79.4	.02	0.13 (0.02-1.0)
Predominant arborizing vessels	3.2	77.7	.02	0.12 (0.01-0.89)
Regular comma vessels	3.2	81.2	.03	0.14 (0.02- 1.1)
Arborizing vessels, small diameter	3.2	81.2	.03	0.14 (0.02-1.1)
Single color	12.9	68.4	.04	0.32 (0.10-0.99)
Symmetrical shape	35.5	42.0	.03	0.40 (0.17-0.91)
Positive				
Blue-white veil[c]	38.7	99.1	<.001	67.4 (8.6-529.4)
Atypical vascular pattern[c,d]	83.9	84.8	<.001	29.1 (9.8-86.4)
Homogeneous blue pigmentation[c]	29.0	97.3	<.001	14.4 (3.7-57.0)
5-6 Colors[c,e]	9.7	99.1	.01	11.8 (1.2-117.2)
Black color[c]	19.4	97.3	.001	8.7 (2.0-37.1)
Central white patch	12.9	98.2	.01	8.1 (1.4-46.5)
Blue color[c]	48.4	88.4	<.001	7.1 (2.9-17.7)
>1 Shade of pink[c]	61.3	80.3	<.001	6.5 (2.7-15.3)
Predominant linear irregular vessels[c]	51.6	85.7	<.001	6.4 (2.7-15.4)
Irregular black dots/globules	9.7	98.2	.03	5.9 (0.9-36.8)
Milky red/pink areas[c]	45.2	86.6	<.001	5.3 (2.2-13.0)
Irregular depigmentation	16.1	96.4	.01	5.2 (1.3-20.7)
Black or brown globules	16.1	96.4	.01	5.1 (1.3-20.3)
Irregular blotches (black, brown, or gray)	19.4	95.5	.01	5.1 (1.5-18.1)
Milky red globules	32.3	90.2	.002	4.4 (1.6-11.6)
Irregular dots/globules	19.4	94.6	.01	4.3 (1.3-14.3)
Hairpin vessels[c]	29.0	91.1	.004	4.2 (1.5-11.5)
Scarlike depigmentation	12.9	96.4	.047	3.9 (0.9-16.7)
Linear irregular vessels	48.4	79.4	.002	3.6 (1.6-8.4)
Irregular brown dots/globules	19.4	93.8	.02	3.6 (1.1-11.7)
Peripheral hairpin vessels	19.4	92.9	.04	3.1 (1.0-9.9)
Predominant peripheral vessels	45.2	77.7	.01	2.9 (1.2-6.6)
Gray color	32.3	85.7	.02	2.9 (1.1-7.2)
Red-blue color	29.0	87.5	.03	2.9 (1.1-7.4)
Tan color	64.5	59.8	.02	2.7 (1.2-6.2)
Small dotted vessels	29.0	86.4	.04	2.6 (1.0-6.7)
Irregular vessels	58.1	64.3	.02	2.5 (1.1-5.6)
White color	45.2	74.1	.04	2.4 (1.0-5.4)

Abbreviations: NM, nodular melanoma; OR, odds ratio.
[a] The percentage of NM lesions with that feature.
[b] The percentage of nonmelanoma lesions without that feature.
[c] Indicates features that are significant with the same OR trend (ie, either all >1 or all <1) in both benign melanocytic and nonmelanocytic lesions compared with melanoma.
[d] Linear irregular or dotted vessels not clearly seen within regression structures.
[e] Colors scored are tan, dark brown, black, blue, gray, and red.

small-diameter NM, although 7 of 11 tumors showed clinical symmetry of pigmentation pattern, 9 of 11 were asymmetrical in pigmentation pattern under dermoscopy.[5] Although the frequency is relatively low, symmetry of pigmentation pattern can occur in NM and is an important reason for misdiagnosis using standard dermoscopy methods.

