ORIGINAL ARTICLE

Dermatoscopic features of thin (≤2 mm Breslow thickness) vs. thick (>2 mm Breslow thickness) nodular melanoma and predictors of nodular melanoma versus nodular non-melanoma tumours: a multicentric collaborative study by the International Dermoscopy Society

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Abstract

Background Thin nodular melanoma (NM) often lacks conspicuous melanoma-specific dermatoscopic criteria and escapes clinical detection until it progresses to a thicker and more advanced tumour.

Objective To investigate the dermatoscopic morphology of thin (≤2 mm Breslow thickness) vs. thick (>2 mm) NM and to identify dermatoscopic predictors of its differential diagnosis from other nodular tumours.

Methods Retrospective, morphological case–control study, conducted on behalf of the International Dermoscopy Society. Dermatoscopic images of NM and other nodular tumours from 19 skin cancer centres worldwide were collected and analysed.

Results Overall, 254 tumours were collected (69 NM of Breslow thickness ≤2 mm, 96 NM >2 mm and 89 non-melanoma nodular lesions). Light brown coloration (50.7%) and irregular brown dots/globules (42.0%) were most frequently observed in ≤2 mm NMs. Multivariate analysis revealed that dotted vessels (3.4-fold), white shiny streaks (2.9-fold) and irregular blue structureless area (2.4-fold) were predictors for thinner NM compared to non-melanoma nodular tumours. Overall, irregular blue structureless area (3.4-fold), dotted vessels (4.6-fold) and serpentine vessels (1.9-fold) were predictors of all NM compared to non-melanoma nodular lesions.

Limitations Absence of a centralized, consensus pathology review and cases selected form tertiary centres maybe not reflecting the broader community.

Conclusions Our study sheds light into the dermatoscopic morphology of thin NM in comparison to thicker NM and could provide useful clues for its differential diagnosis from other non-melanoma nodular tumours.

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Conflicts of interest

The authors have no conflict of interest to declare.

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Introduction

Melanoma is a malignant skin tumour with an increasing incidence over the last decades. Melanoma is responsible for the majority of deaths from cutaneous malignancies, with more than 95 000 new cases and almost 7200 deaths estimated in 2019 in the US representing a major public health issue.[1,2]

Nodular melanoma (NM) comprises 12–30% of all melanomas, but, however, it accounts for at least 50% of all melanomas thicker than 2 mm; hence, it has as worst prognosis and associated survival.[3,4,5] A recent observational study including approximately 120 000 patients showed that the nodular histopathologic subtype was an independent risk factor of mortality, after adjustment for other prognostic factors such as Breslow thickness, ulceration and stage.[6] The early detection of NMs while they are still thin could potentially improve the prognosis, and however, it remains particularly challenging.

Several studies have explored the dermatoscopic characteristics of NM, suggesting that they substantially differ from the features known to typify superficial spreading melanoma.[7–11] However, the diagnostic accuracy of dermatoscopy for NM is considered to be lower when compared with other melanoma subtypes.[11]

The primary aim of this international multicentre study was to investigate the dermatoscopic morphology of NM with Breslow thickness up to 1 mm and identify dermatoscopic predictors for its differential diagnosis from other nodular tumours. However, NM tend to be diagnosed at a more advanced stage, and hence, only 12 NM thinner than 1 mm were collected and the threshold for analysis was re-defined to 2 mm accordingly. The secondary aim of this study was (i) to compare the dermatoscopic features seen in thin NM (as defined above) with those found in thicker NM and (ii) to assess the dermatoscopic morphology of pigmented and non-pigmented NMs in comparison with non-melanoma tumours with nodular appearance.

Materials and methods

This was a retrospective, morphological case–control study, conducted on behalf of the International Dermoscopy Society (IDS), and was publicized on the IDS website calling for participation. The Ethics Committee approval was waived, since the study was retrospective, did not affect in any way patient's management and was conducted on anonymized data sets (waiver decision obtained by Ethics Committee, Andreas Sygros Hospital, Athens, Greece, ref. number 2511/1.3.2017).

