Sensitivity, specificity, and diagnostic accuracy of three dermoscopic algorithmic methods in the diagnosis of doubtful melanocytic lesions

The importance of light brown structureless areas in differentiating atypical melanocytic nevi from thin melanomas

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Background: Over the past decade numerous epiluminescence microscopy (ELM) criteria and algorithmic methods have been developed to improve the diagnosis of cutaneous melanocytic lesions.

Objective: Our purpose was to compare the sensitivity, specificity, and diagnostic accuracy of 3 algorithmic methods (pattern analysis, ABCD rule of dermoscopy, and the 7-point checklist) on a series of highly atypical melanocytic lesions. We also determined the diagnostic value of distinct ELM structures by evaluating their frequency in these lesions.

Methods: A total of 198 consecutive atypical macular melanocytic lesions were studied. ELM assessment was based on the presence or absence of 23 dermoscopic features. Two ELM-experienced dermatologists classified each lesion as benign or malignant using the pattern analysis, the ABCD rule of dermoscopy, and the 7-point checklist method. After surgical excision, 102 lesions were histologically diagnosed as Clark's nevi and 96 as thin melanomas (TMs) (mean tumor thickness, 0.3 mm). ELM and histologic diagnoses were then compared to assess the sensitivity, specificity, and diagnostic accuracy as well as positive and negative predictive values (PPV and NPV, respectively) for TMs of the 3 algorithmic methods. Univariate and multivariate analyses were performed to determine which ELM criteria were most strongly associated with TM.

Results: Of the melanocytic lesions studied, 82.3% were correctly diagnosed by using pattern analysis (85.4% sensitivity, 79.4% specificity, 79.6% PPV, and 70.8% diagnostic accuracy), compared with correct diagnosis of 79.3% (84.4% sensitivity, 74.5% specificity, 75.7% PPV, and 67.8% diagnostic accuracy) and 71.2% (78.1% sensitivity, 64.7% specificity, 67.6% PPV, and 57.7% diagnostic accuracy) with the ABCD and the 7-point checklist methods, respectively. The 7-point checklist yielded the highest number of false-negative results (21.8%) with respect to the ABCD rule (15.6%) and pattern analysis (14.6%). Univariate analysis showed that an atypical pigment network, a pigment network with sharp margins, irregular nonuniform brown globules, a nonuniform pigment distribution, homogeneous areas, and light brown structureless areas were the most sensitive and specific ELM features for TM. A backward stepwise logistic regression analysis revealed that the criterion with the strongest TM association was light brown structureless areas (odds ratio = 27.9; 95% confidence interval, 8.6-90.9).

Limitations: The presence and value of light brown structureless areas should also be investigated in clinically nonatypical macular melanocytic lesions.

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Conclusion: The pattern analysis method showed the highest sensitivity, specificity, and diagnostic accuracy for TM. Light brown structureless areas were both a statistically significant discriminator and the most reliable predictor of TM (PPV = 93.8%, positive likelihood ratio = 16). Therefore the use of this previously underestimated ELM criterion may not only improve diagnostic performance of equivocal macular melanocytic lesions but also significantly decrease the rate of false-negative results obtained with the 7-point checklist method. (J Am Acad Dermatol 2007;56:759-67.)

Epiluminescence microscopy (ELM) is an in vivo, noninvasive technique which significantly improves the clinical diagnosis of cutaneous pigmented lesions.[1-5] During the past decade numerous ELM criteria and diagnostic models have been developed to achieve accurate diagnosis of melanocytic lesions.[6-14] Several studies have shown that 3 algorithmic methods (qualitative pattern analysis, the ABCD rule of dermoscopy and the ELM 7-point checklist) are valid and reliable in distinguishing benign and malignant melanocytic neoplasms.[4-8,12,15-19] The pattern analysis is based on a detailed, qualitative assessment of numerous individual ELM criteria and requires a significant degree of formal training.[1,2,6] The ABCD rule of dermoscopy employs a semiquantitative scoring system based on the evaluation of asymmetry, border, color, and different dermoscopic structures in the lesion.[8] More recently, Argenziano et al,[12] analyzing 342 pigmented skin lesions, developed the ELM 7-point checklist method. They identified 3 major criteria and 4 minor criteria. Each major criterion has a score of 2 points, whereas each minor criterion has a score of 1 point. A minimum total score of 3 is required for the diagnosis of melanoma.

