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ORIGINAL ARTICLE

Dermoscopic features of nevoid melanoma: a retrospective study

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ABSTRACT

BACKGROUND: Nevoid melanoma (NeM) is a rare variant of melanoma resembling melanocytic nevus. The aim of the study was to systematically review the dermoscopic features of NeM.

METHODS: A hospital-based retrospective study was conducted. Dermoscopic features of NeMs diagnosed through excisional biopsy between January 2015 1, and March 1, 2021, were compared to superficial spreading melanomas (SSMs) matched by Breslow's thickness. Then, a literature search was performed. Electronic searches on PubMed database *via* Medline were conducted to retrieve any manuscript reporting detailed dermoscopic features of histopathologically confirmed NeM.

RESULTS: A total of 60 malignant melanomas (MM) comprising 20 NeM and 40 SSM were collected. Twelve out of 20 (60%) NeM showed a nevus-like appearance, including reticular and globular patterns, and in 35% of these cases it was detected because of dermoscopic changes. Then, a total of seven original manuscripts were retrieved from the literature review, comprising 56 cases overall. NeM showed nevus-like pattern in 53% of the cases, multicomponent pattern in 21% and amelanotic in 9%. Enlargement, irregularly distributed dots/globules, irregular pigmentation, and atypical vascular pattern were found in NeM with nevus-like appearance. NeM with multicomponent pattern were characterized by irregular pigmentation, blue-white veil, irregular dots and atypical vascular pattern. Amelanotic NeM is rare and show atypical vascular pattern and milia-like cysts.

CONCLUSIONS: Dermoscopy of NeM is challenging as it frequently shows a nevus-like pattern, but clues and detection of dermoscopic changes may help to identify it.

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KEY WORDS: Dermoscopy; Melanoma; Nevus.

Nevoid melanoma (NeM) is a rare nosological variant of melanoma with significant resemblance to a conventional melanocytic nevus. The term "verrucous and pseudonevoid melanoma" was coined by Levene in 1980 to describe a kind of melanoma with a papillated architecture and clinical/histological overlap with Unna's nevus.[1] Later the term was used by Schmoeckel in a large series of cases and it was defined for the first time diagnostic histologic criteria.[2] NeM clinically may present as a dome-shaped or verrucous, generally pigmented papule, plaque or nodule.[3] Dermoscopy is a well-known noninvasive *in-vivo* technique for the microscopic examination of skin lesions with the potential to improve the diagnostic accuracy.[4] To our knowledge neither comparative studies nor systematic reviews investigating NeM dermoscopic characteristics exists. The aim of this study was to assess the dermoscopic features of NeM compared to non-nevoid superficial spreading melanoma (SSM), and to review all the studies reporting NeM dermoscopic features according to the best evidence.

Materials and methods

Hospital-based retrospective study

An observational retrospective study of clinical and dermoscopic pictures collected from patients from the University hospital of Verona was undertaken. Inclusion crite-

