ORIGINAL ARTICLE

Negative pigment network: An additional dermoscopic feature for the diagnosis of melanoma

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Background: The negative pigment network (NPN) is seen as a negative of the pigmented network and it is purported to be a melanoma-specific structure.

Objectives: We sought to assess the frequency, sensitivity, specificity, and odds ratios (ORs) of NPN between melanoma cases and a group of control lesions.

Methods: Digitalized images of skin lesions from 679 patients with histopathological diagnosis of dermatofibroma (115), melanocytic nevus (220), Spitz nevus (139), and melanoma (205) were retrospectively collected and blindly evaluated to assess the presence/absence of NPN.

Results: The frequency of occurrence of NPN was higher in the melanoma group (34.6%) than in Spitz nevus (28.8%), melanocytic nevus (18.2%), and dermatofibroma (11.3%) groups. An OR of 1.8 emerged for the diagnosis of melanoma in the presence of NPN as compared with nonmelanoma diagnosis. Conversely, for melanocytic nevi and dermatofibromas the OR was very low (0.5 and 0.3, respectively). For Spitz nevi the OR of 1.1 was not statistically significant. When comparing melanoma with dermatofibroma, melanocytic nevus, and Spitz nevus, we observed a significantly higher frequency of multicomponent pattern (68.1%), asymmetric pigmentation (92.9%), irregularly distributed NPN (87.3%), and peripheral location of NPN (66.2%) in melanomas.

Limitations: Further studies can provide the precise dermoscopic-histopathologic correlation of NPN in melanoma and other lesions.

Conclusions: The overall morphologic pattern of NPN, such as the irregular distribution and the peripheral location of NPN, along with the multicomponent pattern and the asymmetric pigmentation could be used as additional features in distinguishing melanoma from Spitz nevus and other benign lesions. (J Am Acad Dermatol 10.1016/j.jaad.2012.08.012.)

Key words: dermoscopy; histiocytoma; melanocytic nevus; melanoma; negative pigment network; Spitz nevus.

The negative pigment network (NPN) consists of relatively light areas making up the "cords" of the network, and darker areas filling the holes; it is seen as a negative of the pigmented network and has also been defined as reticular depigmentation.[1,2] The lighter grid lines tend to be serpiginous, and they surround irregularly shaped pigmented structures that resemble elongated tubular or curved globules.[3] The NPN is purported to be a melanoma-specific structure; however, it is also strongly correlated with Spitz nevi and can also be seen in dysplastic nevi and in growing melanocytic nevi.[4-7] Histopathologically, it has been suggested that NPN represents elongated hypopigmented rete ridges accompanied by the presence of large nests of heavily pigmented melanocytic cells located at the dermal papillae.[8]

The aim of this study was to evaluate the frequency, sensitivity, specificity, and odds ratios (ORs) of NPN between melanoma cases and a group of controls including dermatofibroma, melanocytic nevus, and Spitz nevus.

CAPSULE SUMMARY

- The negative pigment network is purported to be a melanoma-specific structure; however, it is strongly correlated with Spitz nevi and can also be seen in other benign lesions.

- Our study reports sensitivity and specificity data of negative pigment network for melanoma, Spitz nevus, melanocytic nevus, and dermatofibroma.

- The combination of asymmetric pigmentation pattern, irregular distribution, and peripheral location of negative pigment network could be the clue for the diagnosis of early difficult-to-diagnose melanomas.

METHODS

Between January 1 and December 31, 2006, skin lesions that included histopathologically confirmed melanomas and clinically excised atypical lesions histopathologically confirmed as nonmelanoma lesions such as melanocytic nevus (eg, congenital/acquired nevus, Spitz nevus) and dermatofibroma, which were seen at 11 participating centers (9 in Italy, 1 in Australia, and 1 in the Unites States), were considered for the study. The study also included lesions with a history of rapid onset and growth that were excised for this reason.