Inclusion criteria

Patients with available close-up clinical and dermatoscopic images of: (i) tumours surgically excised and histopathologically diagnosed as NMs, routinely defined by the presence of a dermal component with no or with a minimal junctional component with a maximum of three histopathologically involved rete ridges; or (ii) surgically excised tumours with a nodular clinical morphology (with no or minimal flat component), for which melanoma was included in the clinical differential diagnosis, but the histopathologic diagnosis was other than melanoma.

Tumour characteristics and patient epidemiologic data (age and sex) were recorded in a de-identified database.

Exclusion criteria

Non-biopsied lesions and lesions lacking a definite histopathologic diagnosis were not eligible.

Feature selection

The selection of the dermatoscopic variables was based on the latest consensus and an expert consensus meeting held by the IDS particularly for the present study.[12]

The variables included in the analysis were divided into four categories: overall architecture and colours, pigmented structures, non-pigmented structures excluding vessels, vascular structures. (analytic list of criteria in Fig. S1, Supporting Information).

Image evaluation

The clinical and dermatoscopic images were evaluated by five independent investigators (DS, CP, HK, AS and SP) who were blinded for the histopathologic diagnosis. The evaluation of predefined variables was performed using an online platform (Survey Monkey), and the images were randomly presented to the evaluators. The statistical analysis was performed on the basis of agreement by at least three of the five evaluators.

Statistical analysis

Absolute and relative frequencies were obtained for the dermatoscopic characteristics. For the logistic regression analysis, outcome variables were set to thin NM or other diagnosis. Using the threshold of 1 mm of Breslow thickness, the test group (thin NM) consisted of only 12 NM. Because of the large number of variables to be assessed, this sample size was deemed as inadequate for analysis. Therefore, the threshold was changed to 2 mm. Relative risks were calculated for the dichotomous variables. Adjusted odds ratios and corresponding 95% confidence intervals were calculated by conditional multivariate logistic regression (backward elimination according to likelihood criteria). The alpha level was set at 0.05 while an alpha level of 0.10 was used as the cut-off point for removal of the variable in the automated model selection for multivariate logistic regression. Statistical analyses were performed using IBM SPSS ver. 23 (Armonk, NY, USA).

A subgroup analysis for dermatoscopically pigmented vs. non-pigmented tumours was performed for each study group. The tumours were classified as pigmented or not based on the presence of at least one dermatoscopic colour corresponding to melanin (black, light brown, dark brown, grey, blue), according to the dermatoscopic evaluation.

Results

Study sample and patients' demographics

Our study included 254 tumours in 254 unique patients. Sixty-nine lesions (27.2%) were NMs ≤2 mm Breslow thickness, 96 lesions (37.8%) were NMs >2 mm Breslow, and 89 lesions (35.0%) were non-melanoma nodular lesions. The latter group included 31 Seborrheic Keratosis, 28 basal cell carcinoma (BCC), 10 dermal nevi, 10 squamous cell carcinoma, five benign adnexal tumours, and five angiomas. The basic clinical and histopathologic features of the 254 tumours and the demographic characteristics of the patients are shown in Table 1. Sex distribution differed among study groups, with NMs ≤2 mm Breslow thickness being more common among females (female/male = 1.4), whereas thicker NM had a predilection for males (male/female = 1.63). Regarding anatomic location, NMs ≤2 mm Breslow thickness tended to develop on the extremities (60.3%) compared to the group of thicker NM (>2 mm Breslow thickness) which mostly arose on the trunk (44.7%).

Dermatoscopic features

The analytic results of the dermatoscopic analysis are shown in Tables S1–S4 (Supporting Information). Out of the 69 NMs ≤2 mm Breslow thickness, 50 (72.5%) displayed a dermatoscopic asymmetry of colours, and 44 (63.8%) had an asymmetric distribution of structures. Thicker NMs exhibited colour and structure asymmetry in 77.1% and 74.0%, respectively, and non-melanomas in 39.3% and 53.9%, respectively. Light brown was the most commonly observed colour in NMs up to 2 mm Breslow (50.7%), followed by white (46.4%), blue (44.9%) and pink (43.5%). In thicker NMs, the most frequent colours were blue (64.6%), white (53.1%) and pink (52.1%; Table S1, Supporting Information).