ria were adult patients with NeM diagnosed through excisional biopsy between January 1, 2015 and March 1, 2021, verified by at least two dermo-pathologists and classified according to predefined histopathologic criteria previously published in the literature. Particularly the presence of bland cytological appearance of melanocytes, apparent maturation in the deep dermis, absence of epidermotropism, and brisk mitotic activity were considered.[2] On the base of Breslow's thickness, the cases were 1:2 matched with patients of the same Fitzpatrick phototype and diagnosed with SSM (controls). Patients with lentigo maligna, acral, nodular, spitzoid and other rare variants of melanoma were excluded. Clinical and dermoscopic features of the patients meeting the inclusion criteria were subsequently analyzed. Sequential follow-up pictures were also retrieved when available. All the pictures were taken under standardized conditions through video-dermoscopic equipment. For cases and controls the following clinical/histological data were collected: age, gender, date of the diagnosis of melanoma, body site, diameter of melanoma (measured with a ruler before surgery, and reported on the patient's medical records), Breslow's thickness and Clark's level, ulceration, number of mitoses, tumor-infiltrating lymphocytes, regression, associated nevus, clinical signs that aroused suspicion of melanoma (*e.g. de-novo* lesion *versus* change in color, shape, dimension in pre-existing lesion), personal and family history of melanoma. All the lesions were first evaluated for their macroscopic aspects (macule, papule, plaque, nodule) and colors (skin color-pink, red, blue, white, grey, brown, and black). Finally, the analysis of the global pattern (nevus-like, amelanotic, multicomponent pattern) and local dermoscopic features was performed by two dermatoscopists. Nevus-like pattern was initially defined by a papillomatous surface resembling a dermal nevus on clinical inspection and revealing a cobblestone pattern on dermoscopy.[5] Plane or slightly elevated lesions presenting with prevalent globular pattern or reticular pattern and identified because of enlargement were assimilated to nevus-like pattern. Amelanotic pattern was defined by the lack of clinically and dermoscopically significant pigmentation. Multicomponent pattern by melanoma-specific clinical and dermoscopic criteria. As local features the following items were considered: comedo-like openings, milia like cysts, blue-grey ovoid structures, atypical network, blue-white veil, irregular streaks, regression, irregular pigmentation, irregular dots/globules, and atypical vascular pattern, corresponding to any combination of two or more different types of vascular structures (arborizing vessels, hairpin vessels, glomerular vessels, dotted vessels, linear irregular vessels, comma vessels, red lacunae).[5] Finally, the dermoscopic features of the melanomas detected because of changing in a pre-existing lesion were collected through the comparison of the images previously and regularly collected when sequential follow-up was available.

Comparison with the literature

The study was designed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines (Supplementary Digital Material 1: Supplementary Table I).[6] The protocol of the study was registered on PROSPERO Database (registration number CRD42021230070). Electronic searches were performed on PubMed database *via* Medline using ("melanoma" AND "nevoid"). References of the selected publications were additionally screened for other eligible records.

Original articles published until September 06, 2021, were included. There were no restrictions on language, geographic area or publication status. Eligible records comprised any manuscript reporting detailed dermoscopic features of histopathologically confirmed NeM. Exclusion criteria were systematic and narrative review articles and studies not describing the dermoscopic features associated with NeM (*i.e.* only reporting macro photography). The primary outcome of the review was retrieving the dermoscopic features associated with NeM.

Two blinded investigators (FB, PR) independently extracted data by using an extraction form and a third senior author (GG) was consulted to resolve any disagreements. Articles were screened by title and abstract. Reports considered relevant were reviewed in full text and selected or rejected based on the inclusion and exclusion criteria. For each study, the following features were considered: type of the study, number of the patients, age and gender, site of NeM, personal history of melanoma, clinical aspect, Breslow thickness and diameter. Dermoscopic features collected included pattern analysis and clues for melanoma. The risk bias was estimated in the selection, ascertainment, causality, and reporting domains and reported as an aggregate score (ranging from 0 to 8).[7]

Statistical analysis

NeM and SSM were compared using χ^2 test for qualitative variables and Mann-Whitney Rank Test for non-normal distributed quantitative variables. $P<0.05$ was considered statistically significant. Statistical analyses were performed using Stata version 13 (Stata Corp, College Station, TX, USA).

