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Pigmented nodular melanoma: The predictive value of dermoscopic features using a multivariate analysis

Running head: Pigmented nodular melanoma

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Bulleted Statements:

What's already known about this topic?

- Nodular melanoma (NM) often exhibits features associated with deep tumor extension and less commonly displays the classic dermoscopic features of superficial spreading melanoma (SSM).

What does this study add?

- The study identifies dermoscopic features which are significantly associated with pigmented NM compared to pigmented SSM and non-melanoma nodular lesions.
- The authors validates with a multivariate analysis the dermoscopic features leading to a significant increased likelihood of a diagnosis of pigmented NM.

Summary

Background Nodular Melanoma (NM), representing 10%-30% of all melanomas, plays a major role in global mortality related to melanoma. Nonetheless, the literature on dermoscopy of NM is scanty.

Objectives Assessment of odds ratios (ORs) to quantify dermoscopic features of pigmented NM *versus* pigmented superficial spreading melanoma (SSM), and pigmented nodular non melanocytic and benign melanocytic lesions.

Methods Digitized images of 457 pigmented skin lesions from patients with histopathological diagnosis of NM (75), SSM (93), and nodular non melanocytic and benign melanocytic lesions (289), (i.e., 39 basal cell carcinoma, 85 seborrheic keratosis, 81 blue nevi, and 84 compound/dermal nevi), were retrospectively collected and blindly evaluated by three observers to assess the presence or absence of global patterns and dermoscopic criteria.

Results The multivariate analysis showed that ulceration (OR, 4.07), homogeneous disorganized pattern (OR, 10.76), and homogeneous blue pigmented structureless areas (OR, 2.37) were significantly independent prognostic factors for NM vs SSM. The multivariate analysis of dermoscopic features of NM vs non melanocytic and benign melanocytic lesions showed that the positive correlating features leading to a significant increased NM risk were: asymmetric pigmentation (OR, 6.70), blue-black pigmented areas (OR, 7.15), homogeneous disorganized pattern (OR, 9.62), a combination of polymorphous vessels and milky red globules/areas (OR, 23,65) and polymorphous vessels combined with red homogeneous areas (OR, 33.88).

Conclusions Dermoscopy may be helpful in improving the recognition of pigmented NM by revealing asymmetric pigmentation, blue-black pigmented areas, homogeneous disorganized pattern, and abnormal vascular structures including polymorphous vessels, milky red globules/areas and red homogeneous areas.

Introduction

Nodular melanoma (NM) represents 10 - 30% of all melanomas and nearly 50% of all melanomas thicker than 2 mm, and it plays a major role in the global mortality related to this cancer.[1] Unlike other melanoma subtypes, NM appears to lack the initial radial growth phase, beginning with vertical growth.[2]

The "ABCD" warning signs for melanoma are better at detecting superficial spreading melanoma (SSM) than NM, as the latter is often small in diameter, symmetric, with regular borders and less colour variegation, and it is frequently amelanotic.[1,3] For this reason, the EFG rule (Elevation, Firmness on palpation, continuous Growth over 1 month), summarizing the most frequent features of NM, has been introduced for the identification of this subtype of melanoma.[4] Dermoscopically, in a study of 10 NM lesions, an asymmetric color and pattern distribution was observed in all lesions; in addition, all lesions exhibited at least 3 colours, though the number of colors and structures was significantly lower in the NM group than in the SSM group.[5] In a study of 11 thin NM, most lesions had a homogeneous disorganized asymmetric pattern or a featureless pattern; although many dermoscopic features seen in SSM were frequently absent, some features such as a blue-white veil, structureless areas, atypical vessels and pink veil were often identified.[4] In a large series of NM, Menzies et al[6] found that pigmented NM compared with non-nodular invasive melanoma, more frequently displayed a symmetrical pigmentation pattern, large-diameter vessels, areas of homogeneous blue pigmentation, symmetrical shape, predominant peripheral vessels, blue-white veil, pink colour, black colour, and milky red/pink areas.

In this study, 457 pigmented skin lesions, including 75 NM, were evaluated dermoscopically to examine the predictive value of dermoscopic features of NM using a multivariate analysis.

