Dermatoscopic features of nodular melanoma with Breslow thickness up to 2mm: a multicentric collaborative study by the International Dermoscopy Society

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Question: Which are the dermatoscopic characteristics of a thin nodular melanoma up to 2mm Breslow thickness?

Findings: In this multicenter cohort study of 254 nodular tumors, we observed that nodular melanomas with a Breslow thickness ≤ 2mm are asymmetric lesions in terms of colors and dermatoscopic structures. Light brown coloration is the most frequent color seen in these tumors. Irregular brown dots/globules, irregular blue structureless areas, ulceration, white shiny blotches/strands, white shiny streaks, irregular (eccentric) black blotches, dotted and serpentine vessels are typical of features of thin (≤2 mm) nodular melanoma.

Meaning: Based on these findings, dermatoscopy can help detect a nodular melanoma at an early phase of its evolution, based on Breslow thickness.

Abstract

Importance: Thin nodular melanoma (NM) often lacks conspicuous melanoma-specific criteria, and escapes clinical detection until it progresses to an advanced stage.

Objective: To investigate the dermatoscopic morphology of NM with a Breslow thickness up to 2 mm and to identify predictors for its differential diagnosis from other nodular tumors.

Design: Retrospective, morphological case-control study, conducted on behalf of the International Dermoscopy Society. Dermatoscopic images of NM and other nodular tumors were collected and analyzed by 5 independent investigators for the presence of pre-defined dermatoscopic variables. Predictors were calculated by multivariate logistic regression analysis.

Setting: Nineteen specialized skin cancer centers from 13 countries.

Participants: A total set of 254 patients with 254 tumors including 69 NM of Breslow thickness ≤ 2 mm, 96 NM thicker than 2mm and 89 non-melanoma ~~ocular~~ nodular lesions (BCC, dermal nevi, dermatofibromas, seborrheic keratosis, etc).

Main outcome and measures: Frequencies of dermatoscopic findings were calculated based on the categorization into 4 groups of dermatoscopic variables (overall architecture and colors, pigmented structures, non-pigmented structures excluding vessels, and vascular structures). Relative risks were calculated for the dichotomous variables. Adjusted odds ratio (OR) and corresponding 95% confidence intervals (CI) were calculated by conditional multivariate logistic regression.

Results: The most frequent colors seen in NMs with a Breslow thickness up to 2mm were light brown (50.7%), white (46.4%), blue (44.9%) and pink (43.5%).

Irregular brown dots/globules (42.0%), irregular blue structureless areas (33.3%), ulceration (29%), white shiny blotches/strands (27.5%), white shiny streaks (26.0%) and irregular (eccentric) black blotch (24.6%) were the most frequent dermatoscopic structures. The multivariate analysis revealed three dermatoscopic predictors of thin NM, as compared to non-melanoma nodular lesions: dotted vessels (3.4-fold), white shiny streaks (2.9-fold) and irregular blue structureless area (2.4-fold). In the comparative analysis between thinner and thicker NM, irregular brown dots/globules were found to be a predictor of NM up to 2mm of Breslow thickness (1.8-fold) and serpentine vessels a predictor of thicker NM (3.3-fold).

Conclusions and relevance: Our study sheds light into the dermatoscopic morphology of thin NM in comparison to thicker NM and provides useful clues for its differential diagnosis from other nodular tumors.

Keywords: nodular melanoma; thickness; pigmented tumors; non-pigmented tumors; non-melanoma tumors; dermatoscopy; dermoscopy

Introduction

Melanoma is a malignant skin tumor with an increasing incidence over the last decades. Melanoma is responsible for the majority of deaths from cutaneous malignancies, with more than 90000 new cases and almost 9000 deaths recorded in 2018 in the US.[1,2] Despite primary and secondary prevention measures, melanoma represents a major public health issue in fair-skinned populations.

Among the four main histopathological subtypes of melanoma (superficial spreading, nodular, lentigo maligna and acral lentiginous), nodular melanoma (NM) comprises 12-30% of all melanomas, but at least 50% of all melanomas thicker than 2 mm, hence its worst prognosis and associated survival.[3,4,5] A recent observational study including approximately 120000 patients showed that the nodular subtype was an independent risk factor of mortality, after adjustment for prognostic factors such as Breslow thickness, ulceration and stage.[6] The detection of NMs while they are still thin could improve the prognosis, but is particularly difficult.

