Dermoscopic Features of Difficult Melanoma

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BACKGROUND The dermoscopic diagnosis of cutaneous melanoma (CM) may be difficult because some CM lack specific dermoscopic features for melanoma diagnosis.

OBJECTIVE To evaluate whether a diagnosis of CM could be achieved using the classic dermoscopic melanoma-specific criteria, we conducted a retrospective multicenter study of 508 CM samples.

METHODS All the dermoscopic images were analyzed to identify the dermoscopic criteria found in dermoscopically difficult melanomas (DDM) and to examine the possible relation of dermoscopic diagnosis with respect to the difficulty of the dermoscopic diagnosis and the melanoma thickness.

RESULTS A significant percentage of melanomas, 89 of 508 (17.5%), were DDM. The criteria leading to a significant increased risk of DDM were presence of streaks [odds ratio (OR), 2.26; 95% confidence interval (CI), 1.15–4.47), absence or presence of regular pigmentation (OR, 3.41; 95% CI, 1.70–6.85), absence of a blue-whitish veil (OR, 4.04; 95% CI, 2.33–6.99), absence of regression structures (OR, 4.31; 95% CI, 2.42–7.66), and the presence of hypopigmentation (OR, 2.61; 95% CI, 1.49–4.58).

CONCLUSION A significant number of melanomas defy even dermoscopic diagnosis. Only a meticulous comparative and interactive process based on an assessment of all the individual's other nevi (''ugly ducking'' sign) and a knowledge about recent changes can lead to the recognition of DDM.

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The primary goal of melanoma detection is early tumor recognition and subsequent surgical treatment. The "ABCD" method for detecting cutaneous melanoma (CM) has been a useful tool in distinguishing benign lesions from melanoma.[1,2] The clinical diagnosis of CM may be difficult, however, because some melanomas lack all or most of the features of the "ABCD" rule.[3,4] In fact, some authors have identified a subset of melanomas of unusual appearance, clinically indistinguishable from other pigmented and nonpigmented cutaneous lesions, that escape clinical recognition.[3–5] The most common clinical diagnoses of these histopathologically confirmed melanomas were nevus, basal cell carcinoma, seborrheic keratosis, and lentigo, whereas the less common diagnoses included Bowen's disease, verruca vulgaris, dermatofibroma, pyogenic granuloma, and hemangioma.[3,4] On the other hand, atypical nevi, although not malignant, may display one or more of the "ABCD" criteria and so, in some cases, the distinction between benign and malignant melanocytic proliferations may be difficult or even impossible clinically.[6]

Dermoscopy (dermatoscopy, epiluminescence microscopy, incident light microscopy, or surface microscopy) is a noninvasive technique that has been introduced as an additional measure to increase the

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accuracy in diagnosing pigmented skin lesions and to improve the sensitivity and specificity for diagnosing CM.[7–9] Some authors, however, have demonstrated the limitations of dermoscopy in the detection of early melanomas that present an uncharacteristic dermoscopic appearance.[10,11] Some melanomas, the so-called "featureless melanomas," may lack specific dermoscopic features for melanoma diagnosis and dermoscopically may even appear as benign melanocytic lesions ("nevus-like" melanomas) or as atypical nevi, so that the diagnosis is impossible to make on dermoscopic grounds alone.[10,12]

In this retrospective study, 508 CM samples were analyzed dermoscopically by pattern analysis to evaluate whether a diagnosis of CM could be achieved using the classic dermoscopic melanoma-specific criteria.

Materials and Methods

Between January 1994 and December 2002, the dermoscopic images of all CM seen at the three participating Italian centers (Istituto Dermopatico dell'Immacolata, IDI, Rome; Skin Cancer Unit, Ravenna/Niguarda Hospital, Milan; and the Department of Medical Oncology C–Oncologic Prevention–Centro di Riferimento Oncologico, Aviano) were included in the study. The sample of this multicenter retrospective study consisted of 508 dermoscopic images of CM, 438 of which were taken with a digital stereomicroscope and 70 with a Dermaphot camera (Heine Optotechnik, Herrsching, Germany; 10 × magnification) and then digitalized with the Kodak PhotoCD system (Eastman Kodak, East Rochester, NY). The digital stereomicroscope system consisted of a stereomicroscope and a Sony 3CCD DXC-930P color video camera (Sony, San Diego, CA), producing digital images at a magnification of 10 × to 20 ×. The dermoscopic images of CM were evaluated using structured questionnaires investigating certain clinical characteristics such as age, sex, site, previous melanoma, melanoma thickness, and dermoscopic criteria to achieve a dermoscopic diagnosis.