Patients and Methods

Between January 2007 and December 2011, all consecutive cases of histopathologically confirmed pigmented NM, pigmented SSM, pigmented nodular benign melanocytic lesions (e.g. compound /dermal nevus, blue nevus), and pigmented nodular non-melanocytic lesions (e.g. seborrheic keratosis, basal cell carcinoma) seen at the 15 participating Italian centers, were collected for this study, with the aim to identify dermoscopic features which were

significantly associated with pigmented NM compared to pigmented SSM and non-melanoma nodular lesions. In this study only "pigmented" lesions were considered, that were defined as those having black, dark brown, gray, or blue structures that occupied more than 25% of the total surface area of the lesion.[7]

NM was defined as an invasive melanoma that lacks significant intraepidermal tumor cells beyond the margins of the dermal invasive component.[6]

There were no SSM with a nodular component in our series of NM as well as no in situ melanoma in the non-nodular melanoma set.

Two separate files were provided for each case, one containing the dermoscopic images and a second one containing all patient-related information such as gender, age at diagnosis, skin lesion site, type of dermoscopy (polarized or non-polarized), date of excision, clinical diagnosis, dermoscopic diagnosis and histopathological diagnosis.

By the end of December 2011, all the dermoscopic images (N=560) from the 15 centers were merged into a database at the Epidemiology and Biostatistics Unit (R.T.) of the Centro di Riferimento Oncologico, Aviano (Italy), with a new identification link to the patient information on clinical features and diagnosis. Of the 560 submitted images, 457 were found to be of sufficiently good quality for the evaluation of the dermoscopic criteria. Of these, 310 (67.8%) were taken with a camera using non-polarized dermoscopy and 147 (32.2%) with a camera using polarized dermoscopy. All the dermoscopic images were examined to assess the presence or the absence of global patterns and specific dermoscopic criteria in NM, non-nodular melanoma, non-melanocytic and benign melanocytic lesions. We assessed the lesions using the features reportedly associated with melanoma, basal cell carcinoma, seborrheic keratosis, common nevi, and blue nevi;[8-10] all features assessed were also considered in the analysis and in the tables. All cases were evaluated by a panel of three blinded observers; the dermoscopic features were scored based on the agreement of the two observers (M.A.P. and

R.B.) and in the case of disagreement between them, a third observer (I.S.) was consulted. The evaluation of the dermoscopic criteria as well as the final dermoscopic diagnosis was made when 3/3 or 2/3 observers agreed.

Statistical analysis

The statistical analysis was performed by means of the SAS 9.1 (SAS Institute Inc., Cary, NCI) statistical software.[11] Unconditional logistic regression models were used to assess odds ratios (OR) and their corresponding 95% confidence intervals (CI) to quantify dermoscopic features of pigmented NM *versus* pigmented non nodular melanoma and pigmented nodular non melanocytic and benign melanocytic lesions. Variables that resulted statistically significant at the univariate analysis were included in the multivariate model. In addition, the Chi-square test or Fisher exact test was used, when appropriate, to evaluate differences in clinical characteristics and melanoma thickness. Results were considered to be statistically significant when p-values were less than or equal to 0.05 (two-sided).

Results

Patients demographics and classification of lesions

The diagnostic categories of the study lesions are shown in Table 1. Of 457 lesions, 75 were NM, 93 were SSM and 289 were non-melanocytic (39 basal cell carcinoma and 85 seborrheic keratosis) plus benign melanocytic lesions (81 blue nevi and 84 compound/dermal nevi). The study included 457 patients (236 males, 221 females) with a median age of 51 years (range:11-95) (Table 2). The sites of the skin lesions included: head and neck (107 cases); anterior trunk (90 cases); back (129 cases); lower limbs (80 cases); and upper limbs (51 cases). The median ages were 61 years, (range 21-92), 57 years, (range 16-92), and 46 years (range 11-95), for NM, SSM, and non-melanocytic and benign melanocytic lesions respectively (Table 2).

No differences emerged between NM and SSM in the distribution by sex, age and sites of the melanomas. By contrast, the median Breslow thickness of NM (3.40 mm, range: 0.05 -11.00) was significantly greater than that of the SSM (0.80 mm, range: 0.01-5.00; $p<0.0001$) (Table 2).

Dermoscopic features of pigmented NM vs pigmented SSM

Table 3A and 3B show the univariate and multivariate analyses of the dermoscopic features (positive 3A and negative 3B) of pigmented NM vs pigmented SSM. The univariate analysis was used to identify the relevant factors (i.e. listed according to p value) in determining NM. 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 ulceration, homogeneous disorganized pattern and homogeneous blue pigmented structureless areas were significant independent prognostic factors for NM**.** The presence of ulceration was 37.3 % in the NM and 10.8 % in the SSM group and led to a significantly increased risk of diagnosing NM (OR, 4.07; 95% CI, 1.71-9.69). Moreover, significant risks of diagnosing NM were also found when the lesion was characterized by the presence of homogeneous disorganized pattern (OR, 10.76; 95% CI, 2.69 - 42.99) and homogeneous blue pigmented structureless areas (OR, 2.37; 95% CI, 1.08 - 5.22) (Table 3A). Conversely, when evaluating the negative features, the presence of peripheral light brown structureless areas was 12% in NM and 38.7 % in the SSM group, leading to a significantly reduced risk of NM (OR, 0.26; 95% CI, 0.11- 0.65) (Table 3B).