Our aim was to compare the sensitivity, specificity, and diagnostic accuracy of these algorithmic methods on a series of 198 difficult melanocytic lesions and to determine the significance of distinct ELM structures in the diagnosis of atypical melanocytic nevi (AMN) and thin melanomas (TM). In particular, we focused our attention on the presence of peripheral light brown structureless areas because it was a feature frequently observed in our routine ELM diagnosis of TM (Fig 1). Since the diagnostic value of light brown structureless areas has largely been overlooked in previous studies, we calculated the frequency of this feature in AMN and TM and assessed its importance in the differential diagnosis of clinically doubtful melanocytic lesions.

Abbreviations used:

AMN:	atypical melanocytic nevi
CI:	confidence interval
ELM:	epiluminescence microscopy
NPV:	negative predictive value
OR:	odds ratio
PPV:	positive predictive value
TM:	thin melanomas

MATERIAL AND METHODS

We selected a series of equivocal melanocytic lesions seen consecutively from December 2004 to June 2006 in the Dermoscopy Unit of our institute. Clinically, all lesions were larger than 5 mm in diameter, with a flat or barely elevated surface and at least 3 of the following features: (a) asymmetry, (b) irregular margins, (c) ill-defined borders, and (d) color variegation. Good-quality clinical and ELM digital images (×25 magnification) were taken of each lesion with a Leica Wild M-650 microscope (Leica AG, Heerbrugg, Switzerland) and DBDERMO MIPS software (Dell'Eva/Burroni Studio, Florence/Siena, Italy). ELM assessment was based on the presence/absence of 23 dermoscopic features according to the working definitions summarized in Table I. Each lesion was diagnosed as benign or malignant by using the 3 different algorithmic methods (pattern analysis, the ABCD rule of dermoscopy, and the ELM 7-point checklist) previously described.[6,8,12,16] Melanocytic lesions with ABCD scores between 4.76 and 5.45 (suspect lesions) were included in the group of melanomas to reduce the number of false-negative results. The presence or absence of ELM criteria in a lesion and all diagnoses from the 3 methods were agreed on by two ELM-experienced dermatologists. After ELM assessment, all lesions were excised and processed for routine histopathologic examination.

Histopathologic study

The light brown structureless areas of 10 melanocytic lesions were selected for ELM/histopathologic correlation. A line was drawn with computer software across each image of the light brown structureless area (Fig 2, *B*). The exact same line was then reproduced with a similar technique on the clinical image of the corresponding lesion (Fig 2, *A*). Both the ELM and clinical images were then printed in color. Immediately after excision, the sides of each specimen were marked with suture stitches to maintain orientation. In the Dermatopathology Laboratory the point of each specimen corresponding to light brown structureless areas was dotted with alcian blue stain and grossly cut following the line drawn on the clinical

and ELM printed images. Finally, step-sectioned blocks were cut at 4 μm with a microtome, and the resulting sections were stained with hematoxylin and eosin.

Statistical analysis

ELM diagnoses were compared with histologic findings to estimate the sensitivity (true positive/[true positive + false positive]), specificity (true negative/[true negative + false positive]), and diagnostic accuracy (true positive/[true positive + false positive + false negative]) of the 3 algorithmic methods. We calculated the overall frequency of occurrence of each ELM criterion, and then determined separately for each criterion: the TM proportion in which a given criterion was present (sensitivity); the AMN proportion in which a given criterion was absent (specificity); the TM proportion among all lesions in which a given criterion was present (positive predictive value, PPV); and the AMN proportion among all lesions in which a given criterion was absent (negative predictive value, NPV). In addition, we calculated the following: the positive likelihood ratio, that is, the ratio sensitivity/(1 − specificity), which indicates how many times a given criterion is more likely to be seen in patients with TM compared with patients with AMN, and the negative likelihood ratio, that is, the ratio (1 − sensitivity)/specificity, which indicates how many times the absence of a given criterion is more likely to be found in patients with TM compared with patients with AMN. We calculated the *P* value from the chi-square test to evaluate the statistical significance of the association between each criterion and TM. Associations with *P* values less than .05 were considered statistically significant.