Dermoscopic Analysis

The following dermoscopic criteria, which reportedly are associated with melanoma, were used for the evaluation of the 508 CM: pigment network, pigmentation, streaks, dots/globules, blue-whitish veil, regression structures, hypopigmentation, and vascular patterns.[13] For the final dermoscopic diagnosis, we used the classical diagnostic approach for the dermoscopic diagnosis of pigmented skin lesions known as "pattern analysis," which is based on the simultaneous and subjective assessment of the dermoscopic criteria.[14]

The 508 melanomas were then categorized into two groups on the basis of the difficulty of the dermoscopic diagnosis: dermoscopically difficult melanomas (DDM) and dermoscopically nondifficult melanomas (DNDM). The melanomas that were considered difficult to diagnose were those that presented dermoscopic patterns indistinguishable from those of common and atypical nevi. All dermoscopic images were analyzed to identify the dermoscopic criteria found within the group of DDM and to examine the possible relation of dermoscopic diagnosis with respect to the difficulty of the dermoscopic diagnosis (DDM vs. DNDM) and melanoma thickness. All cases were evaluated by a panel of three observers to decide which melanomas were truly difficult on dermoscopic evaluation. The evaluation of the dermoscopic criteria and the definite diagnosis of DDM or DNDM was made when three of three or two of three observers agreed.

Statistical Analysis

Using the unconditional logistic regression models, the odds ratio (OR), and their corresponding 95% confidence intervals (CI) were computed for DDM by clinical characteristics, histopathologic diagnosis, and dermoscopic criteria. Variables that resulted significant in the univariate analysis were computed using the multivariate model.[15] In addition, the chi-square or Fisher exact test was used to evaluate any differences in the qualitative variables. Results were

considered to be statistically significant when p values were not greater than 0.05 (two-sided).

To verify the validity of the histopathologic diagnosis, a sample of 28 (1/3) dermoscopic slides, stratified by center, were randomly selected from 89 DDMs. Three independent dermopathologists (HPS, LC, CM) reviewed the slides separately. Interobserver agreement was evaluated by the κ index. A κ value ≤ 0.20 was considered unsatisfactory, values between 0.21 and 0.40 poor, values between 0.41 and 0.60 fair, values between 0.61 and 0.80 good, and values greater than 0.80 excellent agreement.[16]

Results

Study Population

A total of 508 CM of 494 patients were included in the study (221 men and 273 women; mean age, 51.5 ± 16.5 years). Fourteen patients presented two or more melanomas. The distribution of the sites of the CM was trunk/abdomen (274 cases), lower limb (169 cases), and upper limb (65 cases). The series included 89 cases of DDM and 419 cases of DNDM. Histopathologically, the 89 DDM consisted of 38 in situ melanomas (42.7%), 49 melanomas ≤ 1 mm (55.1%) and 2 melanomas >1 mm (2.2%). The 419 cases of DNDM consisted of 59 cases of in situ melanoma (14.1%), 245 cases of melanoma ≤ 1 mm (58.5%), and 115 cases of melanoma >1 mm (27.4%).

Clinical and Dermoscopic Characteristics

Table 1 shows the univariate and multivariate analysis of the relevant clinical characteristics and of the histopathologic diagnosis of DDM versus DNDM. Univariate analysis was used to identify the relevant factors in determining DDM. The multivariate analysis was used to estimate the independent effect of each factor which had a significant result in the univariate analysis. The multivariate analysis showed that sex and melanoma thickness carried a significant independent prognostic factor for DDM. In particular, female prevalence was significantly higher than male prevalence (70.8% vs. 51.6%, respectively) in the group of DDM with respect to the DNDM control group (OR, 1.87; 95% CI, 1.10–3.19). With regard to melanoma thickness, when compared with melanoma >1 mm, the risk of DDM increased with the reduction in the thickness of the melanoma: the ORs were 10.12 (95% CI, 2.40–42.55) for melanoma ≤ 1 mm and 30.82 (95% CI, 7.11–133.62) for melanoma in situ.