Dermatoscopy is a non-invasive diagnostic technique, widely applied for the clinical diagnosis of melanocytic and non-melanocytic tumors and other skin diseases. Several studies described the dermatoscopic characteristics of NM, suggesting that they substantially differ from the features known to typify superficial spreading melanoma.[7-11] Overall, 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 multicenter study was to investigate the dermatoscopic morphology of NM with a Breslow thickness up to 1mm and identify dermatoscopic predictors for its differential diagnosis from other nodular tumors. Because only a few NM thinner than 1mm were collected, ~~,~~ the threshold for analysis was re-defined to 2mm. Secondary aims were to compare the dermatoscopic features

seen in thin NM (as defined above) with those found in thicker NM, and to separately assess the dermatoscopic morphology of pigmented and non-pigmented NMs and non-melanoma tumors with nodular appearance.

Materials and methods

This was a retrospective, morphological case-control study, conducted on behalf of the International Dermoscopy Society (IDS) following an open call on the IDS website. 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 datasets.

Members of the IDS were invited to submit clinical and dermatoscopic images of: i) tumors 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 3 histopathologically involved rete ridges; or ii) surgically excised tumors 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. Tumors lacking a definite histopathologic diagnosis were not eligible. Members could submit images of tumors fitting to one or both of the above categories. All members submitting NM cases were asked to review the histopathologic slides to ensure that they meet the inclusion criteria. Basic epidemiologic data of the patients (age and sex) were also mandatory. The images were randomized in anonymized datasets.

The selection of the dermatoscopic variables was based on pre-existing literature and an expert consensus held by the IDS particularly for the present study. The variables included in the analysis were divided into 4 categories (overall

architecture and colors, pigmented structures, non-pigmented structures excluding vessels, vascular structures). The analytic list of criteria can be seen in e-figure 1 of the supplementary material.

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The clinical and dermatoscopic images were evaluated by 5 independent investigators (DS, CP, HK, AS, SP) who were blinded for the histopathologic diagnosis. The evaluators were asked to assess the presence or absence of pre-defined variables selected as described above. The evaluation was performed using an on-line 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 1mm 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 2mm. Relative risks were calculated for the dichotomous variables. Adjusted odds ratios (OR) and corresponding 95% confidence intervals (CI) 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 vers. 2 (Armonk, NY, USA).

A subgroup analysis for dermatoscopically pigmented versus non-pigmented tumors was performed for each study group. The tumors were classified as pigmented

or not based on the presence of at least one dermatoscopic color corresponding to melanin (black, light brown, dark brown, gray, blue), according to the dermatoscopic evaluation.

Results

Study sample and patients' demographics.

Our study finally included 254 tumors collected from 254 patients. Of them, 69 (27.2%) were NMs ≤ 2mm Breslow thickness, 96 (37.8%) were thicker than 2mm NMs and 89 (35.0%) were non-melanoma nodular lesions. The latter group included 31 seborrheic keratoses, 28 basal cell carcinomas, 10 dermal nevi, 10 squamous cell carcinomas, 5 benign adnexal tumors, and 5 angiomas. The basic clinical and histopathological features of the 254 tumors and the demographic characteristics of the patients are shown in Table 1. As shown in the table, the sex distribution differed among study groups, with NMs ≤2mm Breslow thickness being more common among females with a female/male ratio of 1.4, whereas thicker NM had a predilection for males with a male/female ratio of 1.63. Regarding anatomic location, NMs ≤2mm 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 e-tables 1-4 in the supplement. Out of the 69 NMs ≤2 mm Breslow thickness, 50 (72.5%) displayed a dermatoscopic asymmetry of colors and 44 (63.8%) an asymmetric distribution of

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structures. ,–Thicker NMs exhibited color 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 color in NMs up to 2mm of Breslow thickness (50.7%), followed by white (46.4%), blue (44.9%) and pink (43.5%). In thicker NMs, the most frequent colors were blue (64.6%), white (53.1%) and pink (52.1%) (e-table 1).

The most common dermatoscopic structures in NMs up to 2mm of Breslow thickness were irregular brown dots/globules (42.0%), irregular blue structureless area (33.3%), ulceration (29%), white shiny blotches/strands (27.5%), white shiny 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%), white shiny blotches/strands (41.6%) and white shiny streaks (23.9%) (e-tables 2 and 3). In terms of vascular structures, the most commonly observed morphologic types of vessels in NMs up to 2mm 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. (e-table 4).