To avoid sample selection, each participating center was requested to provide all consecutive patients seen during the given period for a total of approximately 20 consecutive cases (ie, melanomas) and 60 consecutive controls (ie, 20 melanocytic nevi; 20 Spitz/Reed nevi; 20 dermatofibromas). The participating centers stopped collecting cases and controls as soon as the set number of lesions was reached, independently of the month in which they met their quota. Therefore, the period of collecting the consecutive cases for melanoma versus controls would be different within each image supplying center.

All the dermoscopic images from the 11 centers were merged into a database with a new identification link to the patient information on clinical features and diagnosis. Of the 729 submitted images, 679 were eligible for the study. Of these images, 499 (73.4%) were taken with a camera using nonpolarized dermoscopy and 180 (26.6%) with a camera using polarized dermoscopy. These were randomly reorganized into a new file containing the dermoscopic images for evaluation by a single blinded observer (M. A. P.).

Preliminary phase of the study

In the preliminary phase of the study, NPN was precisely defined and differentiated from its simulators. However, to avoid bias deriving from the analysis of only 1 observer we conducted a pilot study on a random sample of 22 images seen by 2 blinded observers (M. A. P. and S. W. M.). Each observer examined the images, and when in disagreement, they discussed the case with a third observer (A. A. M.) to reach a common opinion and understand the reason of diverging judgments. To validate this alternative approach, we conducted a statistical analysis evaluating the k-value of agreement between the 2 observers, which revealed a good level of agreement (k-value = 0.64); in the human model, a k-value from 0.61 to 0.80 is considered good and reliable.[9] Moreover, the principal investigator (M. A. P.) was a member of a panel of 40 experts who took part in a consensus meeting on dermoscopy of pigmented skin lesions.[10] In this study, the interobserver and the intraobserver agreements on the dermoscopic diagnosis of skin lesion using the first-step algorithm differentiating melanocytic from nonmelanocytic lesions and pattern analysis ranged between 0.55 to 0.63 and 0.72 to 1.00, respectively, in line with our results.[10]

Based on the outcomes of these evaluations, NPN was defined as a negative of the pigment network with relatively light serpiginous lines making up the cords of the network and darker areas, the holes,

resembling elongated tubular and globular-like structures; it had to be in a network pattern with the cords having the same thickness as expected for a pigment network (Fig 1). We defined this NPN as type A, and when the holes were filled with dotted vascular pattern,[11] we classified it as type B (Fig 2). Both types A and B NPN had to display cords of the same thickness, as expected for a pigment network. Nonetheless, in some cases of melanoma, Spitz nevus, melanocytic nevus, and dermatofibroma the overall morphologic pattern of both types A and B NPN may display an increased range of width of the cords, defined as heterogeneous.

The NPN needs to be differentiated from its simulators: globular or cobblestone patterned nevi with wide hypopigmented lines, histopathologically corresponding to fibrosis, separating large or cobblestone-like globules.[8] The differential diagnoses may also include shiny white streaks, metaphorically termed "chrysalis structures," that were defined as thick, short, bright-whitish linear structures, often oriented in an approximately orthogonal or stellate fashion.[12-14] These structures can only be seen with polarized dermoscopy and probably correspond to changes in the composition and orientation of the collagen that can also be found in dermatofibroma, basal cell carcinoma, melanoma, and Spitz nevus.[15] When shiny white streaks are orientated in an orthogonal fashion they can simulate a NPN; however, shiny white streaks can be differentiated from NPN because of thick, short, bright-white (not relatively light), straight lines at right angles (not serpiginous) (Fig 3).[16,17] Furthermore, serpiginous interconnecting lines of NPN surround irregularly shaped pigmented structures resembling elongated tubular and globular-like structures (Fig 3, *B*).

Active phase of the study

To evaluate the frequency of global patterns and to assess the presence or absence of dermoscopic criteria, including NPN, the images were coded with a single identification number, and only the gender, age at diagnosis, and site of the skin lesion were known to the observer.