The ELM criteria that in univariate analysis were most strongly associated with TM were entered as independent variables in a backward stepwise logistic regression analysis to determine which of them remained significantly associated with TM while simultaneously adjusting for all the other criteria included in the regression model. We first considered all the statistically significant associations and then evaluated the co-linearity between these variables. Among the co-linear variables, the one with higher sensitivity and specificity was then included in the initial logistic regression model. The results were expressed as odds ratios (ORs) with 95% confidence interval (95% CI). The SPSS/PC+ version 10.0 statistical package was used in all the statistical analyses.

RESULTS

The study included a total of 198 clinically equivocal melanocytic lesions from the trunk and limbs of 195 patients (89 female and 106 male patients; mean age, 43 years). One hundred two lesions were diagnosed as Clark's melanocytic nevi (68 junctional, 34 compound nevi) and 96 as melanomas on the basis of conventional histopathologic criteria. There were 24 in situ melanomas and 72 superficial spreading melanomas (52 with a Breslow index <0.4 mm and 20 with a Breslow index of 0.4-0.6 mm), with a mean tumor thickness of 0.3 mm. A total of 163 of 198 melanocytic lesions were correctly diagnosed by pattern analysis (82.3%), compared with 157 of 198 (79.3%) and 141 of 198 (71.2%) with the ABCD and 7-point checklist methods, respectively. Table II shows that the ABCD rule revealed a greater sensitivity (84.4% vs 78.1%), specificity (74.5% vs 64.7%), diagnostic accuracy (67.8% vs 57.7%), and PPV (75.7% vs 67.6%) for TM compared with the 7-point checklist. With respect to pattern analysis, the ABCD rule displayed a similar sensitivity (84.4% vs 85.4%) and a lower specificity (74.5% vs 79.4%), diagnostic accuracy (67.8% vs 70.8%), and PPV (75.7% vs

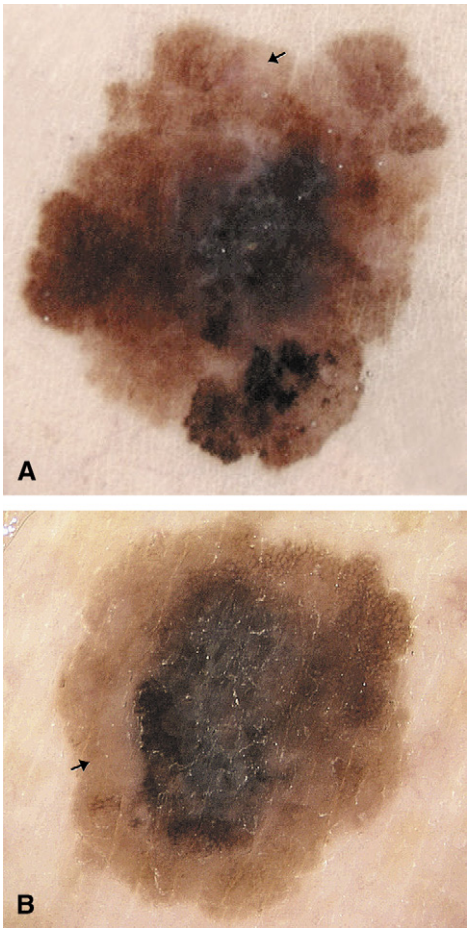

Fig 1. **A** and **B**, Light brown structureless areas appear as irregular areas of light brown to fawn-colored pigmentation (*arrows*) at periphery of TM.