The multivariate analysis revealed three dermatoscopic predictors of NMs ≤2mm Breslow thickness as compared to non-melanomas: dotted vessels, white shiny 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 the comparative analysis between thinner and thicker NM, irregular brown dots/globules were found to be a predictor of NM up to 2mm 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 tumors, the respective numbers of tumors in each group were: 57/69 (82.6%) pigmented and 12/69 (17.4%) non-pigmented NMs ≤ 2mm, 75/96 (78.1%) pigmented and 21/96 (21.9%) non-pigmented NMs thicker than 2mm, and 46/89 (51.7%) pigmented and 43/89 (48.3%) non-pigmented non-melanomas. Obviously, dermatoscopic pigmented structures were detected only in the subgroups of pigmented tumors. Of the remaining dermatoscopic criteria, those with the most important differences in frequency between pigmented and non-pigmented NMs are shown in etables 5 and 6 of the supplement.

As shown in the tables, non-pigmented NMs were generally more symmetric, especially in terms of colors. 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 ≤ 2mm Breslow thickness, the dotted type was the most frequent morphologic type of vessels in non-pigmented tumors and the serpentine type 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 ≤ 2mm 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 tumors and 73.4% for pigmented NMs.

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

Discussion

Our study investigated the dermatoscopic morphology of NM at a relatively early phase of its progression based on histopathologic thickness, to identify dermatoscopic predictors for its differential diagnosis from other tumors and to provide insights into the morphologic evolution of NM as tumor thickness increases.

In this descriptive study, demographic data and the clinical characteristics of the tumors revealed findings of interest. The mean age of patients with NM ≤ 2mm was 8 years younger (52 years) compared to those with thicker tumors (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 of the presence of melanoma warning signs for females as compared to males, which has been repeatedly reported in the literature.[12-16] Additionally, 35% of NMs ≤ 2mm 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.[17-19] However, the dermatoscopic analysis showed that the percentage of NM without pigmentation was 17.4% for NMs ≤ 2mm Breslow thickness and 21.9% for thicker NMs, highlighting that dermatoscopy often reveals clinically invisible pigmentation. The latter finding is particularly relevant for clinical practice, since it is known that dermatoscopic pigmented structures usually provide significant diagnostic information.[20-22]

The descriptive dermatoscopic analysis revealed that NM ≤ 2mm Breslow thickness is usually a polychromatic tumor, combining 2 or more of light brown, blue,

white and pink color (Figure 1). However, in line with previous publications, we found that an important proportion of NMs (up to 30%) remain symmetric in terms of dermatoscopic colors and structures. [2, 8-10, 23, 24]

Irregular brown dots/globules, irregular blue structureless area, ulceration, white shiny blotches/strands and white shiny streaks are the most frequently seen dermatoscopic structures in the group of thin NMs (Figure 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, 25] 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, 26, 27] In terms of vascular structures, dotted vessels and serpentine vessels were the most frequent morphologic types found in NMs up to 2mm of Breslow thickness.

The multivariate analysis revealed 3 important predictors of NM $\leq$ 2 mm Breslow thickness as compared to non-melanomas: dotted vessels, white shiny streaks/lines and irregular blue structureless area (Figure 1). A comparison of these results with previously reported findings is problematic because of the scarce 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 tumors and inflammatory skin diseases, including common nevi, Spitz nevi, dermatofibromas, lichenoid keratoses, Bowen's disease, superficial basal cell carcinomas when located on the legs, psoriasis, eczema and many other entities.[28-33] They have also been reported in flat pigmented and amelanotic melanoma.[10, 34] However, almost all of the aforementioned conditions manifest as clinically flat lesions, whereas dotted vessels

in nodular tumors have not been frequently described. Clear cell acanthoma represents an exception, but it is dermatoscopically characterized by a peculiar reticular arrangement of dotted vessels.[35] Considering that dotted vessels represented the strongest predictor of NM ≤ 2mm thickness in our analysis, our data combined with pre-existing evidence strongly suggest that a nodule displaying dotted vessels should be considered as highly suspicious for NM (Figure 1). [8, 36, 37]

White shiny streaks/lines have been previously suggested to represent a melanoma-specific structure and our findings support this also for NM ≤ 2mm Breslow thickness.[38] White shiny blotches/strands were also frequently detected, but their diagnostic significance was lost in the multivariate analysis. This is because white shiny blotches/strands can also be found in basal cell carcinoma, which represented a significant part of our control group (Figure 1). [39]

Irregular blue structureless area was an independent multivariate predictor of NM ≤ 2mm thickness in the overall set, as well as in the subgroup analysis for pigmented tumors only (Figure 1). The presence of blue pigmentation in NM had been reported in previous studies.[7,-8, 40-41] In one of them, it was suggested that the combination of blue and black color within a nodular lesion is strongly suggestive of NM ("blue-black rule").[11] The results of the present study confirm that a positive "blue-black" rule is highly specific for NM, as compared to non-melanomas. However, only a small minority of NMs ≤2 mm Breslow thickness displayed both blue and black color (13%).