Table 2 shows the univariate and multivariate analysis of the dermoscopic criteria according to DDM or DNDM. The multivariate analysis showed that streaks, pigmentation, blue-whitish veil, regression structures, and hypopigmentation were significantly independent prognostic factors for DDM. The presence of streaks was 83.1% in the DDM group and 63.2% in the negative DNDM group and leads to an increased risk of DDM (OR, 2.26; 95% CI, 1.15–4.47). Moreover, significant risks of DDM were also found when the lesion was characterized by the absence or presence of regular pigmentation (OR, 3.41; 95% CI, 1.70–6.85), the absence of a blue-whitish veil (OR, 4.04; 95% CI, 2.33–6.99), the absence of regression structures (OR, 4.31; 95% CI, 2.42–7.66), and the presence of hypopigmentation (OR, 2.61; 95% CI, 1.49–4.58).

The distribution of DDM and melanoma thickness by dermoscopic diagnosis (i.e., benign nevus, atypical nevus, and melanoma) is summarized in Table 3. Among the 508 cases of melanoma, 89 (17.5%) were DDM whereas 11 cases (12.4%) were diagnosed as common nevi and 78 cases (87.6%) as atypical nevi.

Among the 117 melanomas ≥ 1 mm thick, only 2 cases (1.7%) were diagnosed as atypical nevi. Among the 294 melanomas <1 mm thick, however, 41 cases (14%) were diagnosed as atypical nevus and 8 cases (2.7%) as common nevus. The higher percentage of diagnosis for nonmelanoma concerned the melanoma in situ. In fact, among the 97 cases, 3

TABLE 1. Univariate and Multivariate Analysis of Relevant Clinical Characteristics and Melanoma Thickness of 508 Cases of Melanoma According to the Intrinsic Difficulty of Dermoscopic Diagnosis (DDM vs. DNDM)*

	No. (%)		*OR (95% CI)*†	
	DDM (n = 89)	*DNDM (n = 419)*	*Univariate*	*Multivariate*‡
Age (years)				
≥ 60	20 (22.5)	146 (34.8)	1§	1§
50–59	16 (18.0)	87 (20.8)	1.34 (0.66–2.73)	1.12 (0.52–2.39)
40–49	19 (21.3)	78 (18.6)	1.78 (0.90–3.53)	1.57 (0.75–3.29)
< 40	34 (38.2)	108 (25.8)	2.30 (1.25–4.21)	1.71 (0.88–3.30)
χ^2_1 trend; *p* value			7.89; 0.005	3.06; 0.08
Sex				
Male	26 (29.2)	202 (48.2)	1§	1§
Female	63 (70.8)	216 (51.6)	2.28 (1.39–3.74)	1.87 (1.10–3.19)
Unknown	—	1 (0.2)		
χ^2_1; *p* value			10.60; 0.001	5.28; 0.02
Site				
Trunk/abdomen	44 (49.4)	230 (54.9)	1§	
Lower limbs	36 (40.5)	133 (31.7)	1.42 (0.87–2.31)	
Upper limbs	9 (10.1)	56 (13.4)	0.84 (0.39–1.82)	
χ^2_2; *p* value			2.68; 0.26	
Previous melanoma				
No	61 (68.5)	356 (85.0)	1§	1§
Yes	28 (31.5)	63 (15.0)	2.59 (1.54–4.37)	1.63 (0.92–2.89)
χ^2_1; *p* value			12.83; < 0.001	2.78; 0.10
Melanoma thickness				
> 1 mm	2 (2.2)	115 (27.4)	1§	1§
≤ 1 mm	49 (55.1)	245 (58.5)	11.50 (2.74–48.11)	10.12 (2.40–42.55)
Melanoma in situ	38 (42.7)	59 (14.1)	37.03 (8.63–158.84)	30.82 (7.11–133.62)
χ^2_1 trend; *p* value			45.72; < 0.001	38.22; < 0.001

*Dermoscopically difficult melanomas (DDM) and dermoscopically nondifficult melanomas (DNDM).
†Odds ratio (OR) and 95% confidence interval (CI).
‡Unconditional logistic regression including all significant terms in the univariate analysis.
§Reference category.
DDM, dermoscopically difficult melanomas; DNDM, dermoscopically nondifficult melanomas.