Table I. Working definitions of ELM criteria

Criterion	Definition
Pigment network	Grid of brown to dark brown lines over a diffuse, light brown background
Thin or delicate	Thickness of grid lines similar to that observed in normal, well-tanned skin
Broad or prominent	Grid lines appear hyperpigmented (darker lines compared with average line darkness within the lesion) and thickened (broader lines compared with average line broadness within the lesion
Regular and thin	Pigment network with relatively uniform thin lines delimiting uniform-sized circular or oval meshes
Irregular and thin	Pigment network with thin lines of relatively uniform thickness delimiting variably sized and shaped meshes
Irregular and broad (atypical)	Pigment network with hyperpigmented and thickened lines delimiting variably sized and shaped meshes
Sharp margin	Focal abrupt transition (ie, high contrast) in pigmentation between network margin and surrounding normal skin
Fading margin	Pigment network fades away into surrounding normal skin
Brown dots and globules	Round to oval, well-circumscribed light to dark brown pigment aggregations that are distinguished by their size (globule: a large dot)
Uniform	Relatively symmetrical distribution of brown dots and/or globules within a lesion
Nonuniform	Relatively asymmetrical distribution of brown dots and/or globules within a lesion
Regular and uniform	Brown dots and/or globules relatively similar in size and shape distributed symmetrically within a lesion
Regular and nonuniform	Brown dots and/or globules relatively similar in size and shape distributed asymmetrically within a lesion
Irregular and uniform	Brown dots and/or globules different in size and shape distributed symmetrically within a lesion
Irregular and nonuniform	Brown dots and/or globules different in size and shape distributed asymmetrically within a lesion
Black dots	Punctiform black structures
Uniform	Relatively symmetrical distribution of black dots within a lesion
Nonuniform	Asymmetrical distribution of black dots within a lesion
Radial streaming and pseudopods	
Radial streaming	Nearly parallel, radially oriented linear brown to black structures at the periphery of a lesion
Pseudopods	Bulbous and often kinked brown to black projections that are directly connected to the tumor body or to the pigment network at the edge of a lesion
Uniform radial streaming and pseudopods	Symmetrical distribution of streaks and pseudopods at the periphery of a lesion
Nonuniform radial streaming and pseudopods	Asymmetrical distribution of streaks and pseudopods at the periphery of a lesion
Pigment distribution	
Uniform	Symmetrical pigment distribution within a lesion
Nonuniform	Asymmetrical pigment distribution within a lesion
Structureless light brown areas	Structureless light brown to fawn-colored, peripherally arranged areas of variable size and shape, which are larger than 10% of a lesion. The structureless areas tend to end abruptly at the edge of a lesion
Homogeneous areas (blotches, irregular extensions, irregular diffuse pigmentation	Dark brown or black areas of diffuse pigmentation with irregular shape and abrupt margins
Gray-blue areas	Irregular, confluent areas of diffuse gray-blue pigmentation
Regression pattern	This term includes one or all of the following structures:
White scar-like areas	Irregular and confluent areas of white depigmentation
Blue-gray pepperlike areas	Speckled, multiple, blue-gray dots within a hypo-depigmented area
Whitish veil	White haze or veil over a region of a lesion. It may be uniform or diffuse or may be focally variable and irregular
Atypical vascular pattern	Linear dotted or globular red structures irregularly distributed outside areas of regression and associated with other melanocytic pigment patterns