Table 1 Demographic data of included patients and clinical characteristics of the tumours

	Melanomas ≤2 mm (*n* = 69)	Melanomas >2 mm (*n* = 96)	Non-melanomas (*n* = 89)
Age			
Mean (years)	52.6	60.4	59.4
Range (years)	18–88	23–94	17–95
Sex (%)			
Male	27 (41.5)	49 (62.0)	55 (61.8)
Female	38 (58.5)	30 (38.0)	34 (38.2)
Anatomic site (%)			
Head/neck	2 (2.9)	11 (11.7)	36 (40.4)
Trunk	25 (36.8)	42 (44.7)	34 (38.2)
Upper extremities	21 (30.9)	21 (22.3)	5 (5.6)
Lower extremities	20 (29.4)	17 (18.1)	12 (13.5)
Acral	0	2 (2.1)	1 (1.1)
Mucosal	0	1 (1.0)	1 (1.1)
Clinically pigmented (%)			
No	24 (34.8)	22 (22.9)	48 (53.9)
Yes	45 (65.2)	74 (77.1)	41 (46.1)
Breslow thickness			
Mean (mm)	1.4	4.4	–
Range (mm)	0.5–2.0	2.1–12.0	–

The most common dermatoscopic structures in NMs up to 2 mm of Breslow thickness were irregular brown dots/globules (42.0%), irregular blue structureless area (33.3%), ulceration (29%), shiny white blotches/strands (27.5%), shiny white streaks (26.0%) and irregular (eccentric) black blotch (24.6%). In thicker NMs, the most frequent dermatoscopic structures were ulceration (68.7%), irregular blue structureless area (53.1%), shiny white blotches/strands (41.6%) and shiny white streaks (23.9%; Tables S2 and S3, Supporting Information). In terms of vascular structures, the most commonly observed morphologic types of vessels in NMs up to 2 mm of Breslow thickness were dotted (21.7%) and serpentine (18.8%), whereas in thicker NM, serpentine (43.7%), dotted (24.0%) and corkscrew vessels (17.8%) were the most common. (Table S4, Supporting Information).

Multivariate analysis revealed three important predictors of NMs ≤2 mm Breslow thickness as compared to non-melanomas: dotted vessels, shiny white streaks and irregular blue structureless area, which were associated with a 3.4-fold, 2.9-fold and 2.4-fold higher probability for melanoma, respectively (Table 2). In total, irregular blue structureless areas, dotted vessels and serpentine vessels represented predictors of NMs, irrespectively of Breslow thickness, as compared to non-melanomas with a 3.4-fold, 4.6-fold and 1.9-fold probability, respectively (Table 3). In the comparative analysis between thinner and thicker NM, irregular brown dots/globules were found to be a predictor of NM up to 2 mm of Breslow thickness (1.8-fold) and serpentine vessels a predictor of thicker NM (3.3-fold).

Subgroup analysis

In the subgroup analysis for pigmented and non-pigmented tumours, the respective numbers of tumours in each group were as follows: 57/69 (82.6%) pigmented and 12/69 (17.4%) non-pigmented NMs ≤2 mm, 75/96 (78.1%) pigmented and 21/96 (21.9%) non-pigmented NMs thicker than 2 mm, and 46/89 (51.7%) pigmented and 43/89 (48.3%) non-pigmented non-melanomas. Of the remaining dermatoscopic criteria, those with the most important differences in frequency between pigmented and non-pigmented NMs are shown in Tables S5 and S6 (Supporting Information).

We found that non-pigmented NMs were more symmetric, especially in terms of colours. Vascular structures were more frequently detected in non-pigmented NMs as compared to pigmented ones in both groups (thinner and thicker NMs). In the group of NMs ≤2 mm Breslow thickness, dotted vessels were the predominant type of vessels in non-pigmented tumours whereas serpentine vessels occurred more frequently in pigmented NMs. In the group of thicker NMs, serpentine vessels prevailed in both pigmented and non-pigmented subgroups. A noteworthy finding of the subgroup analysis was the greater frequency of dermatoscopically observed ulceration in non-pigmented NMs ≤2 mm Breslow thickness (41.7%) as compared to pigmented ones (26.3%). This difference was reversed in the group of thicker NMs, with respective frequencies of 51.3% for non-pigmented tumours and 73.4% for pigmented NMs.