Compared with nonnodular invasive pigmented melanoma, pigmented NM lesions were more symmetrical in pattern and shape, had large-diameter vessels and a greater proportion of lesions with a predominance of peripheral vessels, had increased areas of homogeneous blue pigmentation and blue-white veil, and had increased areas of black and pink color (including milky red/pink areas). Less frequently observed characteristics of NM included classic patterns of melanoma, such as pigment network (both typical and atypical), areas of regression (multiple blue-gray dots, irregularly shaped or scarlike depigmentation), tan color, and irregularly shaped and distributed brown dots and globules.

Black dots and globules are an important diagnostic feature of pigmented NM. These represent localized melanin accumulation (often melanoma cells) in the stratum corneum[17,18] or areas associated with nests of melanocytes just beneath the very thinned epidermis shortly before rupture or when already ulcerated (personal communication, Caterina Longo, MD, PhD, Skin Cancer Unit, Areispedale S. Maria Nuova–Istituto di Ricovero e Cura a Carattere Scientifico, Reggio Emilia, Italy; April 16, 2012). Peripheral black dots/globules had the highest OR of any single dermoscopy feature for pigmented NM (OR, 28), with irregular size and irregularly distributed black dots/globules (OR, 14) and central black dots/globules (OR, 7) also being important features. Multiple brown dots, which are seen as aggregations of well-defined dark brown dots and represent suprabasal intraepidermal col-

Table 6. Modified First-Step Method to Determine Whether a Lesion Is Melanocytic

Lesion Characteristic	MM Sensitivity, %		Benign Nodular Melanocytic Sensitivity, %	Nodular Nonmelanocytic Specificity, %[a]
	Nodular	Nonnodular		
Pigmented	98.1[b,c]	99.2[d,e]	94.7	61.9
Amelanotic/hypomelanotic	83.9[f]	50.0[g]	87.5	75.0

Abbreviation: MM, malignant melanoma.
[a] The specificity equals 100 minus the percentage of lesions falsely diagnosed as melanocytic.
[b] There was a significant increase in the sensitivity of pigmented vs amelanotic/hypomelanotic lesions ($P = .02$, χ^2 test).
[c] The solitary nodular MM lesion misclassified as nonmelanocytic had features of pigmented basal cell carcinoma (BCC).
[d] There was a significant increase in the sensitivity of pigmented vs amelanotic/hypomelanotic lesions ($P < .001$, Fisher exact test).
[e] The solitary nonnodular MM lesion misclassified as nonmelanocytic had features of pigmented BCC.
[f] Four of 5 of the nodular MM lesions misclassified as nonmelanocytic had features of BCC, and 1 had features of seborrheic keratosis.
[g] All 5 of the nonnodular MM lesions misclassified as nonmelanocytic had features of pigmented BCC.

Table 7. Pairwise Comparisons of Sensitivity or Specificity Between Second-Step Methods for the Diagnosis of Pigmented Melanoma

Method	Sensitivity, %[b]	Specificity, %	*P* Value[a]			
			CASH	ABCD	7-Point	3-Point
NM						
Menzies	92.3	. . .	.02	.03	.06	.07
CASH	78.8	. . .		>.99	.75	>.99
ABCD	80.8	. . .			>.99	>.99
7-Point	82.7	. . .				>.99
3-Point	80.8	. . .				
Non-NM						
Menzies	98.4	. . .	<.001	<.001	.12	<.001
CASH	83.9	. . .		.65	.004	>.99
ABCD	81.5	. . .			<.001	.68
7-Point	94.4	. . .				.004
3-Point	83.9	. . .				
Benign Melanocytic Lesion						
Menzies	. . .	65.3	.42	.66	.08	<.001
CASH	. . .	72.0		.82	.33	<.001
ABCD	. . .	69.3			.14	<.001
7-Point	. . .	78.7				<.001
3-Point	. . .	40.0				