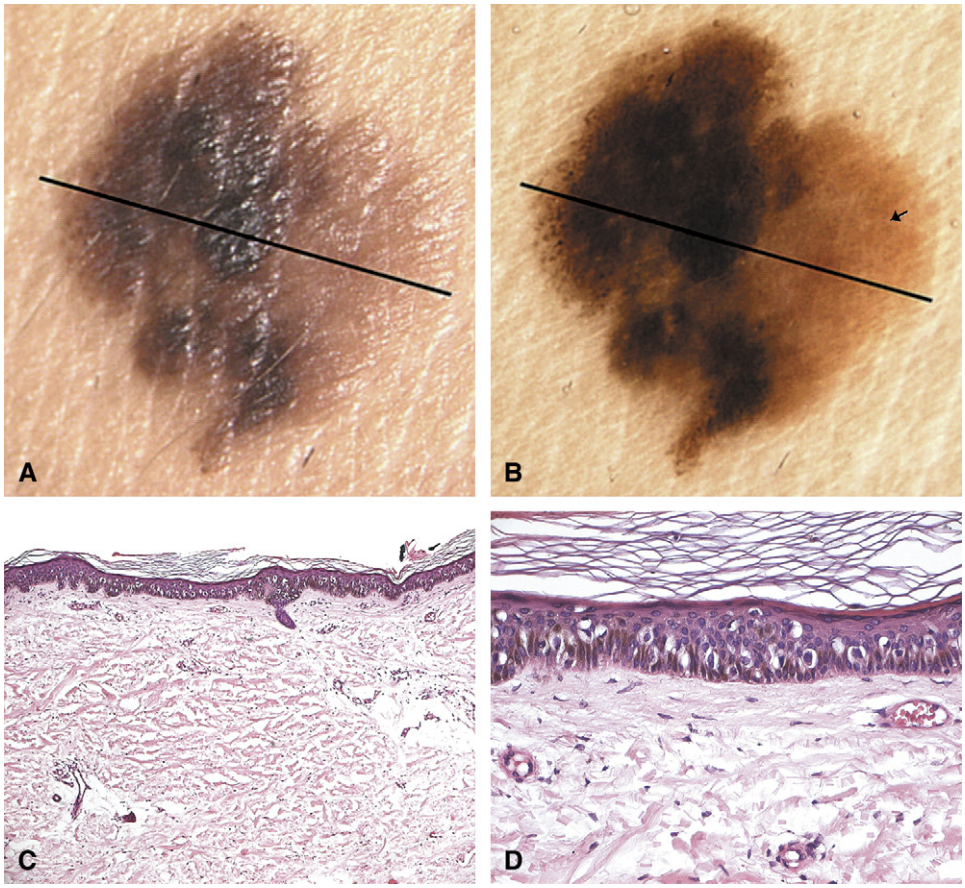

Fig 2. A, Clinical image of a thin melanoma selected for ELM-histopathologic correlation. **B**, Thin melanoma shows light brown structureless areas (*arrow*) on ELM examination. A line has been drawn across the light brown structureless area with computer software. **C** and **D**, Histologically, light brown structureless areas are characterized by flattening of rete ridges and marked scattering of atypical melanocytes in upper epidermal layers in the absence of significant dermal changes. (**C** and **D**, Hematoxylin-eosin stain; original magnifications: **C**, ×32; **D**, ×200.)

79.6%). The 7-point checklist method produced a higher number of false-negative results (21/96, 21.8%) compared with the ABCD rule (15/96, 15.6%) and pattern analysis (14/96, 14.6%). Only 9 histologically proven TM were concordantly classified as melanocytic nevi by all 3 ELM methods.

Univariate analysis (Table III) showed that an irregular pigment network, either thin or prominent, was highly sensitive (88.6%) and moderately specific (59.8%) for TM. Similarly, an atypical pigment network had 77.1% sensitivity and 64.7% specificity. Although a nonuniform pigment distribution was present in 94 TM (97.9%), it was also an ELM feature of 61 AMN (59.8%). The presence of homogeneous areas (blotches), nonuniform irregular globules, a regression pattern and a pigment network with sharp margins were highly specific but scarcely sensitive for TM. Indeed, homogeneous areas were detected in only 12 of 102 AMN (88.2% specificity) and in 36 TM (37.5% sensitivity), whereas nonuniform irregular globules were found in 10 AMN (90.2% specificity) and in 38 TM (39.6% sensitivity). In addition, 11 AMN and 40 TM disclosed a regression pattern (89.2% specificity, 41.7% sensitivity), whereas pigment network with sharp margins had specificity of 81.4% and sensitivity of 51%. Although other ELM criteria, such as nonuniform radial streaming/pseudopods, gray-blue areas, a whitish veil, and an atypical vascular pattern, revealed 94% to 96% specificity, their sensitivity range was only 9.4% to 22.9%. Light brown structureless areas were seen in 60 of 96 TM and in 4 of 102 AMN, with corresponding sensitivity of 62.5% and specificity of 96.1%. The PPV (94%) and the positive likelihood ratio (16) for the light brown structureless areas feature were also extremely high. The backward stepwise logistic regression analysis retained only 5 ELM structures in the final model: light brown structureless areas, OR = 27.9 (95% CI 8.6-90.9);

Table II. Statistical analysis of the methods for ELM diagnosis of melanoma*

Method	SN	SP	PPV	NPV	Diagnostic accuracy	False positive	False negative
Pattern analysis	85.4	79.4	79.6	85.3	70.8	20.6	14.6
ABCD rule of dermoscopy	84.4	74.5	75.7	83.5	67.8	24.5	15.6
7-point checklist	78.1	64.7	67.6	75.9	57.7	35.3	21.8

NPV, Negative predictive value; *PPV*, positive predictive value; *SN*, sensitivity; *SP*, specificity.
*Data expressed as percentages.