Dermoscopic features of pigmented NM vs pigmented nodular non melanocytic and benign melanocytic lesions.

Tables 4A and 4B show the univariate and multivariate analyses of the dermoscopic features (i.e. listed according to p value), of pigmented NM vs pigmented nodular non melanocytic and benign melanocytic lesions. The multivariate analysis showed that the significant positive correlating features, leading to a significant increased risk of NM, were asymmetric pigmentation (OR, 6.70; 95% CI, 1.49 - 30.11), blue-black pigmented areas, (OR, 7.15; 95% CI, 1.54- 33.30), homogeneous disorganized pattern (OR, 9.62; 95% CI, 1.62- 57.13), the combination of polymorphous vessels and milky-red globules/areas (OR, 23.65; 95% CI, 1.65 – 339.93), and the combination of polymorphous vessels and red homogeneous areas (OR, 38.88; 95% CI, 1.72- 877.07) (Table 4A). By contrast, the homogeneous pattern was a negative correlating feature, leading to a significant reduced risk of NM (OR, 0.05; 95% CI, 0.01- 0.22) (Table 4B) .

Discussion

Based on our results, a large number of features such as ulceration, homogeneous disorganized pattern, homogeneous blue pigmented structureless areas, multiple (≥ 3) colours, the combination of polymorphous vessels and milky red globules/areas and symmetric shape were significantly more frequent in pigmented NM compared to pigmented SSM only in the univariate analysis. When we compared our results with those of Menzies et al[6], they appeared in agreement in relation to the areas of homogeneous blue pigmentation and symmetrical shape, which were positively correlated with NM in both studies, while Menzies et al[6] also found symmetrical pigmentation pattern, pink colour, blue-white veil and black color positively correlated with NM. Regarding negative features, we found a large number of features such as atypical network, multicomponent pattern, peripheral light brown

structureless areas, asymmetric shape, irregular streaks and the combination of linear irregular, dotted and milky red globules/area that were negatively correlated with NM in comparison with SSM only in the univariate analysis. When we compared our results with those of Menzies et al[6], the atypical network was the only feature in agreement. By contrast in this study,[6] other negative correlating features of pigmented NM were found such as pigment network/pseudonetwork, multiple blue-gray dots (granularity), scarlike depigmentation, irregular brown dots/globules, tan colour, irregular shape depigmentation, and irregular dots/globules of any colour. The inconsistencies between the two studies could depend on the different sample sizes of both NMs and SSMs and on different terminology used to describe some features regarding the vascular pattern, the regression structures, (including both multiple blue-gray dots (granularity) and scar-like depigmentation,) instead of multiple blue-gray dots (granularity) or scar-like depigmentation, as well as the irregular dots/globules, instead of irregular dots/globules of any color or irregular brown dots/globules.

The most striking results in our study were that the only significant features distinguishing pigmented NM from pigmented SSM in the multivariate analysis were ulceration, homogeneous disorganized pattern, and homogeneous blue pigmented structureless areas. The overall homogeneous pattern is typically exhibited by common and blue nevi, consisting of a diffuse homogeneous tan, brown, or blue structureless pigmentation.[12-13] By contrast, in NM, in agreement with that reported by other authors, [4,14] the colours are distributed in a disorganized and asymmetric fashion, characterizing the overall disorganized homogeneous pattern (Figure 1).

Regarding the homogeneous blue pigmented structureless areas, some authors use a unifying definition of blue-white structures over raised areas associated with dense melanin within melanocytes in the dermis;[14] the uniform distribution of blue hue may be focal in the case of homogeneous blue pigmented structureless areas or diffuse in the case of blue-whitish veil.[15] (Figure 2).