Abbreviations: ABCD, ABCD rule of dermoscopy; CASH, *c*olor, *a*rchitecture, *s*ymmetry, and *h*omogeneity; ellipses, sensitivity relates to the melanoma lesions and specificity relates to the benign lesions; NM, nodular melanoma.
[a] *P* values from the McNemar test of within-patient comparisons of predicted melanoma.
[b] When comparing the sensitivity for the diagnosis of NM vs non-NM within individual methods, there was a significantly decreased sensitivity for NM with the 7-point checklist ($P = .02$) and a borderline but nonsignificant decrease for the Menzies method ($P = .06$) but no significant difference within the other methods (ABCD, $P = .92$; CASH, $P = .42$; and 3-point, $P = .62$).

lections of melanin (usually melanoma cells),[18] was also an important diagnostic feature (OR, 15). This suggests significant focal areas of intraepidermal pagetoid invasion of melanoma cells in NM. According to Elder and Murphy,[19] the epidermis in NM is usually involved by cells similar to those in the dermal tumor, and these cells usually extend upward in a typical pagetoid pattern. Consistent with this, in our study, there was no significant difference in any of the dermoscopy features that histopathologically correlated with pagetoid spread in pigmented nodular vs non-NM. In contrast, although limited studies of in vivo confocal microscopy of NM confirm the presence of pagetoid cells, a trend to a less-moderate infiltration of these cells was seen compared with non-NM.[6]

Consistent with the importance of black dots and globules, recently a large series of invasive melanoma that presented as pigmented nodules with either no or a minimal flat component was examined for the recently described dermoscopy feature of blue-black structures.[4] This feature, defined as the presence of a combination of blue and black pigmented areas involving at least 10% of the lesion surface, had a sensitivity of 78.2% and a specificity of 80.5% for the diagnosis of melanoma. We confirmed this observation in the present study, with blue-black structures significantly increased in pigmented NM compared with pigmented nodular nonmelanoma (sensitivity, 51.9%, and specificity, 87%).

It has been suggested that the vascular morphology is dependent on the tumor volume and thickness in melanoma.[20] In a study of amelanotic/hypomelanotic melanoma,[7] thicker tumors had an increased prevalence of all vessels, greater prevalence of pink color, and more hairpin and large-diameter–type vessels. Dotted/pinpoint ves-