Results

Retrospective study

A total of 60 melanomas, comprising 20 NeM and 40 SSM were collected (mean Breslow thickness 1.0±0.6 [range 0.3-2.3]). Except for younger age in patients with NeM, no differences in demographic, clinical and histopathological features were found (Table I). Macroscopic aspects of NeM included macular, papular, plaque and nodular lesions (Figure 1A-H). Compared to patients with SSM, a higher proportion of patients diagnosed with NeM were regularly followed by regular dermatologic visit 40% *vs*. 15% (P=0.031), respectively. A higher proportion of NeM showed a nevus-like appearance (Figure 2A, B), comprising both reticular (Figure 2C, D) and globular patterns (Figure 1C, D, Figure 2E, F), 60% *vs*. 25%, (P=0.003), respectively. As opposed to SSMs, a higher proportion of NeM presents at least two colors, commonly brown and pink, 85% *vs*. 55%, (P=0.008), respectively. Amongst the local patterns, a higher proportion of SSM presented atypical network, regression and irregular dots/globules compared to NeM (Table II). Overall melanomas were detected because of dermoscopic changes found during the follow-up in 14 out of 60 (23%) cases, particularly in 35% of NeM and 18% of SSM. Among these cases, an associated nevus was reported in four NeMs and in four SSM (Figure 2G, H). Almost all changing lesions showed variable degree of enlargements associated with different clues (*i.e.* irregular dots/globules, eccentric hyperpigmentation, atypical network, blue-white veil), but no specific changing pattern was associated with NeM respect to SSM (Table III) (Figure 3A-F).

Outcomes

A total of 195 references identified through the electronic database search were screened by title and abstract and those deemed relevant were reviewed in full text and selected based on the inclusion and/or exclusion criteria.

TABLE I.—*Demographic, clinical and histopathological features of NeM* vs. *SSM.*

Variables	NeM (N.=20)	SSM (N.=40)	P*
Age at diagnosis, years, median (IQR)	46 (51.5-62)	60 (52-69)	0.011
Male, N. (%)	7 (35)	22 (55)	0.144
Diameter of the lesion, median (IQR)	7 (6-10)	9.5 (7-12)	0.064
Skin localization			
Head and neck	3 (15)	2 (5)	0.186
Anterior chest	2 (10)	2 (5)	0.464
Abdomen	3 (15)	3 (7.5)	0.361
Back	6 (30)	18 (45)	0.624
Upper arms	2 (10)	3 (7.5)	0.741
Hand	1 (5)	0	0.154
Buttocks	1 (5)	3 (7.5)	0.714
Lower limbs	2 (10)	9 (22.5)	0.238
Family history^	3/11	1/21	0.116
Personal history^^	4/15	4/23	0.493
Modality of detection			
Regular dermatologic visit	8 (40)	6 (15)	0.031
De-novo lesion	14 (70)	34 (84)	0.171
Change in pre-existing lesions	7 (35)	7 (18)	0.131
Histopathological features			
Breslow's thickness mm, median (IQR)	0.6 (0.4-0.9)		NA
Clark level, N. (%)			0.166
II	5 (25)	20 (50)	
III	12 (60)	17 (42.5)	
IV	3 (15)	3 (7.5)	
Ulceration	1 (5)	1 (2.5)	0.611
Mitoses/mm^2	0 (0-1)	1 (0-2)	0.075
TIL	8 (40)	25 (62.5)	0.099
Lympho-vascular invasion	0	1 (2.5)	0.476
Regression	4 (20)	18 (45)	0.058
Associated nevus	9 (45)	12 (30)	0.279

*χ^2 test for qualitative variables, Mann-Whitney Rank Test for non-normal distributed quantitative variables; ^24 missing; ^^22 missing.
NeM: Nevoid melanoma; SSM: superficial spreading melanoma; IQR: interquartile range; TIL: Tumor-infiltrating lymphocytes.