Concerning negative features, the only significant negatively correlated feature of pigmented NM in the multivariate analysis were peripheral light brown structureless areas, which are already reported to be associated with thin melanoma.[16]

When comparing the univariate analyses of the positive features of pigmented NM vs pigmented nodular non-melanocytic and benign melanocytic lesions in both our study as well as that of Menzies and colleagues, [6] most of the features were in agreement, i.e. peripheral black dots/globules, irregular black dots/globules, blue-white veil, pseudopods, homogeneous blue pigmentation, multiple colors, black colour, irregular blotches, irregular dots/globules, blue-black structures, and asymmetric shape. The differences between the two studies concerned some positive correlating features found only in our study, such as linear irregular vessels + milky red globules/areas, more than one shade of pink, red homogeneous areas, asymmetric pigmentation pattern, multicomponent pattern, regression structures, ulceration, homogeneous disorganized pattern, atypical network, shiny white structures, predominant blue clods, featureless pattern, peripheral light brown structureless areas and irregular depigmentation. Conversely, some positive correlating features found by Menzies and colleagues [6] did not correspond to those evaluated in our study, such as pink color, abrupt edge, blurred “out of focus” colours, red-blue colour, multiple brown dots and central black dots/globules. Regarding negative features, the agreement emerged only for milia-like cysts and comedo-like openings, while arborizing vessels, multiple blue globules, leaf like areas,

and large blue-gray ovoid nests, were negatively associated with NMs only in Menzies' study [6]. The different terminology of some features as well as the different diagnostic categories of lesions included in the two studies may explain the differences in the results between these two different series; our series did not include, in relation to benign melanocytic lesions, Spitz nevi and deep penetrating nevi, and in relation to non-melanocytic lesions, hemangioma, dermatofibroma and other nodular lesions.

Asymmetric pigmentation, blue-black pigmented areas, homogeneous disorganized pattern, the combination of polymorphous vessels and milky red globules/areas and polymorphic vessels associated with red homogeneous areas were significantly more frequent in pigmented NM compared to pigmented nodular non-melanocytic and benign melanocytic lesions in the multivariate analysis. In agreement with our results, Argenziano et al [17] found that blue-black pigmented areas, defined as a combination of structureless blue areas, black dots/ globules, and blotches, involving at least 10% of the lesion surface, were significantly associated with NM, (Figures 1,2,3). These areas correspond to different histopathologic correlates, with blue area corresponding to pigmented melanocytes in the deep dermis and black areas, arising from superficial intraepidermal melanin or a dense dermal proliferation of pigmented melanocytes under a thinned epidermis that may predict ulceration.[18] This could also explain why we found ulceration to be significantly more frequent in NM compared to SSM. Abnormal vascular structures, including polymorphic vessels, milky red globules/areas and red homogeneous areas are also significant relevant features of NM which have been reported to be associated with NM by other authors. [19] Polymorphous vessels are defined as having more than one morphological type of vessel; the most frequent combination of vessel types seen in melanoma is linear irregular and dotted vessels, as the thickness increases, the vascular polymorphism increases with hairpin, linear coiled (glomerular), linear helical (cork-

screw like), and arborizing vessels (seemingly emerging from the dermal plexus of the adjacent skin, possibly because vertical growth cannot be maintained by further elongation of the capillary loops), associated with milky red globules/areas and/or red homogeneous areas (Figure 4). [19] Milky red globules have been defined as unfocused large ovoid or polygonal structures of pink-white colour, often showing a central linear irregular or corkscrew vessel, separated from each other by blurred whitish lines, that may be seen within or near areas with a milky red color, the so-called milky red areas, also knows as pink veil or more than one shade of pink that probably correspond to areas with increased vascular volume (Figure 2). [19-20] The red homogeneous areas were seen in NM and in pyogenic granuloma as structureless areas of red homogeneous colour covering the structures lying below (Figure 3). [19,21]The milky red globules/areas as well as the red homogeneous areas probably represent an increased vascular volume reflecting neoangiogenesis. [19-21]

Dermoscopy may be helpful in improving the recognition of pigmented NM by revealing asymmetric pigmentation, blue-black pigmented areas, homogeneous disorganized pattern, and abnormal vascular structures including polymorphic vessels, milky red globules/areas and red homogeneous areas. In conclusion, the abnormal vascular structures (Figure 4) as well as the blue-black pigmented areas (Figure 1) may be the only clue for the correct diagnosis of pigmented NM in examining asymmetrically pigmented lesions with a homogeneous disorganized pattern.

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Figure Legends

Fig 1. Clinical and dermoscopic image of a nodular melanoma, 2.4 mm thick on the cheek of an 80-year-old woman. (a) In the clinical image (inset), a blue-grayish scaly symmetrical nodule can be observed. (b) An overall homogeneous disorganized pattern consisting of a diffuse homogeneous blue pigmentation plus foci of irregular black dots/globules and blotches can be seen. The presence of additional features and colors distributed in disarray and in an asymmetric fashion help to distinguish NM from blue nevus. (Original magnification x 10.)