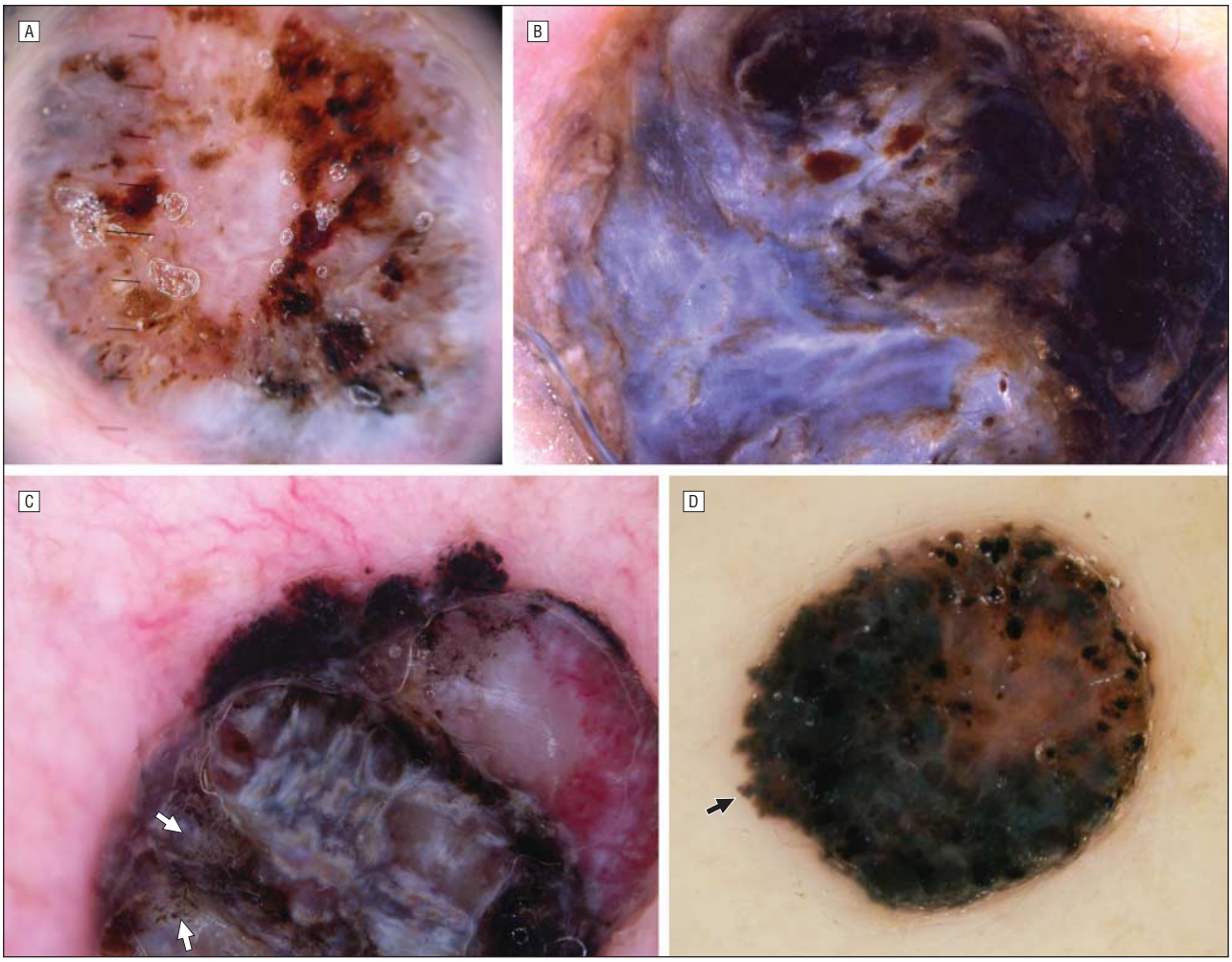

Figure 2. Typical nodular pigmented melanoma. A, This asymmetrical pigmented nodule has the significant positive predictors of blue-white veil, multiple (5-6) colors (scored from tan, dark brown, red, blue, gray, and black), irregular blotches, irregular brown dots and globules, and black color (Breslow thickness, 4.5 mm). B, This asymmetrical pigmented nodule has a blue-white veil, irregular blotches, and irregular dots and globules, some of which are black, that are found both in a central and peripheral position (Breslow thickness, 5.0 mm). C, This asymmetrical pigmented nodule has a blue-white veil, multiple brown dots (white arrows), 5 or 6 colors, peripheral black dots and globules, milky red and pink areas, and irregular blotches (Breslow thickness, 6.7 mm). D, This asymmetrical pigmented nodule has peripheral black dots and globules, irregular dots and globules (size and distribution), pseudopods (arrow), and black color (Breslow thickness, 1.2 mm).

sels were less frequently found as the predominant vessel type in thicker tumors. Consistent with this, in our study, when comparing nodular and other invasive melanoma (which were significantly thinner), NM had an increased prevalence of large-diameter vessels, pink color, and milky red/pink areas.

Thirteen percent of our amelanotic/hypomelanotic NM lesions were reported to have a central white patch. Such patches are common in dermatofibroma[21]; however, the findings of our study suggest that when they are present, other features indicating malignancy should be carefully sought. Vascular patterns are clearly important in distinguishing amelanotic/hypomelanotic NM from nodular nonmelanomas. Nodular melanoma uncommonly has arborizing or regular comma vessels (3.2%). In contrast, NM lesions exhibit an atypical vascular pattern, with the most important single vascular structures being a predominance of linear irregular vessels and the presence of hairpin vessels. Milky red/pink areas, also indicating greater angiogenesis, are an important feature of amelanotic/hypomelanotic NM.