The multivariate analysis was repeated within the subgroups of pigmented and non-pigmented tumours in order to identify predictors of NM ≤2 mm Breslow thickness as compared to non-melanomas (Table 2). No predictor was found for non-pigmented tumours, whereas irregular blue structureless area represented a melanoma predictor among pigmented tumours (two-fold increased probability).

Table 2 Multivariate dermatoscopic predictors of nodular melanoma up to 2 mm of Breslow thickness

Dermatoscopic predictor	*P*	Adjusted odds ratio	95% confidence intervals	
			Min	Max
vs. non-melanoma				
Irregular blue structureless area	0.009	2.4	1.2	4.8
White shiny streaks/lines	0.034	2.9	1.1	7.8
Dotted vessels	0.015	3.4	1.3	8.9
vs. melanoma thicker than 2 mm				
Irregular brown dots/globules	0.037	1.8	1.0	3.2
Serpentine vessels	0.008	0.3	0.1	0.7
vs. non-melanoma among non-pigmented tumours only				
None detected				
vs. non-melanoma among pigmented tumours only				
Irregular blue structureless area	0.049	2.0	1.0	3.9

Table 3 Multivariate dermatoscopic predictors of nodular melanoma (irrelevant of Breslow thickness)

Dermatoscopic predictor	*P*	Adjusted odds ratio	95% confidence intervals	
			Min	Max
Irregular blue structureless area	0.001	3.4	1.7	6.6
Dotted vessels	0.003	4.6	1.7	12.6
Serpentine vessels	0.040	1.9	1.0	3.6

Discussion

Herein, we investigated the dermatoscopic morphology of NM at a relatively early phase of its progression based on histopathologic thickness. We attempted to identify dermatoscopic predictors for its differential diagnosis from other tumours and provide insights into the morphologic evolution of NM as tumour thickness increases.

Interestingly, patients presenting with NM ≤2 mm had a mean age of 52 years, 8 years younger when compared to those with thicker tumours (60 years). In addition, patients with thinner NMs were more likely to be female compared with the male-

dominated thicker NMs (Table 1). While this difference might be partially attributed to sex-related biologic characteristics, it is more likely to be explained by the increased awareness for the presence of melanoma among females as compared to males.[13–17] Additionally, 35% of NMs ≤2 mm Breslow thickness and 23% of thicker NMs were clinically non-pigmented. This finding is in line with prior literature suggesting that NM is much more frequently hypo- or amelanotic, as compared to other melanoma subtypes.[18–20] A noteworthy finding in our dataset was NMs of the head/neck area accounted for only 2% of NMs ≤2 mm and for 11% of NMs >2 mm. Similarly, none of the NMs ≤2 mm was located on acral sites, whereas 2.1% of thicker melanomas were acral. This findings highlight that early diagnosis of NM is more problematic on the head/neck area and on acral skin as compared to the trunk and extremities. (Table 1).

Dermatoscopic analysis revealed that NM ≤2 mm Breslow thickness typically presents with 2 or more colours, usually light brown, blue, white and pink colour (Fig. 1). However, in line with previous publications, we found that an important proportion of NMs (up to 30%) remain symmetric in terms of dermatoscopic colours and structures.[2,8–10,21,22]