(3.1%) were diagnosed as benign nevi, 34 (35.0%) as atypical nevi, and only 60 (61.9%) as melanomas.

In addition, we verified the validity of the histopathologic diagnosis by reviewing 28 cases, randomly selected among the 89 DDM, on the part of three independent dermopathologists. We found a good level of agreement among the three dermopathologists, with a median value of $\kappa = 0.75$ (range, 0.63–0.92). Nonetheless, one-fourth (26%) of the reevaluated melanomas were interpreted as atypical nevi by these three independent observers. The percentage of diagnosis for nonmelanoma ranged from 18% to 32% (Table 4).

Discussion

Based on our results, a significant percentage, 89 of 508 (17.5%), of melanomas were difficult to diagnose dermoscopically. Almost all cases of DDM were early melanomas, 38 of 89 (42.7%) were melanoma in situ, and 49 of 89 (55.1%) were melanomas with a thickness ≤ 1 mm, whereas only 2 cases (2.2%) had a thickness ≥ 1 mm. These data are similar to those reported by Skvara and coworkers[11] on 63 cases of melanoma presenting uncharacteristic dermoscopic features, where 31 of the 63 melanomas (49.2%) were in situ melanomas and only one had a thickness > 1 mm.[11] The identification of some early

TABLE 2. Univariate and Multivariate Analysis of Dermoscopic Criteria of 508 Cases of Melanoma According to the Intrinsic Difficulty of the Dermoscopic Diagnosis (DDM vs. DNDM)*

	No. (%)		*OR (95% CI)*‡	
	DDM (n = 89)	*DNDM (n = 419)*	*Univariate*	*Multivariate*‡
Pigment network				
Absent/typical	41 (46.1)	201 (48.0)	1§	
Atypical	48 (53.9)	218 (52.0)	1.07 (0.68–1.71)	
χ^2_1; *p* value			0.11; 0.74	
Streaks				
Absent	15 (16.9)	154 (36.8)	1§	1§
Present	74 (83.1)	265 (63.2)	2.87 (1.59–5.17)	2.26 (1.15–4.47)
χ^2_1; *p* value			12.26; <0.001	5.55; 0.02
Pigmentation				
Irregular	63 (71.8)	380 (90.7)	1§	1§
Absent/regular	26 (29.2)	39 (9.3)	4.02 (2.29–7.06)	3.41 (1.70–6.85)
χ^2_1; *p* value			23.44; <0.001	11.93; <0.001
Irregular globules/dots				
Present	67 (75.3)	375 (89.5)	1§	1§
Absent	22 (24.7)	44 (10.5)	2.80 (1.58–4.97)	1.00 (0.49–2.03)
χ^2_1; *p* value			12.35; <0.001	0.00; 0.99
Blue-whitish veil				
Present	28 (31.5)	277 (66.1)	1§	1§
Absent	61 (68.5)	142 (33.9)	4.25 (2.60–6.94)	4.04 (2.33–6.99)
χ^2_1; *p* value			33.35; <0.001	24.70; <0.001
Regression structures				
Present	24 (27.0)	275 (65.6)	1§	1§
Absent	65 (73.0)	144 (34.4)	5.17 (3.11–8.61)	4.31 (2.42–7.66)
χ^2_1; *p* value			39.92; <0.001	24.73; <0.001
Hypopigmentation				
Absent	53 (59.6)	318 (75.9)	1§	1§
Present	36 (40.4)	101 (24.1)	2.14 (1.33–3.45)	2.61 (1.49–4.58)
χ^2_1; *p* value			9.68; 0.002	11.22; <0.001
Vascular patterns				
Absent/typical	10 (11.2)	81 (19.3)	1§	
Atypical	79 (88.8)	338 (80.7)	1.89 (0.94–3.82)	
χ^2_1; *p* value			3.18; 0.07	

*Dermoscopically difficult melanomas (DDM) and dermoscopically nondifficult melanomas (DNDM).
†Odds ratio (OR) and 95% confidence interval (CI).
‡Unconditional logistic regression including all significant terms in the univariate analysis.
§Reference category.
DDM, dermoscopically difficult melanomas; DNDM, dermoscopically nondifficult melanomas.

melanomas can be difficult because the lesions may not have sufficiently developed the atypical clinical and dermoscopic features that permit their diagnosis, so that they appear dermoscopically as benign. Melanomas, because of their loss of normal growth controls, have changing features and tend to grow in an atypical manner leading to asymmetry, irregular borders, and a haphazard coloration that become apparent with its growth;[2] as the lesion grows, specific dermoscopic features associated with melanomas may become more evident, and hence they become easier to diagnose.