Fig 2. Clinical and dermoscopic images of an ulcerated nodular melanoma, 5.8 mm thick on the leg of a 69-year-old woman. (a) In the clinical image (inset), a black-grayish symmetrical nodule can be observed. (b) In the polarized dermoscopic image of the same melanoma, blue

pigmented structureless areas with different shades of blue-white pigmentation are intermixed with black dots/globules (blue-black pigmented areas) and black hemorrhagic crusts from ulceration in the center of the lesion; framed is the area with polymorphous vascular pattern and milky-red globules/areas. (c) Magnified detail of polymorphous vascular pattern, having linear irregular vessels (white arrow), irregular hairpin vessels (black arrows), combined with milky-red globules (circle), appearing as unfocused polygonal structures of milky red color with a central linear irregular vessel and separated from each other by blurred whitish lines that may be seen within or near unfocused areas of milky red color, the so-called milky red areas, also knows as pink veil or more than one shade of pink structures (arrowheads).

Fig 3. Clinical and dermoscopic images of an ulcerated nodular melanoma, 1.95 mm thick, on the right upper arm of a 70-year-old woman. (a) In the clinical image (inset), a black- blue reddish symmetrical nodule can be observed; interestingly, an urticaria eruption with erythematous plaques around the lesion extending on the upper arm and shoulder can be seen; the eruption disappeared completely without any therapy once the lesion was excised. (b) In the dermoscopic image of the same melanoma, an asymmetric pigmentation, blue-black pigmented area, and red homogeneous structureless areas, covering the structures lying below (white arrowheads), can be seen; framed is the area with a polymorphous vascular pattern. Interestingly, adherent fibers of clothing, as a dermatoscopic clue to ulceration (circle), can also be observed. (c) Magnified detail of polymorphous vascular pattern, having linear irregular vessels (black arrow), irregular hairpin vessels (white arrows), linear coiled (glomerular) vessels (black circle) and linear helical (cork-screw like) vessels (white arrowheads). (Original magnification x 10).

Fig 4. Clinical and dermoscopic images of a nodular melanoma, 3.0 mm thick, on the flank of a 57-year-old man. (a) In the clinical image (inset) a brown-grayish scaly symmetrical nodule with a peripheral reddish halo can be seen. (b) In the dermoscopic image of the same melanoma, an asymmetrically pigmented lesion with a homogeneous disorganized pattern and focal blue pigmented areas can be observed, framed is the area with a polymorphous vascular pattern. (c) Magnified detail of the polymorphous vascular pattern, having linear irregular vessels (black arrow), linear helical (cork-screw like) vessels (white arrows) and arborizing vessels (black arrowheads), (Original magnification x 10.)

Table 1. Frequency of histopathological diagnosis of 457 pigmented skin lesions

Diagnosis	N. (%)
Invasive melanoma	
Nodular melanoma	75 (16.4)
Superficial spreading melanoma	93 (20.4)
Non melanocytic lesions	
Basal cell carcinoma	39 (8.5)
Seborrheic keratosis	85 (18.6)
Benign melanocytic lesions	
Blue nevus	81 (17.7)
Compound/dermal nevus	84 (18.4)

Table 2. Clinical characteristics and melanoma thickness of 457 pigmented skin lesions by histopathological diagnosis

	Nodular melanoma (N. 75)	Superficial spreading melanoma (N. 93)	Non melanocytic and benign melanocytic lesions (N. 289)
	N. (%)	N. (%)	N. (%)
Sex			
Male	39 (52.0)	54 (58.1)	143 (49.5)
Female	36 (48.0)	39 (41.9)	146 (50.5)
		p=0.43[1]	p=0.70[1]
Age (years)			
Median (range)	61 (21-92)	57 (16-92)	46 (11-95)
		p=0.55[2]	p<0.0001[2]
Sites			
Back	26 (34.7)	32 (34.4)	71 (24.6)
Lower limbs	20 (26.7)	28 (30.1)	32 (11.1)
Anterior trunk	13 (17.3)	15 (16.1)	62 (21.4)
Head and neck	9 (12.0)	7 (7.5)	91 (31.5)
Upper limbs	7 (9.3)	11 (11.8)	33 (11.4)
		p=0.86[1]	p=0.0003[1]
Melanoma thickness (mm)			
≤1.00	9 (12.0)	59 (63.4)	-
1.01-2.00	16 (21.3)	13 (14.0)	-
2.01-4.00	34 (45.3)	19 (20.4)	-
>4.00	16 (21.3)	2 (2.2)	-
Median (range)	3.40 (0.05-11.00)	0.80 (0.01-5.00)	-
		p<0.0001[2]	

[1] In comparison with nodular melanoma p-value of the chi-square test. [2] In comparison with nodular melanoma p-value of the Wilcoxon rank test.