Statistical analysis

Statistical analyses were performed with the χ^2 test or Fisher exact test, when appropriate, to evaluate the differences between the various types of lesions in terms of frequency of the occurrences of global patterns and dermoscopic criteria.[18] ORs and 95% confidence intervals (CIs) were assessed by means of an unconditional regression model. Differences were considered to be statistically significant when *P* was less than or equal to .05 (2-sided). To evaluate the efficiency of the tests (dermoscopic diagnosis), for each value we estimated the sensitivity (the ratio between true positives and the sum of true positives and false negatives) and specificity (the ratio between true negatives and the sum of true negatives and false positives).

RESULTS

Patient demographics and classification of lesions

Digitalized images of skin lesions of 679 patients were eligible for the study: 302 were male and 377 were female with a mean age of 43 years (±17 SD). The sites of the skin lesions included the lower limbs (216 cases), trunk (371 cases), and upper limbs (92 cases). The series included 115 cases of dermatofibroma, 220 melanocytic nevus (13 congenital nevus, 207 acquired nevus), 139 Spitz/Reed nevus, and 205 cases of melanoma. Of the melanoma cases, 94 were male and 111 were female with a mean age of 54 years (±17 SD). The distribution of the sites of melanoma were: trunk (123 patients), lower limbs (54 patients), and upper limbs (28 patients). Of the 205 melanoma cases, 48 (23.4%) were in situ and 157 (76.6%) were invasive. The latter were subdivided into 2 groups based on Breslow thickness: 1 mm or less, thin melanoma, 111 cases; and greater than 1 mm, thick melanoma, 38 cases. Eight melanoma cases had unspecified thickness.

Dermoscopic classification

Table I presents the frequency of occurrence of NPN in 679 skin lesions, according to the histopathological diagnosis (ie, dermatofibroma, melanocytic nevus, Spitz nevus, and melanoma).

The dermatofibroma and melanocytic nevus groups differed significantly from the melanoma group in the frequency of occurrence of NPN (11.3% and 18.2%, respectively, vs 34.6%; $P \leq$ .01). Conversely, NPN was present in 28.8% of Spitz nevus and 34.6% of the melanoma group; the difference was not statistically significant (Table I).

In evaluating the frequency of occurrence of NPN in thin melanoma, thick melanoma, and melanoma in situ, no statistically significant difference emerged between scores of Breslow thickness, melanoma in situ, and presence or absence of NPN (data not shown).
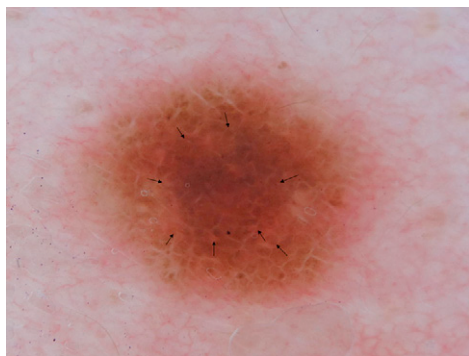
Fig 1. Dermoscopic image of melanocytic nevus on back of 37-year-old man. Negative pigment network (NPN) with relatively hypopigmented serpiginous lines making up "cords" of network surrounding elongated tubular and brownish globular-like structures (type A NPN) (*arrows*) regularly distributed around periphery of lesion. (Original magnification: ×10.)
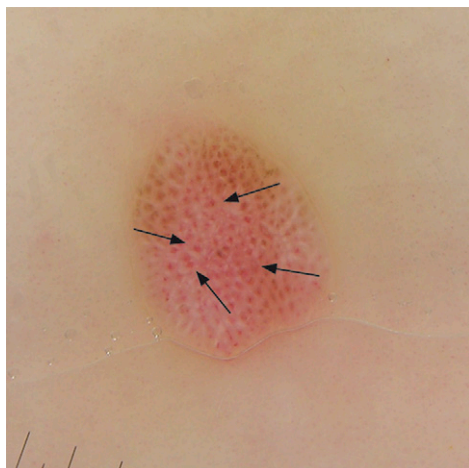

Fig 2. Dermoscopic image of Spitz nevus on trunk of 13-year-old boy. Negative pigment network (NPN) with relatively light-pink areas making up "cords" of network and dotted vascular pattern filling "holes" of reticular depigmentation (type B NPN), regularly distributed almost throughout lesion (*arrows*). (Original magnification: ×10.)