These findings are in contrast, however, with the results reported by Wolf and associates.[17] They showed that thick melanoma lesions (Breslow

TABLE 3. The Dermoscopic Diagnosis in Relation to the Difficulty of the Dermoscopic Diagnosis (DDM vs. DNDM) and Melanoma Thickness of 508 Cases of Melanoma

	Dermoscopic diagnosis, No. (%)			
	Benign nevus	*Atypical nevus*	*Melanoma*	*Total*
Difficulty of dermoscopic diagnosis				
DDM	11 (12.4)	78 (87.6)	—	89
DNDM	—	—	419 (100)	419
χ^2_2, *p* value			<0.001	
Melanoma thickness				
≥1 mm	—	2 (1.7)	115 (98.3)	117
<1 mm	8 (2.7)	42 (14.0)	244 (83.3)	294
Melanoma in situ	3 (3.1)	34 (35.0)	60 (61.9)	97
χ^2_4, *p* value			<0.001	

DDM, dermoscopically difficult melanomas; DNDM, dermoscopically nondifficult melanomas.

thickness >4 mm) were more difficult to diagnose clinically than thinner ones. Most probably, dermoscopic documentation is not performed in these cases of thick melanomas which simulate nonmelanomas because of their benign clinical appearance, leading to a sampling bias. In fact, thick melanomas were practically nonexistent in our sample of DDM, with only two melanomas having a thickness >1 mm.

In our cases of DDM, the dermoscopic criteria commonly associated with melanoma such as atypical pigment network, blue-whitish veil, irregular dots/globules, irregular pigmentation, and regression structures were absent.[9] The dermoscopic criteria that significantly lead to an increased risk of DDM were found to be the presence of streaks and hypopigmentation and the presence of regular pigmentation as well as the absence of pigmentation, blue-whitish veil, and regression structures. A CM lacking certain dermoscopic criteria such as irregular pigmentation, a blue-whitish veil, and regression structures can therefore be difficult to diagnose dermoscopically. The presence of streaks seems to be the only relevant dermoscopic criterion for the diagnosis of DDM. The term streaks includes radial streaming and pseudopods that, even if morphologically dissimilar, have a common histopathologic substrate correlating with confluent junctional nests of melanocytes indicating the radial growth phase of melanoma and thus the early phases of melanoma development.[13,18] The significant presence of streaks in our cases of DDM can explain why these cases were almost exclusively early melanomas (87/89 in situ melanomas and melanomas ≤1 mm thick). In our melanoma cases, streaks were irregularly distributed at the edge of the lesion (Figure 1) or were in a radial arrangement over the lesion in a symmetrical or an asymmetrical starburst-like pattern; therefore, atypical Spitz/Reed nevi and Reed nevi should be included in the differential diagnosis. Atypical Spitz/Reed nevi are characterized by an atypical or multicomponent pattern in which, besides irregular streaks, other melanoma-specific dermoscopic features are present;[19] thus they can be differentiated from relatively featureless melanomas that lack the other specific dermoscopic criteria for melanoma.

TABLE 4. Intraobserver Agreement (κ test) between Three Observers* of a Set of 28 Histologic Specimens of Cutaneous Melanoma

	Agreement			
Observer	*Perfect agreement*	*%*	κ	*Range*†
1 vs. 2	24/28	86	0.63	0.32–0.94
1 vs. 3	25/28	89	0.70	0.40–1.00
2 vs. 3	27/28	96	0.92	0.75–1.00

*HPS (Observer 1), LC (Observer 2), and CM (Observer 3).
†95% confidence interval.