In a previously reported large series of amelanotic/hypomelanotic melanoma, the most important single vascular feature of melanoma was the predominance of centrally positioned vessels.[7] In contrast, our study showed that amelanotic/hypomelanotic NM had a significantly greater proportion of lesions with vessels positioned in a predominantly peripheral position. However, this is consistent with the former study's[7] findings that thick melanomas (>1 mm Breslow thickness) had twice the frequency of peripheral vessels as thin melanomas (<0.75 mm).

The median Breslow thickness of our series of NM was 2.7 mm. Because NM has a greater vertical growth rate than other melanoma subtypes,[22] it is rare to image NM lesions as thinner small papules, which they presumably are on first appearance. A small series of relatively thin (<1.3 mm) NM has been reported.[5] Nine of 11 lesions were asymmetrical in pigmentation pattern, and many had specific features of melanoma, including blue-white veil and atypical vessels. Nevertheless, it remains a challenge to report the diagnostic features of thin papular NM.

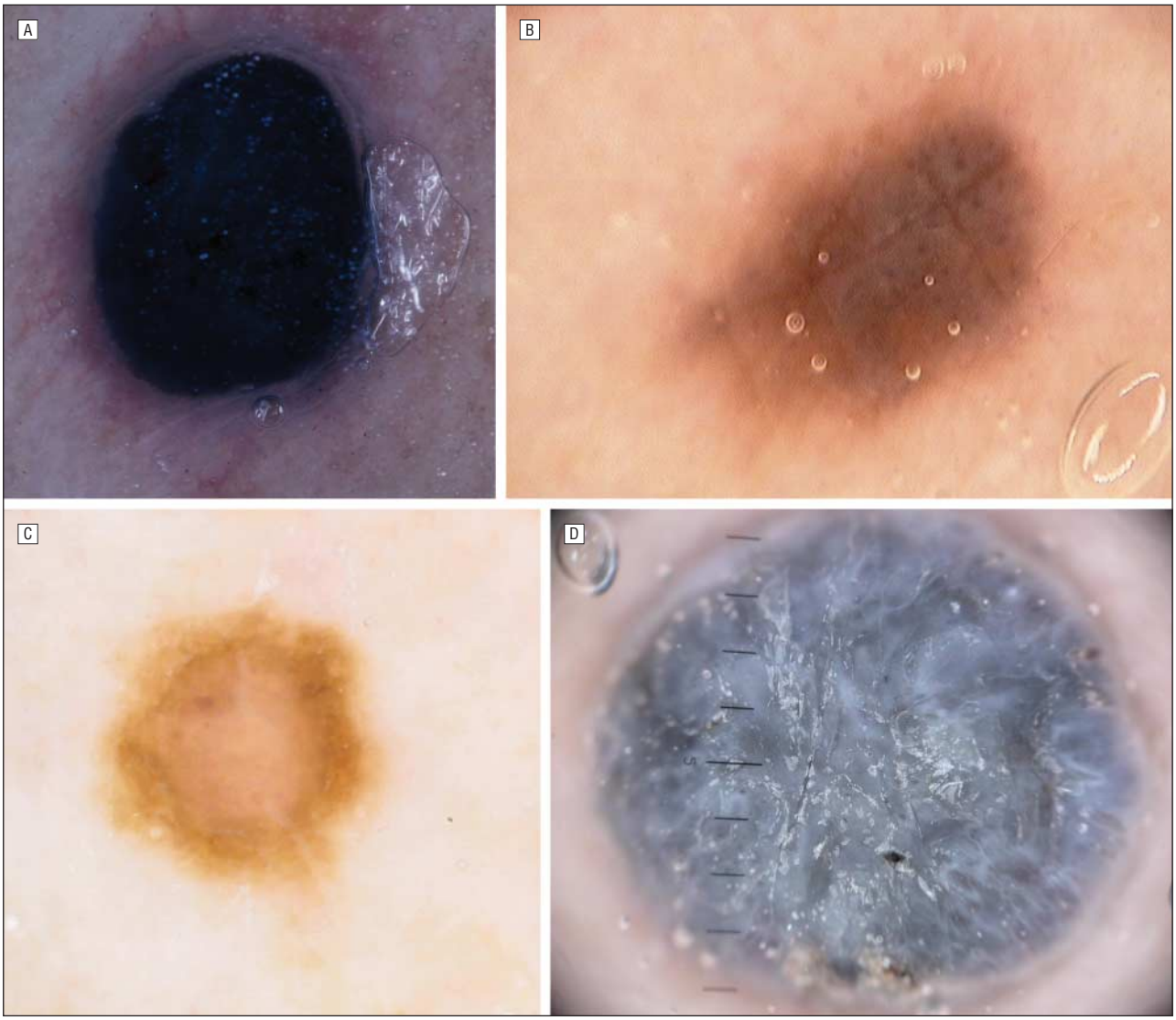

Figure 3. Symmetrical pigmented nodular melanoma. Although most nodular pigmented melanoma lesions have asymmetrical pigmented patterns, 5.8% have symmetrical pigmentation, as seen here. The Breslow thicknesses are A, 1.7 mm; B, 1.0 mm; C, 0.9 mm; and D, 4.3 mm.

A limitation of our study is the use of mixed photographic systems, most with incident light dermoscopy devices but some with cross-polarization. It is well documented that differences occur between these 2 methods of dermoscopy,[23] with crystalline structures seen only with the cross-polarized devices and comedolike openings (crypts), milialike cysts, multiple blue-gray dots (granularity), and blue-white veil less visualized compared with conventional incident light devices. In our study, we did not score dermoscopy features found exclusively with cross-polarized devices (crystalline structures).