Table II shows the sensitivity and specificity of NPN according to the histopathological diagnosis: melanoma (34.6% and 77.2%, respectively), Spitz nevus (28.8% and 73.9%, respectively), melanocytic nevus (18.2% and 67.7%, respectively), and dermatofibroma (11.3% and 73.2%, respectively). In addition, we found an approximately 2-fold higher probability of NPN presence in melanoma (OR 1.8; 95% CI 1.3-2.7) as compared with nonmelanoma. For Spitz nevi we found a 10% probability (OR 1.1; 95% CI 0.7-1.8) of having a NPN, although it was not statistically significant. In contrast, for melanocytic nevi and dermatofibromas, the probability of having a NPN

was very low (OR 0.5; 95% CI 0.3-0.7 and OR 0.3; 95% CI 0.2-0.6, respectively).

Table III presents the global dermoscopic pattern and overall morphologic pattern of the lesions with NPN according to the histopathological diagnosis. There was a significantly greater frequency of multicomponent pattern in melanoma lesions (68.1%) as compared with dermatofibroma, melanocytic nevus, and Spitz nevus lesions (16.7%, 40.5%, and 31.4%, respectively; $P \leq .01$) (Table III). Moreover, the presence of NPN was significantly associated with an asymmetric pigmentation pattern in melanoma lesions (92.9%) compared with dermatofibroma, melanocytic nevus, and Spitz nevus lesions (53.9%, 77.5%, and 59.0%, respectively; $P \leq .001$) (Table III).

With regard to melanocytic nevus lesions, a significantly higher frequency of globular-homogeneous pattern was present in these compared with melanoma lesions (29.7% and 4.4%, respectively; $P \leq .01$). Instead, a significantly greater incidence of globular pattern and starburst pattern were present in Spitz nevus lesions (25.7% and 22.9%, respectively) compared with melanoma lesions (2.9% and 1.5%, respectively; $P \leq .01$) (Table III). In addition, melanoma lesions differed significantly from dermatofibroma, melanocytic nevus, and Spitz nevus lesions in the frequency of the occurrence of irregularly distributed NPN (87.3%, 61.5%, 70.0%, and 57.5%, respectively; $P \leq .01$) (Table III). Moreover, the NPN was significantly distributed in the periphery of the melanoma lesions (66.2%) compared with dermatofibroma, melanocytic nevus, and Spitz nevus lesions (23.1%, 37.5%, and 40.0%, respectively; $P \leq .01$) (Table III). Conversely, the NPN was more frequently distributed throughout the lesions in dermatofibroma (53.9%) and Spitz nevus (45.0%), whereas in melanocytic nevus it was frequently more regularly distributed on the periphery (37.5%) (Table III).