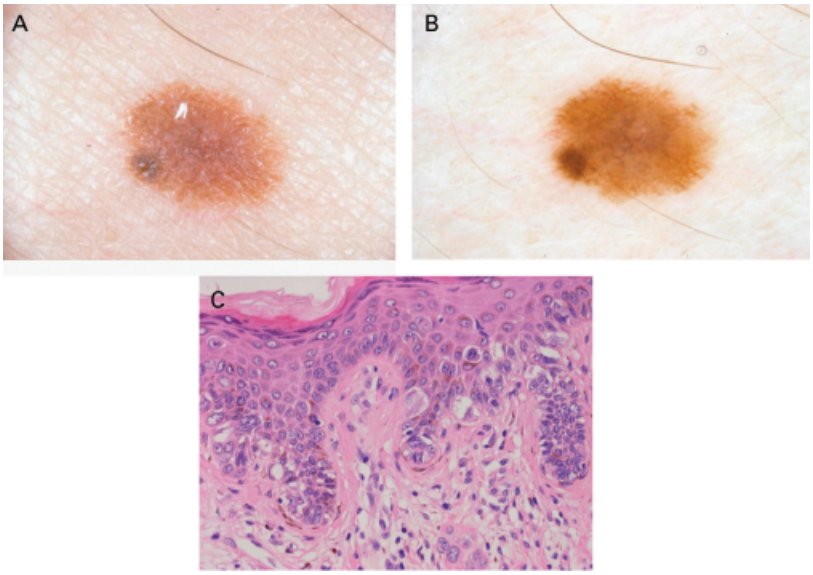

Figure 1. (A) Clinical image of an invasive melanoma, 0.2 mm thick on the left thigh of a 41-year-old woman. A light brown papule with a regular border and an eccentric focus of darker brown hyperpigmentation localized in the left lower periphery of the lesion can be observed (original magnification, × 10). (B) In the dermoscopic image of the same melanoma, irregularly distributed streaks at the edge of the lesion, that appear as a linear extension arising at the periphery of an atypical pigment network, can be recognized. An area of localized brown pigmentation asymmetrically distributed at the left lower periphery of the lesion can also be observed (original magnification, × 10). (C) The histopathologic image of the same melanoma shows an atypical proliferative melanocytic lesion characterized by nests of junctional melanocytes arranged singly or in small groups and extending upward into the epidermis. A microinvasive component is seen in the papillary dermis as a small aggregate of atypical melanocytes. Scattered lymphocytes permeate the superficial dermis (original magnification, × 400).

Instead, the differential diagnosis between Reed nevi and melanomas displaying the starburst patterns is extremely difficult or impossible. These melanomas present more frequently with an asymmetric starburst-like pattern at the periphery, in which only a portion of the peripheral rim have the starburst pattern, and so they may differ from Reed nevi where streaks are usually homogeneously distributed at the periphery with a symmetric radial arrangement over the entire lesion. Some Reed nevi, however, present with an asymmetric starburst-like pattern[20] whereas, on the other hand, some melanomas displayed symmetry in the starburst pattern. Therefore, there are instances in which dermoscopy cannot conclusively differentiate between Reed nevi and melanomas displaying an asymmetric or symmetric starburst-like pattern. When Reed nevi arise in adults or a change in their appearance has been reported, surgical excision of these lesions is always recommended.[21] Other authors have also found that some early melanomas, including spitzoid melanomas with symmetry in the starburst pattern, cannot be discriminated with sufficient accuracy by using the classic dermoscopic criteria.[10–12]

Melanomas that lack specific dermoscopic features, so-called featureless melanomas, do not have any of the positive criteria described in Menzies' diagnostic method such as a blue-white veil, multiple brown dots, pseudopods, radial streaming, scarlike depigmentation, peripheral black dots/globules, multiple colors, multiple blue/gray dots, and a broadened network.[10] Moreover, in some early melanomas, no dermoscopic features or global patterns can be identified that reliably differentiate them from melanocytic nevi.[11]

The dermoscopic diagnosis of melanoma is based on the presence of classical dermoscopic features and is therefore limited in melanomas which simulate