TABLE II.—*Dermoscopic features of NeM* vs. *SSM.*

Variables	NeM (N.=20)	SSM (N.=40)	P*
Macroscopic aspects			0.081
Macule	6 (30)	7 (17.5)	
Papule	7 (35)	13 (32.5)	
Plaque	4 (20)	19 (47.5)	
Nodule	3 (15)	1 (2.5)	
Colors			0.022
≤2	17 (85)	22 (55)	
>3	3 (15)	18 (45)	
Global pattern			0.003
Nevus-like	12 (60)	10 (25)	
Reticular	8/12 (66)	9/10 (90)	
Globular	4/12 (33)	1/10 (10)	
Multicomponent	4 (20)	28 (70)	
Amelanotic	1 (5)	0	
Uncategorized	3 (15)	2 (5)	
Local pattern			
Comedo-like openings	0	0	-
Milia like cysts	2 (10)	1 (2.5)	0.209
Atypical network	13 (65)	36 (90)	0.018
Blue-white veil	9 (45)	24 (60)	0.271
Irregular streaks	2 (10)	13 (32.5)	0.058
Regression	5 (25)	23 (57.5)	0.017
Irregular pigmentation	15 (75)	38 (95)	0.023
Irregular dots/globules	10 (50)	33 (82.5)	0.008
Atypical vascular pattern	8 (40)	18 (45)	0.713
Inverse reticule	3 (15)	3 (7.5)	0.361

*χ^2 test for qualitative variables, Mann-Whitney Rank Test for non-normal distributed quantitative variables.
NeM: nevoid melanoma; SSM: superficial spreading melanoma; IQR: interquartile range.

Full text article eligibility assessment was performed for 33 references. All the articles were retrieved according to the algorithm presented in Supplementary Digital Material 2: Supplementary Figure 1. Finally, only seven original manuscripts reporting dermoscopic features of NeM were analyzed, including two case series and five case reports, for a total of 56 cases, including the present study (Supplementary Digital Material 3: Supplementary Table II).[5, 8-13] The mean score to assess the risk of bias across the studies was estimated as 5 out of 8.

Nevus-like pattern was found in 30 out of 56 (53%) of the cases, followed by multicomponent pattern in 12 (21%) and amelanotic pattern in 9 (22%). Interestingly, the most reported clues for melanoma found in NeM showing nevus-like pattern were irregularly distributed dots/globules (50%), irregular pigmentation (40%) and atypical vascular pattern (37%), including combinations of dotted, comma, glomerular, linear or arborizing vessels. Conversely in NeM showing multicomponent pattern where frequently found irregular pigmentation (67%), blue-white veil (58%), irregular dots (33%) and atypical vascular pattern (25%). The most frequently reported dermoscopic criteria for amelanotic NeM were atypical vascular pattern and milia-like cysts.

TABLE III.—*Dermoscopic features of NeM and SSM diagnosed because changing lesions.*

NeM (N.=7)	SSM (N.=7)
Enlargement (6)	Enlargement (7)
Eccentric hyperpigmentation (2)	Irregular dots/globules (5)
Atypical network (1)	Eccentric hyperpigmentation (2)
Blue-white veil (1)	Atypical network (2)
Irregular dots/globules (1)	Blue-white veil (2)
Atypical vascular pattern (1)	Area of regression (2)
Area of inverse network (1)	Area of inverse network (1)

NeM: nevoid melanoma; SSM: superficial spreading melanoma.

Discussion

NeM is a rare entity that can closely simulate both clinically, dermoscopically and histologically benign nevi (*i.e.* congenital, dermal, compound and keratotic nevi). Clinically, NeM has been described as a brown papillomatous polypoid or slightly elevated lesion located on the trunk or proximal limbs.[7, 14] Most important histopathological diagnostic criteria include relative symmetry, cytologic appearance of melanocyte similar to small round or polygonal nevus cells (*i.e.* vesicular nucleus and appreciable amounts of cytoplasm), evidence of maturation and minimal junctional component.[2] Other clues are the presence of "parallel theque" pattern at the base and the so-called "puffy shirt appearance" at low magnification.[15, 16] Although the gold standard for the diagnosis of NeM is histopathology, dermoscopy may provide clues to help identify this rare malignancy.[7] Hence, a possible pitfall may be mistake NeM an intradermal nevus. The dermoscopic characteristics associated with intradermal nevus were widely described and includes globular, cobblestone or structureless pattern associated with comma vessels, and homogeneously pigmented color.[17] Our findings suggest that NeM, although resembling clinically and histopathologically common raised melanocytic nevus, presents certain peculiar dermoscopic features suggestive for melanoma. We found that the most common global dermoscopic aspect of NeM is the nevus-like pattern, that can be found in more than half of the cases. Longo *et al.* defined nevus-like pattern in those lesions with papillomatous surface resembling a dermal nevus on clinical inspection and revealing a cobblestone pattern on