DISCUSSION

Based on our results, a significant number and percentage of melanomas (71/205; 34.6%) revealed NPN, which may be helpful in distinguishing melanoma from melanocytic nevi. However, these findings are in contrast with those reported by Skvara et al,[2] who showed no significant differences in reticular depigmentation between melanocytic nevi and melanomas. Multiple factors are likely to contribute to the differences seen between these 2 studies. Firstly, the NPN definition we used was fairly strict and attempted to exclude structures mimicking or mistaken with a NPN (ie, cobblestone/globular nevi and white network). Secondly, NPN was seen more frequently in invasive melanomas (36.8%) than in situ melanomas (28.0%).[2] Our study and that of
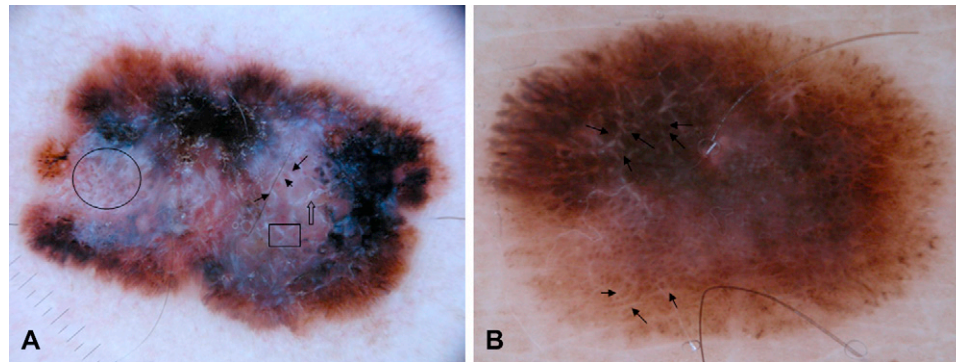
Fig 3. Dermoscopic images of invasive melanoma. **A**, 0.85-mm Thick on upper aspect of left arm of 37-year-old man: shiny white streaks (SWS), metaphorically termed "chrysalis structures." These structures were defined as thick, short, bright-whitish linear structures often oriented in approximately orthogonal (*full head arrows*) or stellate (*square*) fashion. White shiny areas (*arrows*), also known as clods, consisting in larger structureless areas of shiny white color, can also be seen. Left, blue-white veil and white scarlike depigmentation surrounding vascular spaces (*circle*). **B**, 0.50-mm Thick on leg of 35-year-old woman. Negative pigment network (NPN) asymmetrically located in lower left periphery of lesion. NPN, unlike SWS, consists of relatively light (not bright-white) serpiginous (not straight) interconnecting lines that surround irregularly shaped pigmented structures resembling elongated tubular and globular-like structures (*full head arrows*). (**A** and **B**, Original magnifications: **A**, ×10; **B**, ×20.)

Table I. Frequency of occurrence of negative pigment network by histopathological diagnosis

	Diagnosis			
	Dermatofibroma	Melanocytic nevus*	Spitz nevus†	Melanoma
NPN	N (%)	N (%)	N (%)	N (%)
Absent	102 (88.7)	180 (81.8)	99 (71.2)	134 (65.4)
Present	13 (11.3)‡	40 (18.2)‡	40 (28.8)	71 (34.6)
Total	115	220	139	205

NPN, Negative pigment network.

*Including 13 cases of congenital nevi.

†Because of clinical, dermoscopic, and histopathologic similarity between Spitz and Reed nevus, latter were grouped together with Spitz nevus.

‡In comparison with melanoma P value of χ^2 test was P ≤ .01.

Skvara et al[2] had different proportions between in situ and invasive melanoma: of the 63 melanomas in the latter study, 31 were in situ and 32 were invasive, whereas in our series of 205 melanomas, only 50 (24.4%) were in situ and 155 (75.6%) were invasive.

We found a high specificity (77.4%) but a low sensitivity (34.6%) of NPN for the diagnosis of melanoma, which is consistent with a sensitivity of 22% and a specificity of 95% reported by Menzies et al[1] for this criterion. Although Spitz nevi often reveal a NPN, the presence of a NPN in a pigmented lesion does not confer an increased probability that the lesion is a Spitz nevus; for these nevi the risk of having a NPN is 10% (OR 1.1), not statistically significant. Conversely, the presence of NPN significantly leads to an increased risk of melanoma (OR 1.8) whereas its absence was significantly associated with the diagnosis of melanocytic nevus and dermatofibroma.