Table III. Statistical analysis of ELM features in 198 doubtful melanocytic lesions

ELM criterion	Frequency % (No.)	SN, %	SP, %	PPV, %	NPV, %	+LR	−LR	*P* value*
Regular, thin pigment network	54.0 (107)	40.6	33.3	36.4	37.4	0.6	1.8	<.001
Regular, broad pigment network	6.1 (12)	3.1	91.2	25.0	50.0	0.4	1.1	.136
Irregular, thin pigment network	8.1 (16)	11.5	95.1	68.8	53.3	2.3	0.9	.119
Atypical pigment network	55.6 (110)	77.1	64.7	67.3	75.0	2.2	0.4	<.001
Irregular pigment network	63.7 (126)	88.6	59.8	67.4	84.7	2.2	0.2	<.001
Sharp margin of pigment network	34.3 (68)	51.0	81.4	72.1	63.8	2.7	0.6	<.001
Fading margins of pigment network	65.7 (130)	49.0	18.6	36.2	27.9	0.6	2.7	<.001
Atypical pigment network + sharp margins	27.3 (54)	43.8	88.2	77.8	62.5	3.7	0.6	<.001
Regular, uniform brown globules	20.2 (40)	6.3	66.7	15.0	43.0	0.2	1.4	<.001
Regular, nonuniform brown globules	35.4 (70)	40.6	69.6	55.7	55.5	1.3	0.9	.140
Irregular, uniform brown globules	3.0 (6)	2.1	96.1	33.3	51.0	0.5	1.0	.684
Irregular, nonuniform brown globules	24.2 (48)	39.6	90.2	79.2	61.3	4.0	0.7	<.001
Uniform black dots	14.1 (28)	3.1	75.5	10.7	45.3	0.1	1.3	<.001
Nonuniform black dots	44.9 (89)	56.3	65.7	60.7	61.5	1.6	0.7	.003
Uniform radial streaming/pseudopods	0.5 (1)	—	99.0	—	51.3	0	1.0	1.000
Nonuniform radial streaming/pseudopods	8.6 (17)	13.5	96.1	76.5	54.1	3.5	0.9	.021
Uniform pigment distribution	21.7 (43)	2.1	59.8	4.7	39.4	0.1	1.6	<.001
Nonuniform pigment distribution	78.3 (155)	97.9	40.2	60.6	95.3	1.6	0.1	<.001
Homogeneous areas (blotches)	24.2 (48)	37.5	88.2	70.0	60.0	3.2	0.7	<.001
Light brown structureless areas	32.3 (64)	62.5	96.1	93.8	73.1	16.0	0.4	<.001
Regression pattern	25.7 (51)	41.7	89.2	78.4	61.9	3.9	0.7	<.001
Gray-blue areas	13.6 (27)	22.9	95.1	81.5	56.4	4.7	0.8	<.001
Whitish veil	11.1 (22)	16.7	94.1	72.7	54.5	2.8	0.9	.016
Atypical vascular pattern	6.6 (13)	9.4	96.1	69.2	53.0	2.4	0.9	.122

+LR, Positive likelihood ratio; *−LR*, negative likelihood ratio; *NPV*, negative predictive value; *PPV*, positive predictive value; *SN*, sensitivity; *SP*, specificity.
**P* value derived from the chi-square test.

nonuniform pigment distribution, OR = 11.6 (95% CI 2.2-60.5); a regression pattern, OR = 7.8 (95% CI 2.9-21.0); irregular nonuniform brown globules, OR = 3.2 (95% CI 1.1-8.8); pigment network with sharp margins, OR = 2.5 (95% CI 0.99-6.4).

All the light brown structureless areas examined histologically were from TM. Histologic sections showed an irregular epidermal profile with partial or complete flattening of the rete ridges. Atypical melanocytes arranged as solitary units predominated overwhelmingly over atypical melanocytes arranged in small and ill-defined nests at the dermoepidermal junction. A marked scattering of single atypical melanocytes in the spinous layer was characteristically observed in all cases (Fig 2, *C* and *D*). Both the intraepidermal melanocytes and surrounding keratinocytes contained a scarce to moderate amount of melanin, and occasional melanophages were detected in the papillary dermis.