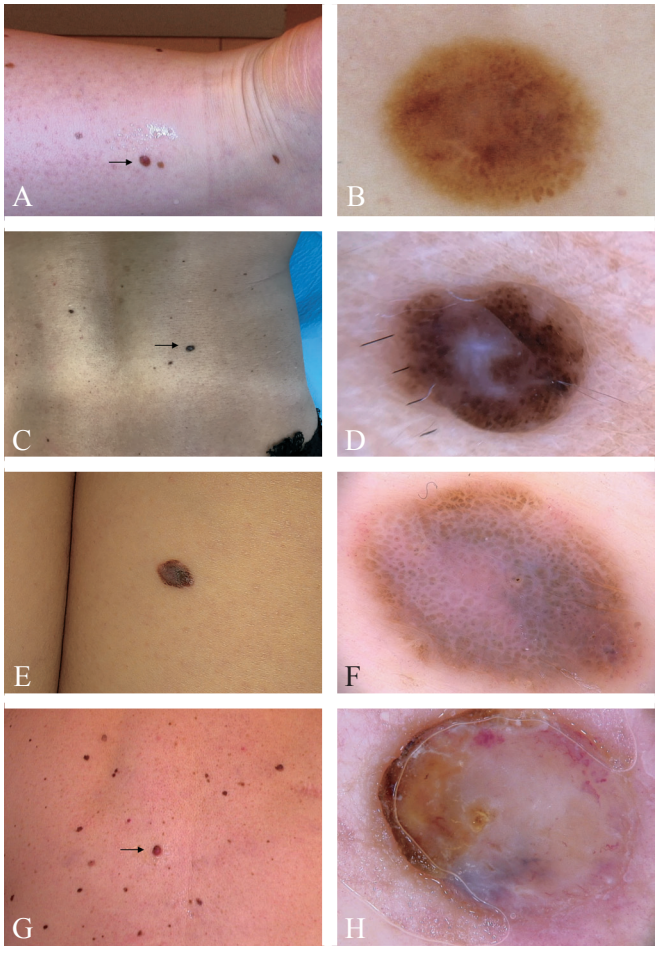

Figure 1.—Clinical and dermoscopic presentation of different macroscopic aspects of NeM (*i.e.* macular, papular, plaque and nodular NeM). A, B) Macular NeM of the ankle (Breslow 0.5 mm) presenting as a flat, *de-novo* lesion with prevalently globular naevus-like pattern, irregular pigmentation, network and dots. C, D) Papular NeM of the lumbar region (Breslow 0.2 mm) presenting as a polypoid *de-novo* lesion with globular naevus-like pattern and blue-white veil. E, F) Plaque NeM of the thigh (Breslow 1.2 mm) presenting as a plaque with globular naevus-like pattern accompanied by blue-white veil, irregular pigmentation, dots and vessels. G, H) Nodular hypomelanotic NeM of the back (Breslow 2.3 mm) presented as a *de-novo* lesion with multicomponent pattern characterized by irregular pigmentation, irregular vessels and milia-like cysts.