The globular-homogeneous pattern was significantly associated with NPN in the melanocytic nevus group whereas globular and starburst patterns were significantly associated with NPN in the Spitz nevus group, in agreement with that reported by other authors.[4,5]

The NPN associated with the multicomponent pattern and asymmetric pigmentation pattern was significantly correlated only with the melanoma group (Fig 3, *B*), and can discriminate melanoma from Spitz nevus and other lesions. The irregular distribution and the peripheral location of the NPN (Fig 3, *B*, and Fig 4) also seem to discriminate melanoma lesions from Spitz nevus and other control lesions. In melanocytic nevus, the NPN was more frequently regularly distributed in the periphery (Fig 1) whereas in Spitz nevus, as also recently reported by other authors,[11] it was mostly regularly distributed throughout the lesion displaying a type B pattern (Fig 2), which differed from dermatofibroma in which NPN was more frequently regularly distributed throughout the lesion but displayed a type A pattern (Fig 5).

Because of the relatively low diagnostic OR of NPN, the irregular distribution and the peripheral location of NPN could be added to the multicomponent pattern and/or asymmetric pigmentation pattern in distinguishing melanoma

Table II. Sensitivity and specificity of negative pigment network by histopathological diagnosis

	NPN Absent	NPN Present				
	N	N	Sensitivity%	Specificity%	OR (95% CI)	*P* value
Melanoma (N = 205)	134	71	34.6*	77.2	1.8 (1.3-2.7)[†]	.001
Spitz nevus (N = 139)[‡]	99	40	28.8	73.9	1.1 (0.7-1.8)[†]	ns
Melanocytic nevus (N = 220)[§]	180	40	18.2	67.7	0.5 (0.3-0.7)[†]	.0002
Dermatofibroma (N = 115)	102	13	11.3	73.2	0.3 (0.2-0.6)[‖]	.0004

CI, Confidence interval; *NPN*, negative pigment network; *ns*, not significant; *OR*, odds ratios.

*34.6% of melanomas show presence of NPN whereas only 22.8% of nonmelanomas show this feature.

[†]OR for histopathological diagnosis with presence of NPN lesion vs all other diagnoses, except dermatofibroma.

[‡]Because of clinical, dermoscopic, and histopathologic similarity between Spitz and Reed nevus, latter were grouped together with Spitz nevus.

[§]Including 13 cases of congenital nevi.

[‖]OR for dermatofibroma diagnosis with presence of NPN lesion vs all other diagnoses.

Table III. Dermoscopic types and overall morphologic pattern of 164 lesions with negative pigment network present by histopathological diagnosis

	Diagnosis			
	Dermatofibroma	Melanocytic nevus*	Spitz nevus[†]	Melanoma
	N (%)	N (%)	N (%)	N (%)
Lesions, N	13	40	40	71
Dermoscopic types				
Reticular	0 (0.0)	1 (2.8)	0 (0.0)	1 (1.5)
Globular	1 (8.3)	3 (8.1)	9 (25.7)[‡]	2 (2.9)
Homogeneous	1 (8.3)	1 (2.7)	0 (0.0)	0 (0.0)
Globular-reticular	0 (0.0)	2 (5.4)	0 (0.0)	0 (0.0)
Globular-homogeneous	2 (16.7)	11 (29.7)[‡]	3 (8.6)	3 (4.4)
Reticular-homogeneous	0 (0.0)	1 (2.7)	1 (2.9)	3 (4.4)
Starburst	0 (0.0)	0 (0.0)	8 (22.9)[‡]	1 (1.5)
Multicomponent[§]	2 (16.7)[‡]	15 (40.5)[‡]	11 (31.4)[‡]	47 (68.1)
Asymmetric pigmentation pattern[‖]	7 (53.9)[‡]	31 (77.5)[‡]	23 (59.0)[‡]	65 (92.9)
Overall morphologic pattern				
Homogeneous[¶]	1 (7.7)[‡]	21 (52.5)	20 (50.0)	26 (36.6)
Heterogeneous[#]	11 (84.6)	18 (45.0)	19 (47.5)	45 (63.4)
Irregular distribution	8 (61.5)[‡]	28 (70.0)[‡]	23 (57.5)[‡]	62 (87.3)
NPN localization				
Peripheral	3 (23.1)[‡]	15 (37.5)[‡]	16 (40.0)[‡]	47 (66.2)
Central	3 (23.1)	11 (27.5)[‡]	6 (15.0)	6 (8.5)
Throughout lesion	7 (53.9)[‡]	13 (32.5)	18 (45.0)	18 (25.4)

NPN, Negative pigment network.