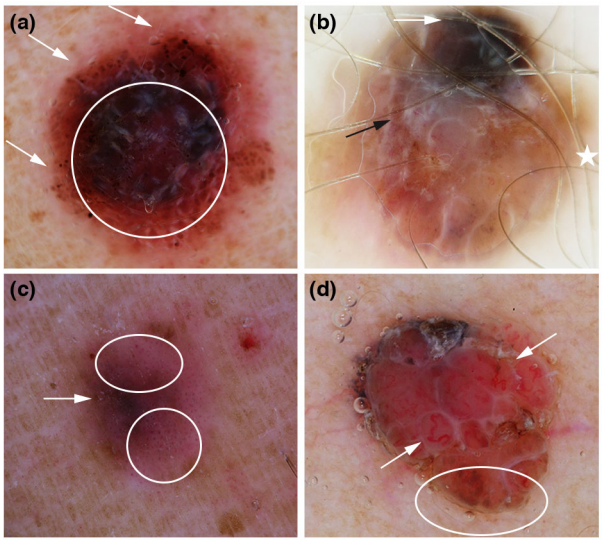

Figure 1 Nodular Melanoma (NM) with a Breslow thickness ≤2 mm. (a) Irregular brown dots and globules (white arrows) at the periphery of a 1.7 mm Breslow thickness melanoma along with white shiny strands and blue structureless area (white circle) in the centre of the lesion. (b) A thin NM (1.5 mm Breslow thickness) with an eccentric black blotch (white arrow), irregular light brown coloration (white star) and white shiny structures (black arrow). (c) Dotted vessels (white circles) prevail in this 0.5 mm Breslow thickness NM along with an irregular blue structureless area (white arrow). (d) Serpentine vessels (white arrows) are prominent in this hypopigmented thin NM (1.1 mm Breslow thickness) with scarce light brown coloration (white circle) at the periphery.

Irregular brown dots/globules, irregular blue structureless area, ulceration, white shiny blotches/strands and white shiny streaks were the most frequently encountered dermatoscopic structures in the group of thin NMs (Fig. 1). In contrast, atypical network, regression structures and irregular streaks were rarely found in our overall sample of NM. The latter finding is consistent with pre-existing literature[8,10,22,23] and is explained by the fact that these features correspond to histopathologic alterations at the level of the dermo-epidermal junction, which are absent or minimal in NM.[11,24,25]

The multivariate analysis revealed three important predictors of NM ≤2 mm Breslow thickness as compared to non-melanomas: dotted vessels, white shiny streaks/lines and irregular blue structureless area (Fig. 1). A comparison of these results with previously reported findings is problematic because of the scarcity of published evidence. The largest previous case–control study that included 83 cases of NM reported numerous univariate predictors of NM, but a multivariate logistic regression analysis was not performed.[8]

Dotted vessels can be found in several benign and malignant skin tumours and inflammatory skin diseases (i.e. common nevi, Spitz nevi, dermatofibromas, lichen planus-like keratosis, Bowen's disease, superficial BCCs on the legs, psoriasis, eczema)[26–31] as well as in flat pigmented and amelanotic melanoma.[10,32] However, almost all of the aforementioned conditions manifest as clinically flat lesions, whereas dotted vessels in nodular tumours have not been frequently described. Considering that dotted vessels represented also the strongest predictor in the entire set of NM, irrespectively of Breslow thickness, (Tables 2 and 3), our data combined with pre-existing evidence strongly suggest that a nodule displaying dotted vessels should be considered as highly suspicious for NM (Fig. 1).[8,18,33]

White shiny streaks/lines have been previously suggested to represent a melanoma-specific structure and our findings support this also for NM ≤2 mm Breslow thickness,[18] while white shiny blotches/strands—a feature of BCC as well—lost their diagnostic significance in the multivariate analysis (Fig. 1).[34]

Irregular blue structureless area was an independent multivariate predictor of NM in the entire set, of NM ≤2 mm (Tables 2 and 3), and in the subgroup analysis for pigmented tumours only (Fig. 1). The presence of blue pigmentation in NM had been reported in previous studies.[7–8,35,36] Our results corroborate Argenziano *et al.*[11] findings that the combination of blue and black colour within a nodular lesion is strongly suggestive of NM ('blue-black rule'). However, only 13% of NMs ≤2 mm Breslow thickness displayed blue-black coloration.