DISCUSSION

The differentiation between AMN and TM is often a considerable challenge for the clinician. Several studies have shown that ELM improves the ability to distinguish between benign and malignant melanocytic lesions, thereby assisting an early diagnosis of melanoma.[1-5,15] In this study we have estimated the sensitivity, specificity, and diagnostic accuracy of 3 algorithmic methods (pattern analysis, the ABCD rule of dermoscopy, and 7-point checklist) on a

series of 198 melanocytic lesions with highly suspect clinical features of melanoma. A comparison between ELM and histologic diagnoses revealed that pattern analysis was the most sensitive (85.4%) and specific (79.4%) method for identifying TM. The pattern analysis also showed the highest diagnostic accuracy (70.8%) and PPV (79.6%). In practice, this means that when a clinically atypical, macular melanocytic lesion was classified as a thin melanoma by this algorithm, in 4 out of 5 times, the diagnosis was histologically confirmed. Conversely, the 7-point checklist yielded the lowest values of sensitivity (78.1%), specificity (64.7%), diagnostic accuracy (57.7%), and PPV (67.6%). Low specificity suggests that, even in the hands of experienced observers, the 7-point checklist scoring method tends to overclassify AMN as TM, with 35.3% false-positive results. Although slightly inferior to pattern analysis, the ABCD rule proved to be a simple and reliable method for recognizing TM, with 84.4% sensitivity, 74.5% specificity, and 67.8% diagnostic accuracy. In addition, the rate of false-negative results was higher with the 7-point checklist (21.8%) compared with the ABCD rule (15.6%) and pattern analysis (14.6%). In general, the sensitivity and specificity values we obtained with the 3 methods were substantially lower than those reported by previous studies. Indeed, Nachbar et al[16] found that the ABCD rule had a sensitivity of 92.8% and a specificity of 91.2%, whereas Argenziano et al[12] detected an overall sensitivity of 95% and 75% specificity using the 7-point checklist compared with 91% sensitivity and 90% specificity with the pattern analysis. The discrepancies between previous studies and ours could be partly attributed to the differences in the selection criteria including the clinical features of the melanocytic lesions and the type, site, and thickness of the melanomas. For instance, Argenziano et al extracted their data from 117 melanomas with a mean thickness of 0.9 mm and 225 melanocytic nevi regarded as atypical by clinicians. They, however, did not provide the criteria used by clinicians to classify the nevi as atypical. In this study, we were interested in testing the diagnostic validity of the 3 methods on a series of melanocytic lesions, which were extremely difficult to diagnose on a clinical basis. Therefore we only selected melanocytic lesions with a diameter greater than 5 mm, with a flat or barely elevated surface and with at least 3 of the following features: asymmetry, an irregular margin, ill-defined border, and color variegation. Thus each lesion fulfilled at least 3 of the ABCD criteria for melanoma, and 96 of 198 were subsequently confirmed as TM with histologic study (mean thickness, 0.3 mm). Furthermore, our use of digital images could have influenced the interpretation of ELM criteria, thereby leading to different results. Anyway, our findings indicate that although all 3 algorithmic methods are valid and reliable in the diagnosis of doubtful melanocytic lesions, their sensitivity, specificity, and diagnostic accuracy tend to decrease when used to differentiate highly atypical macular melanocytic nevi from TM.

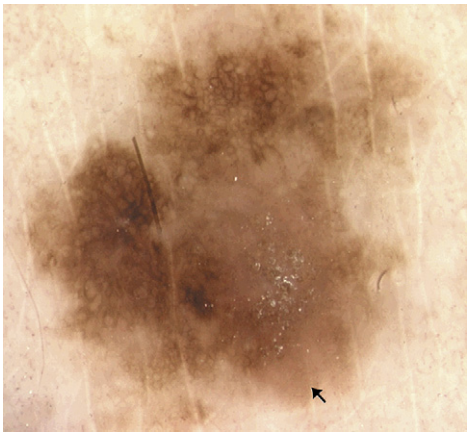

Fig 3. Thin melanoma with a false-negative diagnosis determined by ABCD (score 4.7) and 7-point checklist (score 2) methods. If light brown structureless areas (*arrow*) had been considered a minor criterion, this lesion would have been correctly diagnosed as a melanoma with the 7-point checklist method (score 3).