We tested a modified first-step dermoscopy procedure (that included vascular structures) aimed at defining melanocytic from nonmelanocytic lesions. The results differed for pigmented compared with amelanotic/hypomelanotic lesions. For pigmented lesions, the method showed a very high sensitivity for both NM and nonnodular invasive melanoma (>98%) and a high sensitivity for benign nodular melanocytic lesions (95%). However, the specificity was significantly less (62%). In principle, this results in overcalling nodular lesions as melanocytic, which in practice leads the clinician to consider the diagnosis of NM more frequently. We believe this is beneficial to decrease the misdiagnosis of NM.

In contrast, the modified first-step method, as previously reported with the original first-step method,[7] did not achieve an adequate sensitivity for detecting amelanotic/hypomelanotic nodular lesions as being truly melanocytic (84% NM, 88% benign lesions). Nevertheless, in both pigmented and light-colored lesions, of the 12 melanomas misclassified as nonmelanocytic with the modified first-step dermoscopy method, 11 had features of basal cell carcinoma and hence would have been excised.

As previously described,[7] light-colored lesions are best distinguished as malignant vs benign rather than attempting to differentiate within malignant subtypes. We confirmed this, with the previously reported method achieving a high sensitivity for the diagnosis of amelanotic/hypomelanotic NM in our study.

We tested a variety of second-step methods previously described for the diagnosis of pigmented melanoma. A limitation of our study is that individual scor-