Our comparative analysis between the two groups of NMs may provide insights into the dermatoscopic evolution of NM. A reasonable finding of the latter analysis was that the proportion of NMs with a dermatoscopic symmetry decreases as the thickness of NM increases. In terms of colours, the most

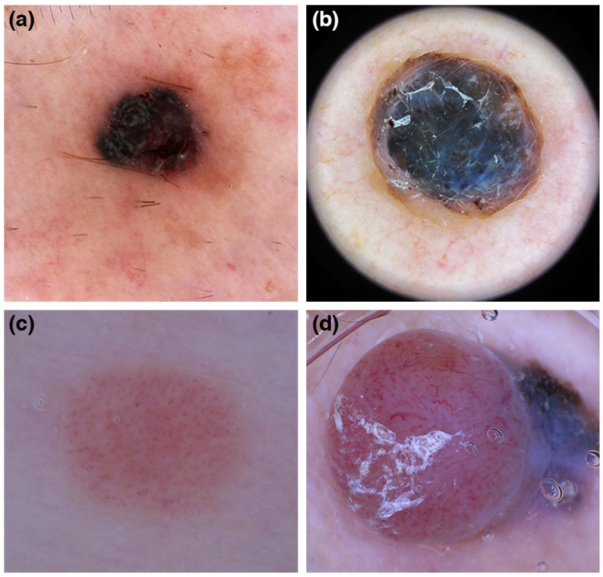

Figure 2 The dermatoscopic evolution of nodular melanoma (NM). As the thickness increases from a 1.05 mm Breslow thickness (a) to a thicker 2.7 mm Breslow thickness NM (b) blue-black pigmentation becomes more intense. In the same context, vascularization is more polymorphic in more advanced NM in terms of Breslow thickness (c = 0.6 mm Breslow thickness and d = 2.1 mm Breslow thickness).

important difference was the predominance of light brown colour in thinner NMs and blue colour in thick NMs. The most striking difference in terms of dermatoscopic structures was the predominance of irregular brown dots/globules in NMs ≤2 mm Breslow thickness (Fig. 1), as compared to their much lower frequency in thicker NMs. Concerning vascular morphology, dotted vessels prevailed in NMs ≤2 mm Breslow thickness (Fig. 1) whereas serpentine vessels in the group of thicker tumours (Fig. 2). Corkscrew vessels were also much more frequent in thicker NMs, possibly corresponding to the increased tumour neo-angiogenesis (Fig. 2). These findings are consistent with pre-existing literature on the vascular pattern of melanoma.[8,26,33,37–40] In summary, the main dermatoscopic changes in NM as thickness increases are that brown colour becomes less evident and blue more prominent, dermatoscopically observed ulceration increases and dotted vessels are replaced by serpentine and highly tortuous linear vessels (Fig. 2).

The subgroup analysis of non-pigmented and pigmented tumours revealed that non-pigmented NMs were much more frequently symmetric in terms of colours as compared to pigmented ones, a feature that reflects a common problem in everyday practice leading to delayed diagnosis or inappropriate treatment.[41] In contrast, most of the pigmented NMs displayed a dermatoscopic asymmetry of colours and structures which is consistent with two previous case–control studies on pigmented NM that reported a high frequency of asymmetric pigmentation.[9,24]

Limitations

The main limitation of our study is that it included a highly selected case series, from tertiary centres, which may not be representative of the broader community. However, our study represents the largest to date collection of images from NM of different tumour thicknesses, including thinner tumours of Breslow ≤2 mm. Another limitation is the absence of a centralized, consensus pathology review, which carries the potential of diagnostic misclassification, a problem often seen with the diagnosis of NM.

Conclusion

In conclusion, our study confirms the insidious nature of a NM at its early stages and suggests that irregular brown dots/globules, irregular blue structureless area, white shiny streaks/lines and dotted vessels can be useful dermatoscopic clues for its clinical diagnosis. Considering the scant available evidence on the topic, our findings need to be further elucidated, but may assist in the early recognition of this aggressive type of melanoma.

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IRB approval status

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Analytic list of the dermatoscopic criteria for each study group.

Table S1. Dermatoscopic analysis per study group (Variable Group I: Overall architecture and colors).

Table S2. Dermatoscopic analysis per study group (Variable Group II: pigmented structures).

Table S3. Dermatoscopic analysis per study group (Variable Group III: non-pigmented structures excluding vessels).

Table S4. Dermatoscopic analysis per study group (Variable Group IV: vascular structures).

Table S5. Differences in dermatoscopic criteria between pigmented and non-pigmented nodular melanomas up to 2 mm of Breslow thickness.

Table S6. Differences in dermatoscopic criteria between pigmented and non-pigmented nodular melanomas with a Breslow thickness more than 2 mm