Univariate analysis disclosed that 4 ELM criteria (a pigment network with sharp margins, homogeneous areas, a regression pattern, and nonuniform irregular globules) were highly specific (specificity range, 81.4%-90.2%) and significant predictors of TM. Indeed, a macular, atypical melanocytic lesion with just one of these features was likely to be a thin melanoma (positive likelihood ratio range, 2.7-4.0). Although gray-blue areas, nonuniform radial streaming/pseudopods, a whitish veil, and an atypical vascular pattern proved to be the most specific criteria (95.1%, 95.1%, 94.1%, and 96.1%, respectively), they were infrequently seen in TM (sensitivity range, 9.4%-22.9%). Nevertheless, the high specificity of these features indicates that the presence of any one of them should raise the clinician's suspicion for TM. A nonuniform pigment distribution showed the highest sensitivity (97.9%) and NPV (95.3%), which means that only less than 5% of TM were not expected to have this feature. Other statistically significant sensitive criteria were an irregular pigment network (88.6%, $P < .001$) and an atypical pigment network (77.1%, $P < .001$). In particular, when an atypical, macular melanocytic lesion with one of these two features was designated as a thin melanoma, such diagnosis was confirmed

histologically in approximately 67% of cases. This proportion increased to 77.8% when an atypical pigment network and a pigment network with sharp margins were contemporaneously present in a lesion. In fact, the association of these two criteria resulted as highly specific (88.2%), although it was uncommon in TM (43.8%). We also found that a regular and thin pigment network and the presence and distribution of black dots were unhelpful in identification of TM since they were similarly detected in both benign and malignant lesions.

Several ELM studies have emphasized the importance of dark brown or black homogeneous areas (blotches, irregular extensions, irregular diffuse pigmentation) in the diagnosis of melanoma.[4,5,7,20,21-24] Accordingly, this feature has been included among the different structures (score 0.5) and the minor criteria (score 1) of the ABCD and 7-point scored diagnoses, respectively.[8,12,16] To our knowledge, however, no study has emphasized the presence or examined the relevance of light brown structureless areas in atypical melanocytic lesions. We observed light brown structureless areas in 62.5% of TM and in only 4 of 102 AMN (specificity 96.1%) and consequently found it to be both a statistically significant discriminator and one of the most reliable predictors of TM. In fact, about 94 of 100 clinically atypical melanocytic lesions with this feature were then diagnosed histologically as TM with a 93.8% PPV; in addition, a lesion with light brown structureless areas was 16 times more likely to be a thin melanoma than an atypical melanocytic nevus (positive likelihood ratio = 16). It is worth noting that the backward stepwise logistic regression analysis retained in the final model only 5 variables (ie, light brown structureless areas, nonuniform pigment distribution, a regression pattern, irregular nonuniform brown globules, and a pigment network with sharp margins). In particular, pigmented lesions with light brown structureless areas had an almost 30-fold risk of being TM compared with lesions without light brown structureless areas, when simultaneously controlling for all the other criteria associated with TM in univariate analysis. Histologically, light brown structureless areas were characterized by partial or complete flattening of the rete ridges, an increased number of poorly pigmented atypical melanocytes mostly arranged as single units at the dermoepidermal junction and a diffuse scattering of melanocytes in the spinous layer of the epidermis in the absence of significant dermal changes. The disappearance of the rete ridges and the scarcity of intraepidermal melanin may explain the lack of an evident pigmented network and the light brown diffuse pigmentation of these areas on ELM examination. Similarly, even in the cases of partial flattening of the rete ridges, the marked spreading of melanocytes in the spinous layer of the suprapapillary epidermis may contribute to blur the pigmented network and to produce a structureless light brown pigmentation. It is common knowledge that a marked scattering of melanocytes in the upper epidermal layers is never a feature of Clark's melanocytic nevi.[25,26] In addition, histologic flattening of the epidermal profile at the periphery of a clinically macular melanocytic nevus is usually observed only in regression areas of Clark's nevi.[25] In those regions, however, we would expect to see a regression pattern instead of light brown structureless areas on ELM examination.[27,28]

On the whole, these considerations may explain why we found light brown structureless areas in a very low number of AMN and at the same time the high specificity of this feature for TM. Interestingly, if the light brown structureless areas had been considered a minor criterion for the 7-point checklist in our series, the sensitivity of this method would have changed from 78% to 95.8%, and the rate of false-negative results would have been reduced from 21.8% to 4.1%. Furthermore, 7 of 9 TM classified as melanocytic nevi by all 3 algorithms could have been diagnosed correctly with the 7-point checklist method if the presence of light brown structureless areas had been considered (Fig 3).

Hence our results suggest that the presence of light brown structureless areas in clinically atypical macular melanocytic lesions may be very useful in differentiating AMN from TM. The use of this criterion may not only improve diagnostic performance but also decrease significantly the rate of false-negative results obtained with the 7-point checklist scoring method.

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