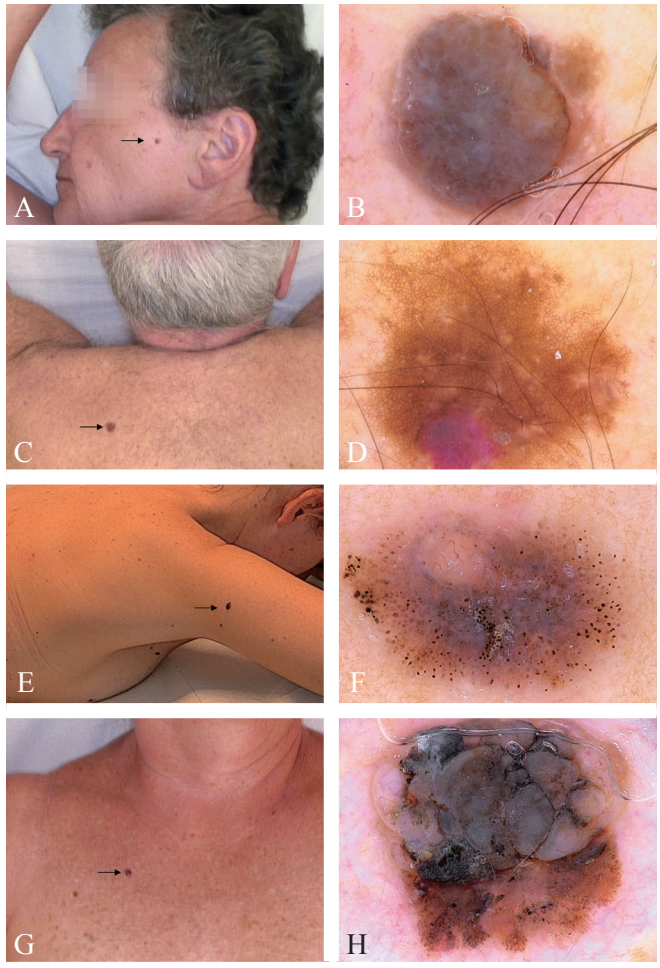

Figure 2.—Clinical and dermoscopic features of most common global patterns of NeMs (*i.e.* polypoid nevus-like, reticular nevus-like, globular nevus-like and multicomponent pattern). A, B) NeM showing a polypoid naevus-like pattern of the cheek (Breslow 1.9 mm) characterized by polypoid and papillomatous appearance diagnosed because of enlargement and appearance of eccentric hyperpigmentation area at 2 o'clock. C, D) NeM of the back showing a reticular naevus-like pattern (Breslow 0.4 mm) presenting as a slightly raised lesion with thick network diagnosed because of enlargement and appearance of area of atypical network. E, F) NeM of the shoulder (Breslow 0.7 mm) presenting as a slightly raised *de-novo* lesion with predominantly globular naevus-like pattern with irregular dots, blue-white veil and arborizing vessels on a raised pink area at 11 o'clock. G, H) NeM of the subclavear region (Breslow 0.9 mm) presented with a multicomponent pattern with a flat area of irregular network and pigmentation with dots and pseudopods at the base of a pre-existing polypoid and papillomatous nevus.

dermoscopy.[5] However, in our cases we found that NeM may show not only polypoid and papillomatous appearance (Figure 1C, D, Figure 2A, B), but also flat or slightly raised aspect presenting with reticular (Figure 2C, D) or globular pattern (Figure 1C, D, E, F) that can be detected because of changes during the dermoscopic follow-up (Figure 3). We speculate that this distinction may probably reflect the two histologic groups found by Cook *et al.*, namely papillomatous NeM, composed of small, atypical cells showing numerous mitoses and no change with depth, and maturing NeM, presenting with flat/slightly raised lesion with a SSM-like component with maturation but still atypical.[18] The common nevus-like pattern was frequently accompanied by different local dermoscopic clues of melanoma, namely irregularly distributed dots/