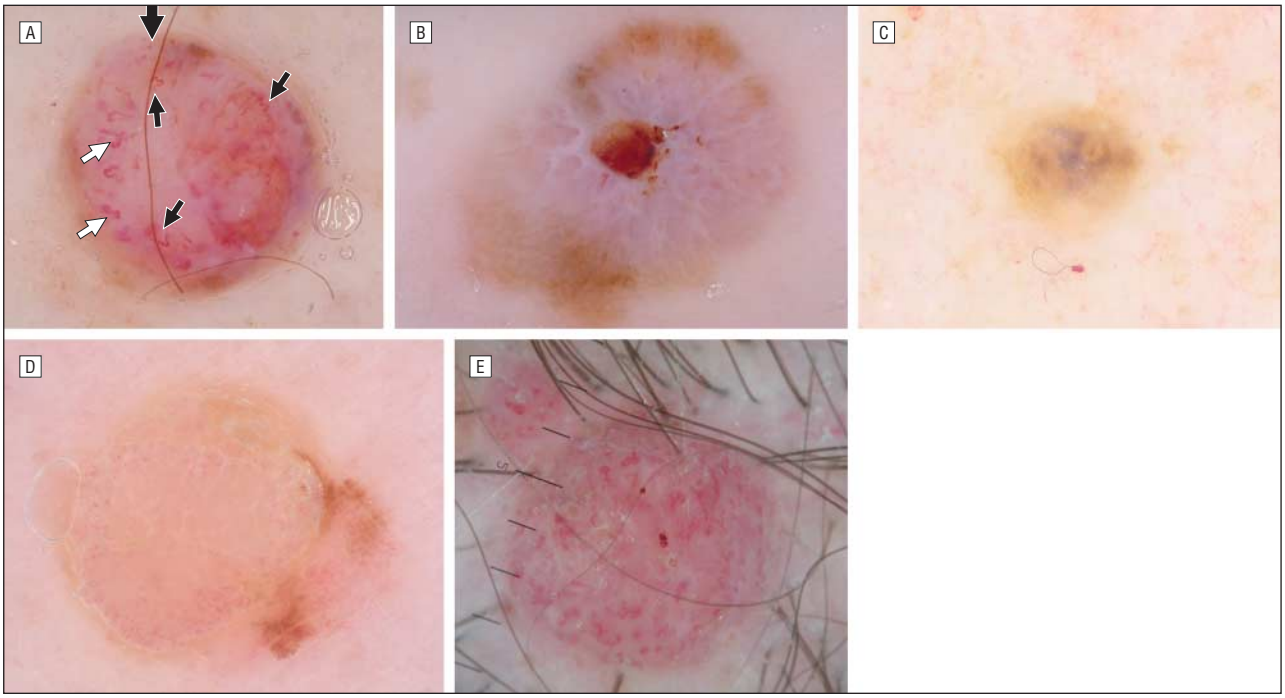

Figure 4. Amelanotic/hypomelanotic nodular melanoma (NM). A, This hypomelanotic nodule has atypical vasculature shown as combinations of dotted (thick arrow), linear irregular (thin black arrows), and hairpin vessels (white arrows) (Breslow thickness, 2.2 mm). B, This lesion has a central white patch mimicking a dermatofibroma. A total of 12.9% of amelanotic/hypomelanotic NMs were reported to have central white patches. In this case the ulceration led to a suspicion of malignancy (Breslow thickness, 2.2 mm). C, This small-diameter hypomelanotic (light-colored) nodule has asymmetrical pigmentation with areas of blue-white veil (Breslow thickness, 0.94 mm). D, This hypomelanotic lesion has fine, predominantly linear irregular vessels at the periphery of the nodule (Breslow thickness, 1.87 mm). E, This amelanotic nodule has diffuse hairpin vessels throughout the lesion in a symmetrical pattern (Breslow thickness, 2.0 mm).

ers were assigned to each method, with these scorers having varying degrees of experience with their scoring method. Hence, these results may differ if a larger group of more- or less-experienced scorers is recruited. Nevertheless, all methods tested showed a decrease in absolute sensitivity with pigmented NM compared with nonnodular invasive melanoma.

In conclusion, although there may be a bias in this study toward lesions that were suspicious and hence photographed, most pigmented and hypomelanotic NM lesions had dermoscopy features that allow their diagnosis. In the pigmented variety, the clinician needs to be aware of the small but significant number of lesions that have symmetry of pattern under dermoscopy examination. Hence, when a progressively growing, symmetrically patterned melanocytic nodule is identified, the diagnosis of NM needs to be excluded. Indeed, we believe any nodular lesion that cannot be confidently diagnosed as benign should be excised.

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