Table 3-A. Univariate and multivariate analyses of positive dermoscopic features of pigmented nodular melanoma *versus* pigmented superficial spreading melanoma

Positive features	Nodular melanoma (N. 75)	Superficial spreading melanoma (N. 93)	OR (95% CI)[1]	
	N. (%)	N. (%)	Univariate	Multivariate[2]
Ulceration	28 (37.3)	10 (10.8)	4.95 (2.21-11.07) p=0.0001	4.07 (1.71-9.69) p=0.002
Homogeneous disorganized pattern	15 (20.0)	3 (3.2)	7.50 (2.08-27.02) p=0.002	10.76 (2.69-42.99) p=0.0008
Homogeneous blue pigmented structureless areas	28 (37.3)	16 (17.2)	2.87 (1.41-5.85) p=0.004	2.37 (1.08-5.22) p=0.03

Multiple (≥ 3) colours	69 (92.0)	73 (78.5)	3.15 (1.20-8.31) p=0.02	ns
Polymorphous vessels + milky red globules/ areas	10 (13.3)	4 (4.3)	3.42 (1.03-11.39) p=0.05	ns
Symmetric shape	32 (42.7)	26 (28.0)	1.92 (1.01-3.65) p=0.05	ns
Polymorphous vessels + red homogeneous areas	7 (9.3)	2 (2.2)	4.68 (0.94-23.26) p=0.10	
Blue-whitish veil	58 (77.3)	61 (65.6)	1.79 (0.90-3.57) p=0.10	
Linear irregular vessels	2 (2.7)	0 (0.0)	6.36 (0.30-134.53) p=0.11	
Diffuse homogeneous blue pigmentation	7 (9.3)	3 (3.2)	3.09 (0.77-12.38) p=0.11	
Milky red globules/areas	7 (9.3)	3 (3.2)	3.09 (0.77-12.38) p=0.11	
Blue-black pigmented areas	32 (42.7)	30 (32.3)	1.56 (0.83-2.94) p=0.17	
Linear irregular vessels + milky red globules/areas	7 (9.3)	4 (4.3)	2.29 (0.64-8.14) p=0.20	
Featureless pattern	3 (4.0)	1 (1.1)	3.83 (0.39-37.63) p=0.25	
Arborizing vessels	1 (1.3)	0 (0.0)	3.77 (0.15-93.77) p=0.27	
Red homogeneous areas	4 (5.3)	2 (2.2)	2.56 (0.46.14.39) p=0.29	
Irregular black dots/globules	48 (64.0)	54 (58.1)	1.28 (0.69-2.40) p=0.43	
Polymorphous vessels	3 (4.0)	2 (2.2)	1.90 (0.31-11.66) p=0.49	
More than one shade of pink	13 (17.3)	13 (14.0)	1.29 (0.56-2.98) p=0.55	

continues

Table -3A. Continued

Globular-homogeneous pattern	3 (4.0)	3 (3.2)	1.25 (0.25-6.38) p=0.79	
Homogeneous pattern	2 (2.7)	2 (2.2)	1.25 (0.17-9.07) p=0.83	
Black color	51 (68.0)	62 (66.7)	1.06 (0.56-20.3) p=0.85	
Hairpin vessels	1 (1.3)	1 (1.1)	1.24 (0.08-20.21) p=0.88	
Linear irregular vessels + red homogeneous areas	1 (1.3)	1 (1.1)	1.24 (0.08-20.21) p=0.88	

[1] OR: odds ratio and 95% confidence interval (CI). [2] Unconditional multiple logistic regression including all significant features in the univariate analysis. ns = non significant.

Table 3-B. Univariate and multivariate analyses of negative dermoscopic features of pigmented nodular melanoma *versus* pigmented superficial spreading melanoma