*Including 13 cases of congenital nevi.

[†]Because of clinical, dermoscopic, and histopathologic similarity between Spitz and Reed nevus, latter were grouped together with Spitz nevus.

[‡]In comparison with melanoma *P* value of χ^2 test was $P \le .01$.

[§]Combination of ≥ 3 distinctive dermoscopic structures within same lesion.

[‖]Found in lesions that lack symmetry over ≥ 1 axes through its center; symmetry in symmetric pigmentation pattern refers to pigmentation and not shape.

[¶]Uniform in width of "cords."

[#]Increased range of width of "cords."

lesions from Spitz nevus and other control lesions. The presence of additional criteria and their combination is always crucial to address the final diagnosis, especially in cases of early, difficult-to-diagnose melanomas (Fig 4).

Lozzi et al,[19] have also reported some cases of early melanomas dermoscopically characterized by reticular depigmentation.

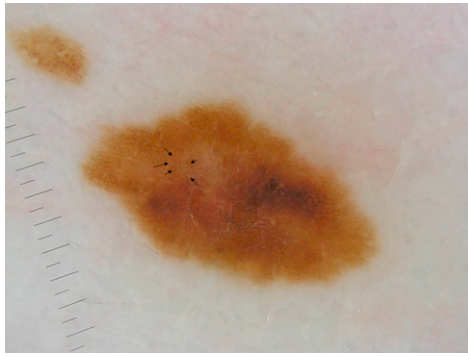The use of polarized dermoscopy did not seem to influence the visualization of NPN; it

Fig 4. Dermoscopic image of invasive melanoma, 0.48-mm thick on trunk of 39-year-old woman. Combination of asymmetrical pigmentation pattern, irregular distribution, and peripheral location (*full head arrows*) of negative pigment network was found to be clue for diagnosis of this difficult-to-diagnose melanoma. (Original magnification: ×20.)

Fig 5. Dermoscopic images of dermatofibroma on thigh of 45-year-old woman. Negative pigment network (NPN) with relatively lighter lines making up "cords" of network and brown areas, "holes" (type A NPN), regularly distributed almost throughout lesion (*full head arrows*). In center, shiny white streaks (*arrows*). (Original magnification: ×10.)

has a thickness of 4 μm and reveals the morphology in the vertical plane. The dermoscopic image displaying the NPN phenomenon is plotted on the horizontal plane and our conclusion is that based on conventional dermoscopic-pathologic correlation, definition of the phenomenon of NPN is nearly impossible. Still, the phenomenon of NPN is clearly present in our dermoscopic images (Fig 3, *B*, and Fig 4) and seems to have the overall correlation with the various diagnoses as outlined. Whether further studies will provide the precise dermoscopic-histopathologic correlation of NPN remains open.

was seen in the same percentage in both polarized (24.3%) and nonpolarized (24.2%) dermoscopy.

Histopathologically, NPN was described in Spitz nevi representing elongated hypomelanotic rete ridges; however, in some early melanomas, the histopathologic substrate of NPN did not permit the identification of a specific correlation as only focal epidermal acanthosis was found.[19] We agree with this observation as we also did not find a clear-cut histopathologic substrate of NPN. The only consistent finding was the presence of a compact orthohyperkeratosis and a more or less distinct undulation of the epidermis, which makes us believe that the epidermal invagination could be part of NPN. A conventional histologic specimen

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