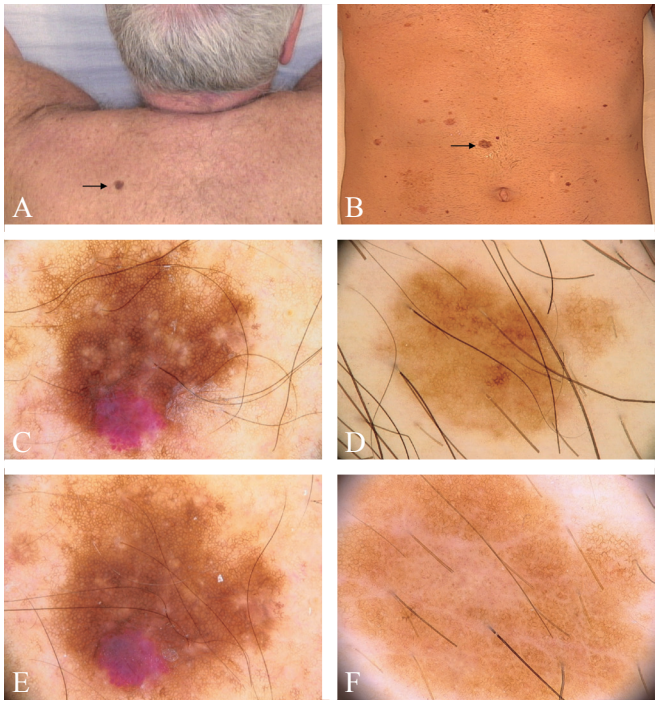

Figure 3.—A-F) Clinical and dermoscopic features of two NeMs detected because of changings during the video-dermoscopic follow-up. A, C) NeM of the back (Breslow 0.4 mm); E) showing enlargement and appearance of area of atypical network after one year follow-up. B, D) Slow growing NeM of the abdomen (Breslow 0.5 mm); F) showing enlargement and slight modifications of the network after four years follow-up.

globules, irregular pigmentation and atypical vascular pattern. The presence of atypical vascular patterns was already found to be the most predictive features for amelanotic melanoma, and it can be adapted to amelanotic NeM.[19] In our study only one NeM was categorized as amelanotic, that is a lower proportion compared to almost one third of NeM previously reported as amelanotic in another series. Moreover, none of the other case reports described amelanotic NeM.[8-13] Compared to SSMs, that show a wider hue variety, NeM presents commonly with few colors (brown and pink). The multicomponent pattern is considered the most characteristic and most common pattern associated with melanoma and it is frequently found in invasive forms.[20] Interestingly we found seldom NeM showing a clear multicomponent pattern. NeM with multicomponent pattern were characterized by irregular pigmentation, atypical network, blue-white veil, irregular dots, streaks/pseudopods and atypical vascular pattern (Figure 1G, H, Figure 2G, H).[7]

Initially NeM can be indistinguishable clinically and even dermoscopically. Certain NeMs showing an apparently reassuring nevus-like pattern could be detected because of changes during the regular dermoscopic follow-up (Figure 3).[21, 22] We found that these lesions showed an enlargement in almost all the cases accompanied by other prejudicial clues (*i.e.* atypical network, irregular pigmentation, eccentric hyperpigmentation), however no specific changing pattern was associated with changing NeM compared to SSM.

The strength of the study is the precise tracking of the dermoscopic differences found in the excised NeM. Interestingly, the large proportion of patients with NeM followed by regular dermoscopic follow-up (40% *vs*. 15% with SSM) may explain the relatively thin Breslow thickness of our sample compared to other studies.

Limitations of the study

This study is burdened by some limitations. The higher proportion of patients following regular dermatologic visit diagnosed with NeM may probably reflect a selection bias. Another limitation of the study is the monocentric design and the relatively small sample size. Nonetheless NeM represents a rare entity, and it is quite difficult to obtain a larger study population. It would be also interesting to compare NeM to nevus, but several biases related to different thickness and different degrees of dysplasia in nevi may limit such study design.

Conclusions

In conclusion, NeM may resemble dermoscopically common melanocytic nevi. Dermoscopy of NeM is tricky as in more than half of the cases shows a nevus-like appearance. Nonetheless different clues and detection of changes of an otherwise reassuring lesion may help to identify this malignancy.

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