Negative features	Nodular melanoma (N. 75)	Superficial spreading melanoma (N. 93)	OR (95% CI)[1]	
	N. (%)	N. (%)	Univariate	Multivariate[2]
Atypical network	17 (22.7)	50 (53.8)	0.25 (0.13-0.50) p<0.0001	ns
Multicomponent pattern	34 (45.3)	70 (75.3)	0.27 (0.14-0.52) p<0.0001	ns
Peripheral light brown structureless areas	9 (12.0)	36 (38.7)	0.22 (0.10-0.49) p=0.0002	0.26 (0.11-0.65) p=0.004
Asymmetric shape	39 (52.0)	69 (74.2)	0.38 (0.20-0.72) p=0.003	ns
Irregular streaks	22 (29.3)	47 (50.5)	0.41 (0.21-0.77) p=0.006	ns
Linear irregular + dotted vessels + milky red globules/areas	2 (2.7)	11 (11.8)	0.20 (0.04-0.95) p=0.04	ns
Shiny white structures	13 (17.3)	28 (30.1)	0.49 (0.23-1.03) p=0.06	
Irregular dots/globules	58 (77.3)	82 (88.2)	0.46 (0.20-1.05) p=0.06	
Milia-like cysts	0 (0.0)	5 (5.4)	0.11 (0.06-1.96) p=0.07	
Linear irregular + dotted vessels	1 (1.3)	7 (7.5)	0.17 (0.02-1.38) p=0.10	
Depigmentation /Structureless areas	40 (53.3)	59 (63.4)	0.66 (0.35-1.22) p=0.19	
Comedo-like openings	0 (0.0)	1 (1.1)	0.41 (0.02-10.17) p=0.37	
Symmetric pigmentation pattern	3 (4.0)	6 (6.5)	0.60 (0.15-2.50) p=0.49	
Peripheral black dots /globules	34 (45.3)	45 (48.4)	0.89 (0.48-1.63) p=0.69	
Asymmetric pigmentation pattern	69 (92.0)	87 (93.6)	0.79 (0.25-2.57) p=0.70	
Regression structures	54 (72.0)	68 (73.1)	0.95 (0.48-1.87) p=0.87	
Irregular blotches	49 (65.3)	61 (65.6)	0.99 (0.52-1.87) p=0.97	
Predominant blue clods	7 (9.3)	9 (9.7)	0.98 (0.35-2.78) p=0.97	

[1] OR: odds ratio and 95% confidence interval (CI). [2] Unconditional multiple logistic regression including all significant features in the univariate analysis. ns= non significant.

Table 4-A. Univariate and multivariate analyses of positive dermoscopic features of pigmented nodular melanoma *versus* pigmented non melanocytic and benign melanocytic lesions

Positive features	Nodular melanoma (N. 75)	Non melanocytic and benign melanocytic lesions (N. 289)	OR (95% CI)[1]	
	N. (%)	N. (%)	Univariate	Multivariate[2]
Linear irregular vessels + milky red globules/areas	7 (9.3)	0 (0.0)	63.39 (3.58-1123.46) p<0.0001	ns
More than one shade of pink	13 (17.3)	1 (0.4)	60.39 (7.76-470.18) p<0.0001	ns
Red homogeneous areas	4 (5.3)	0 (0.0)	36.44 (1.94-648.62) p<0.0001	ns
Asymmetric pigmentation	69 (92.0)	94 (32.5)	23.86 (10.00-56.93) p<0.0001	6.70 (1.49-30.11) p=0.01
Irregular blotches	49 (65.3)	26 (9.0)	19.06 (10.22-35.56) p<0.0001	ns
Irregular black dots/globules	48 (64.0)	26 (9.0)	17.98 (9.67-33.44) p<0.0001	ns
Multicomponent pattern	34 (45.3)	13 (4.5)	17.61 (8.58-36.11) p<0.0001	ns
Regression structures	54 (72.0)	37 (12.8)	17.51 (9.51-32.26) p<0.0001	ns
Blue-black pigmented areas	32 (42.7)	12 (4.2)	17.18 (8.22-35.90) p<0.0001	7.15 (1.54-33.30) p=0.01
Peripheral black dots/ globules	34 (45.3)	15 (5.2)	15.15 (7.59-30.22) p<0.0001	ns
Ulceration	28 (37.3)	11 (3.8)	15.06 (7.02-32.29) p<0.0001	ns
Blue-whitish veil	58 (77.3)	57 (19.7)	13.89 (7.52-25.64) p<0.0001	ns
Multiple (≥ 3) colours	69 (92.0)	132 (45.7)	13.67 (5.75-32.49) p<0.0001	ns
Black color	51 (68.0)	42 (14.5)	12.50 (6.96-22.44) p<0.0001	ns
Irregular streaks	22 (29.3)	12 (4.2)	9.58 (4.47-20.54) p<0.0001	ns
Irregular dots/globules	58 (77.3)	110 (38.1)	5.55 (3.08-10.02) p<0.0001	ns
Homogeneous disorganized pattern	15 (20.0)	13 (4.5)	5.31 (2.40-11.74) p<0.0001	9.62 (1.62-57.13) p=0.01
Asymmetric shape	39 (52.0)	52 (18.0)	4.94 (2.87-8.50) p<0.0001	ns