common nevi that do not display these features (12.4% of our cases) and also in melanomas that share several features with atypical nevi (representing 87.6% of our cases). Therefore, the largest part of our DDM revealed dermoscopic patterns indistinguishable from those of atypical nevi. At present, it is not possible to differentiate atypical nevi from melanomas both clinically and dermoscopically because the dermoscopic features most frequently seen in melanomas, namely, an atypical pigment network, irregular dots and globules, areas of regression, a blue-gray veil, and branched streaks can also be found in atypical nevi.[22] Conversely, according to Salopek and coworkers,[23] the dermoscopic criteria that are statistically significant and highly specific in discriminating early melanomas from atypical nevi include pigment network ending abruptly at the periphery, white scarlike areas, depigmented areas, and a whitish veil. Nowadays, however, there is a general consensus that for a considerable number of lesions, a distinction between melanomas and nonmelanomas is difficult or impossible because dermoscopically, atypical lesions span a continuum from minimally atypical to markedly atypical nevi that share some features with early melanoma.[24–26] Furthermore, in this subset of lesions, which includes atypical nevi and early melanoma, the histopathologic diagnosis may be complex and thorny because of the intrinsic diagnostic difficulty and due to the lack of a histopathologic standard threshold that allows differentiation between severely atypical nevi and early melanomas by certainty.[27,28]

Our results showed a good level of agreement among the dermopathologists, with a median value of $\kappa = 0.75$ (range, 0.63–0.92). Nonetheless, one-fourth (26%) of the histopathologic specimens of CM were interpreted as atypical nevi. Remarkably, the percentage of the histopathologic diagnosis of nonmelanomas originally diagnosed as melanomas in this subset of lesions ranged from 18% to 32%. In our estimation, a combined morphologic approach using both dermoscopy and histopathology might help the dermopathologist to reach a more reliable diagnostic conclusion.[29]

Dermoscopy alone is not sufficient to diagnose all early melanomas because there is a subset of melanomas that are difficult to diagnose dermoscopically and therefore dermoscopy cannot be used as the sole indicator for excision.[10] A more useful system to diagnose early melanomas is the tracing of the growth of the lesion over time and the careful observation for dermoscopic nonuniformity.[30] For the recognition of early and featureless melanomas, other authors have also underlined the role of changes documented by the medical history or by short-term follow-up with digital dermoscopic devices.[10–12] In our study, the DDMs were excised either because of morphologic changes such as a modification of shape or color or an increase in their dimension or due to the recent appearance of a lesion reported by the affected individuals themselves.

Melanoma recognition relies mainly on a cognitive and a comparative process based on an unconscious reference to the overall pattern and an assessment of all the other nevi of a given individual ("ugly ducking" sign) as well as an interactive process with the patient to gain knowledge about recent changes.[31–33] In this study, we have demonstrated that a significant number of melanomas, the so-called DDM, defy even the dermoscopic diagnosis. In this instance, only a meticulous comparative and interactive process can lead to the recognition of these melanomas.

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References

1. Friedman RJ, Rigel DS, Kopf AW. Early detection of malignant melanoma: the role of physician examination and self-examination of the skin. Cancer J Clin 1985;35:130–51.
2. Whited JD, Grichnik J. Does this patient have a mole or a melanoma? JAMA 1998;27:696–701.
3. Anderson WK, Silvers DN. "Melanoma? It can't be melanoma": a subset of melanomas that defies clinical recognition. JAMA 1991;266:3463–5.
4. Grant-Kels JM, Bason ET, Grin CM. The misdiagnosis of malignant melanoma. J Am Acad Dermatol 1999;40: 539–48.

5. Pizzichetta MA, Talamini R, Stanganelli I, et al. Amelanotic/hypomelanotic melanoma: clinical and dermoscopic features. Br J Dermatol 2004;150:1117–24.

6. Schneider JS, Moore DH, Sagebiel RW. Risk factors for melanoma incidence in prospective follow-up: the importance of atypical (dysplastic) nevi. Arch Dermatol 1994;130:1002–7.

7. Massone C, Di Stefani A, Soyer HP. Dermoscopy for skin cancer detection. Curr Opinion Oncol 2005;17:147–53.

8. Stanganelli I, Serafini M, Bucchi L. A cancer registry assisted evaluation of the accuracy of digital epiluminescence microscopy associated with clinical examination of pigmented skin lesions. Dermatology 2000;200:11–6.

9. Argenziano G, Soyer HP. Dermoscopy of pigmented skin lesions a valuable tool for early diagnosis of melanoma. Lancet Oncol 2001;2:443–9.

10. Menzies SW, Ingvar C, Crotty KA, McCarthy WH. Frequency and morphologic characteristics of invasive melanomas lacking specific surface microscopic features. Arch Dermatol 1996;132:1178–82.

11. Skvara H, Teban L, Fiebiger M, et al. Limitations of dermoscopy in the recognition of melanoma. Arch Dermatol 2005;141: 155–60.