Our comparative analysis between NM ≤ 2mm Breslow thickness and thicker NMs may provide insights into the evolution of NM from a dermatoscopic point of view. A reasonable finding of the latter analysis was that the proportion of NMs that retain a dermatoscopic symmetry decreases as the thickness of NM increases. In terms

of dermatoscopic colors, the most important difference was the predominance of light brown color in thinner NMs and blue color in thick NMs. The most striking difference between thinner and thicker NMs in terms of dermatoscopic structures was the predominance of irregular brown dots/globules in NMs ≤ 2mm Breslow thickness (Figure 1), as compared to their much lower frequency in thicker NMs. Concerning vascular morphologic types, dotted vessels prevailed in NMs ≤ 2mm Breslow thickness (Figure 1) and serpentine vessels in the group of thicker tumors (Figure 2). Corkscrew vessels were also much more frequent in thicker NMs, possibly corresponding to the increased tumor neo-angiogenesis (Figure 2). These findings are consistent with pre-existing literature on the vascular pattern of melanoma.[8, 28, 36, 42-45] In summary, the main dermatoscopic changes in NM as thickness increases are that brown color becomes less evident and blue more prominent, dermatoscopically observed ulceration increases and dotted vessels are replaced by serpentine and highly tortuous linear vessels (Figure 2).

The subgroup analysis of non-pigmented and pigmented tumors revealed some interesting findings. First, non-pigmented NMs were much more frequently symmetric as compared to pigmented ones, especially in terms of color. This lack of asymmetry is consistent with previous evidence and reflects a common problem in everyday practice leading to delayed diagnosis or inappropriate treatment.[46] In contrast, most of the pigmented NMs displayed a dermatoscopic asymmetry of colors and structures. The latter is consistent with 2 previous case-control studies on pigmented NM that reported a high frequency of asymmetric pigmentation.[9, 26]

Our study represents the largest collection of images from NM of different tumor thicknesses, including thinner tumors of Breslow less than 2 mm. Even though it includes a highly selected case series with potential selection bias and, in the

absence of a central pathology review, carries the potential of diagnostic misclassification, a problem often seen with the diagnosis of nodular melanoma, our study identifies important morphologic criteria that can help distinguish this particular subtype from non-melanoma nodular lesions and even help to identify thinner NM.

In conclusion, our study confirms the insidious nature of a NM at its early stages, suggests irregular brown dots/globules, irregular blue structureless area, white shiny streaks/lines and dotted vessels as useful dermatoscopic clues for its clinical diagnosis and sheds light into the morphologic evolution of the tumor. 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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Figure Legends

e-figure 1: Analytic list of the dermatoscopic criteria for each study group

Figure 1: Nodular Melanoma (NM) with a Breslow thickness ≤ 2mm. **A**, Irregular brown dots and globules (white arrows) at the periphery of a 1.7mm Breslow thickness melanoma along with white shiny strands and blue structureless area (white circle) in the center 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 (1.1mm Breslow thickness) with scarce light brown coloration (white circle) at the periphery.

Figure 2: Nodular Melanoma (NM) with a Breslow thickness >2mm. **A**, Irregular blue-white structureless areas (white circle) prevail at the upper part of this 3mm Breslow thickness NM, while pink-whitish coloration with a combination of serpentine vessels (black circle) are prominent at the lower part of the lesion. **B**, Areas of ulceration (white circle) along with serpentine vessels prevail in this amelanotic NM (4.3 mm Breslow thickness). **C**, At the same context with B ulceration (white arrow) is also striking in this advanced NM (7mm Breslow thickness). On the contrary this tumor is heavily pigmented with blue-black coloration (white circle). **D**, Corkscrew vessels (white circle) can be seen in the amelanotic part of the lesion along with serpentine vessels (black arrow). At the right part an area of blue-black pigmentation can be observed with a combination of a whitish hue (white arrow) in this 2.1 mm Breslow thickness NM.