continue

Table 4-A. continued

Atypical network	17 (22.7)	18 (6.2)	4.41 (2.15-9.08) p<0.0001	ns
Homogeneous blue pigmented structureless areas	28 (37.3)	35 (12.1)	4.32 (2.41-7.77) p<0.0001	ns
Polymorphous vessels + milky red globules/areas	10 (13.3)	1 (0.4)	44.30 (5.57-352.16) p=0.0003	23.65 (1.65-339.93) p=0.02
Shiny white structures	13 (17.3)	15 (5.2)	3.83 (1.73-8.46) p=0.0009	ns
Polymorphous vessels + red homogeneous areas	7 (9.3)	1 (0.4)	29.63 (3.59-244.79) p=0.002	38.88 (1.72-877.07) p=0.02
Milky red globules/areas	7 (9.3)	1 (0.4)	29.63 (3.59-244.79) p=0.002	ns
Predominant blue clods	7 (9.3)	8 (2.8)	3.57 (1.25-10.19) p=0.02	ns
Featureless pattern	3 (4.0)	1 (0.4)	12.00 (1.23-117.05) p=0.03	ns
Peripheral light brown structureless areas	9 (12.0)	14 (4.8)	2.68 (1.11-6.45) p=0.03	ns
Depigmentation/structureless areas	40 (53.3)	114 (39.5)	1.75 (1.05-2.93) p=0.03	ns
Linear irregular + dotted vessels + milky red globules/areas	2 (2.7)	1 (0.4)	7.89 (0.71-88.22) p=0.10	
Linear irregular + dotted vessels	1 (1.3)	0 (0.0)	11.66 (0.47-289.08) p=0.10	
Polymorphous vessels	3 (4.0)	3 (1.0)	3.97 (0.79-20.09) p=0.10	
Linear irregular vessels + red homogeneous areas	1 (1.3)	2 (0.7)	1.94 (0.17-21.68) p=0.59	

[1] OR: odds ratio and 95% confidence interval (CI). [2] Unconditional multiple logistic regression including all significant features in the univariate analysis. ns=non significant.

Table 4-B. Univariate and multivariate analyses of negative dermoscopic features of pigmented nodular melanoma *versus* pigmented non melanocytic and benign melanocytic lesions

Negative features	Nodular melanoma (N. 75)	Non melanocytic and benign melanocytic lesions (N. 289)	OR (95% CI)[1]	
	N. (%)	N. (%)	Univariate	Multivariate[2]
Milia-like cysts	0 (0.0)	77 (26.6)	0.02 (0.01-0.30) p<0.0001	ns
Comedo-like openings	0 (0.0)	80 (27.7)	0.02 (0.01-0.28) p<0.0001	ns
Symmetric pigmentation	3 (4.0)	152 (52.6)	0.04 (0.01-0.12) p<0.0001	0.05 (0.02-0.19) p<0.0001
Symmetric shape	32 (42.7)	193 (66.8)	0.37 (0.22-0.62) p=0.0002	ns
Homogeneous pattern	2 (2.7)	71 (24.6)	0.08 (0.02-0.35) p=0.0007	0.16 (0.04-0.73) p=0.02
Diffuse homogeneous blue pigmentation	7 (9.3)	65 (22.5)	0.36 (0.16-0.81) p=0.12	
Comma vessels	0 (0.0)	20 (6.9)	0.09 (0.01-1.46) p=0.10	
Leaf-like areas	0 (0.0)	19 (6.6)	0.09 (0.01-1.54) p=0.10	
Large blue-gray ovoid nests	2 (2.7)	27 (9.3)	0.27 (0.06-1.14) p=0.10	
Multiple blue globules	1 (1.3)	23 (8.0)	0.16 (0.02-1.18) p=0.12	
Globular-homogeneous pattern	3 (4.0)	27 (9.3)	0.40 (0.12-1.37) p=0.15	
Hairpin vessels	1 (1.3)	19 (6.6)	0.19 (0.03-1.46) p=0.11	
Arborizing vessels	1 (1.3)	11 (3.8)	0.34 (0.04-2.69) p=0.31	
Linear irregular vessels	2 (2.7)	10 (3.5)	0.76 (0.16-3.57) p=0.73	

[1] OR: odds ratio and 95% confidence interval (CI). [2] Unconditional multiple logistic regression including all significant features in the univariate analysis. ns=non significant.