12. Malvehy J, Puig S. Follow-up of melanocytic skin lesions with digital total-body photography and digital dermoscopy: a two-step method. Clin Dermatol 2002;20:297–304.

13. Argenziano G, Soyer HP, Chimenti S, et al. Dermoscopy of pigmented skin lesions. Results of a consensus meeting via the internet. J Am Acad Dermatol 2003;48:679–93.

14. Pehamberger H, Steiner A, Wolff K. In vivo epiluminescence microscopy of pigmented skin lesion. I. Pattern analysis of pigmented skin lesions. J Am Acad Dermatol 1987;17:571–83.

15. Breslow NE, Day NE. Statistical methods in cancer research, Vol. I, The analysis of case-control studies. IARC Scientific Publication, 32. Lyon: IARC Press, 1980.

16. Fleiss JL. The measurement of interrater agreement. In: Statistical methods for rates and proportions, 2nd ed. New York: Wiley, 1981:p. 212–36.

17. Wolf IH, Smolle J, Soyer HP, Kerl H. Sensitivity in the clinical diagnosis of malignant melanoma. Melanoma Res 1998;8:425–9.

18. Argenziano G, Fabbrocini G, Carli P, et al. Epiluminescence microscopy: criteria of cutaneous melanoma progression. J Am Acad Dermatol 1997;37:68–74.

19. Ferrara G, Argenziano G, Soyer HP, et al. The spectrum of Spitz nevi: a clinicopathologic study of 83 cases. Arch Dermatol 2005;141:1381–7.

20. Blum A, Metzler G, Braun RP, et al. Spitz and reed nevi. In: Marghoob AA, Braun RP, Kopf AW, editors. Atlas of dermoscopy. London and New York: Taylor & Francis, 2005:p. 195–203.

21. Peris K, Ferrari A, Argenziano G, et al. Dermoscopic classification of Spitz/Reed nevi. Clin Dermatol 2002;20:259–62.

22. Tripp JM, Kopf AW. Dysplastic nevus (atypical mole). In: Marghoob AA, Braun RP, Kopf AW, editors. Atlas of dermoscopy. London and New York: Taylor & Francis, 2005:p. 160–72.

23. Salopek TG, Kopf AW, Stefanato CM, et al. Differentiation of atypical moles (dysplastic nevi) from early melanomas by dermoscopy. Dermatol Clin 2001;19:337–45.

24. Binder M, Kittler H, Steiner A, et al. Reevaluation of the ABCD rule for epiluminescence microscopy. J Am Acad Dermatol 1999;40:171–6.

25. Pizzichetta MA, Talamini R, Piccolo D, et al. The ABCD rule of dermatoscopy does not apply to small melanocytic skin lesions. Arch Dermatol 2001;10:1376–8.

26. Seidenari S, Pellacani G, Martella A. Acquired melanocytic lesions and the decision to excise: role of color variegation and distribution as assessed by dermoscopy. Dermatol Surg 2005;31:184–9.

27. Ferrara G, Argenziano G, Soyer HP, et al. Dermoscopic and histopathologic diagnosis of equivocal melanocytic skin lesions: an interdisciplinary study on 107 cases. Cancer 2002;95: 1094–100.

28. Soyer HP, Massone C, Ferrara G, et al. Limitations of histopathologic analysis in the recognition of melanoma: a plea for a combined diagnostic approach of histopathologic and dermoscopic evaluation. Arch Dermatol 2005;141:209–11.

29. Bauer J, Metzler G, Rassner G, et al. Dermatoscopy turns histopathologist's attention to the suspicious area in melanocytic lesions. Arch Dermatol 2001;137:1138–0.

30. Lucas CR, Sanders LL, Murray JC, et al. Early melanoma detection: non-uniform dermoscopic features and growth. J Am Acad Dermatol 2003;48:663–71.

31. Gachon J, Beaulieu P, Sei JF, et al. First prospective study of the recognition process of melanoma in dermatological practice. Arch Dermatol 2005;141:434–8.

32. Grob JJ, Bonerandi JJ. The "ugly duckling" sign: identification of the common characteristics of nevi in an individual as a basis for melanoma screening. Arch Dermatol 1988;134:103–4.

33. Grichnik JM. Difficult early melanomas. Dermatol Clin 2001;19:319–25.

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