Clinical and dermoscopic characteristics of congenital and noncongenital nevus-associated melanomas

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Background: No specific features of nevus-associated melanoma (NAM) are currently defined.

Objective: To identify clinical/dermoscopic features of NAM.

Methods: Retrospective evaluation of histopathologically diagnosed NAM.

Results: Eighty of 165 NAMs had a clinically recognizable nevus component, often raised or nodular, most frequently characterized by different morphologic clones and/or colors. In 111 of 165 NAMs, dermoscopy showed a nevus component, prevalently characterized by regular dots/clods and structureless brown areas. Clinically, the melanoma component was eccentric/peripheral in 45 of 80 cases and central in 35 of 80; dermoscopically, the figures were 59 of 111 and 52 of 111, respectively. Melanomas associated with congenital nevi (C-NAMs) occur at a younger age and have a thicker Breslow depth than melanomas associated with acquired nevi (NC-NAMs). Dermoscopically, regular dots/globules characterize C-NAMs, and hypopigmented structureless areas characterize NC-NAMs.

Limitations: Retrospective analysis.

Conclusion: C-NAMs are more often central to a congenital nevus, with a clod/globular or structureless brown pattern, typical of young patients. NC-NAMs are frequently hypopigmented nodules/plaques, eccentric/peripheral, with hypopigmented structureless areas, typical of older patients. (J Am Acad Dermatol 2020;83:1080-7.)

Key words: dermoscopy; melanoma; nevogenesis; nevus; nevus-associated melanoma; skin cancer.

The traditional model of progression suggests that melanoma develops through a stepwise transformation process from a common to dysplastic nevus and, finally, to melanoma in situ, eventually becoming invasive with metastatic potential.[1,2] However, most melanomas develop de novo, and only very few nevi progress toward melanoma. Moreover, when melanoma arises in a pre-existing nevus, the associated nevus will turn out, most frequently, to be banal, often showing congenital-like features and no evidence of dysplasia.[3,4] As a consequence, this model is increasingly abandoned by clinicians and researchers.

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Undoubtedly, some melanomas may arise within a nevus. Large congenital melanocytic nevi have the best documented risk of malignant transformation, whereas the risk of small congenital and acquired nevi is poorly defined and documented.[5] According to histopathologic studies, approximately 30% of melanomas arise associated with a nevus.[6] However, this is not the true frequency of the event, because histopathologic studies rely on selection bias and refer only to excised lesions. Real-life estimations suggest that the annual transformation rate of nevi into melanomas is exceedingly low, ranging from 0.0005% or less (ie, 1/200,000) in those younger than 40 years to 0.003% (approximately 1/33,000) in persons older than 60 years.[7] Dermoscopy improves the early diagnosis of melanoma and categorization of nevi, and multiple studies focus on the dermoscopic patterns of melanomas and nevi. In contrast, clinical and dermoscopic criteria of nevus-associated melanoma (NAM) are less studied.[8,9] We observed that the location of melanoma in nevi varies with age. This retrospective study aimed to gain insights into the morphologic spectrum of NAMs.

CAPSULE SUMMARY

- Our study confirms current data about the epidemiology of nevus-associated melanomas and opens novel insights into their morphologic variability, which suggests different pathways leading to melanoma formation in nevi.
- Knowledge of age-related context and characteristic clinical and dermoscopic features facilitates the early recognition of congenital and noncongenital nevus-associated melanoma.

MATERIALS AND METHODS

This study involved dermatologic clinics in Austria (Graz, Vienna) and Italy (Messina, Napoli, Reggio Emilia, and Trieste). The protocol was approved by the local institutional review board.

Each center searched its database for clinical and dermoscopic images of histopathologically diagnosed NAM. Each case was given an identification number to guarantee anonymization of sensitive data. Clinical and dermoscopic images with identification number, patient age and sex, tumor location, clinical diameter, histopathologically reported nevus component, and Breslow thickness were sent to the collecting center.

Cases where images were missing, of poor quality, or showing only tumor parts were excluded.

All images were reviewed by 4 dermatologists with more than 5 years of experience in dermoscopy (IZ, RG, EM, and CL) and evaluated for predefined clinical and dermoscopic criteria. The analysis was made by consensus among the evaluators. If no consensus was reached, the criterion was scored as absent.

The evaluation was based on 3 main funnel questions with a trichotomous (yes/no/unsure) answer (Fig 1). The first question verified whether a nevus component was clinically visible. Only if the answer was *yes* or *unsure* were the subsequent evaluations required. The second question concerned the presence of a dermoscopically recognizable nevus component. If the answer was *yes* or *unsure*, the further items were evaluated. If a nevus component was not clinically or dermoscopically, the evaluation proceeded to question 3, which aimed to assess melanoma-specific patterns.

Statistical analysis

Results were expressed as mean ± standard deviation, minimum and maximum (continuous variables), or absolute frequency and percentage (qualitative variables). Differences between subgroups were evaluated with Mann-Whitney test (continuous variables) and chi-square or Fisher's exact test, as appropriate, for qualitative variables. $P < .05$ was considered significant. Calculations were performed using Microsoft Excel (Microsoft, Redmond, WA) with the Real Statistics Resource Pack software (available at http://www.real-statistics.com).

RESULTS

General results

We included 165 patients (94 male and 71 female; mean age, 47.64 ± 17.20 years; range, 10-89 years) with 165 NAMs; 33 did not meet inclusion criteria. The locations of NAMs were the upper portion of the back (31.52%), mid-lower portion of the back (16.97%), upper portion of the arms (13.33%), lower extremities (10.91%), abdomen (8.48%), chest (8.48%), and head/neck area (7.88%); other sites were affected in the remaining 2.42%. The mean clinical size was 11.68 ± 12.12 mm (range, 3-150 mm).

Clinical features

Clinically, a nevus component was not recognized in 85 cases (51.52%) and was recognizable in 80 cases (48.48%). Of the latter, a nevus was clear in 69 (86.25%) and likely in 11 (13.75%). The strongest feature suggestive of a nevus was the simultaneous presence of 2 different morphologic components (46 cases, 57.5%), followed by different colors (28 cases,

Abbreviations used:

C-NAM: melanoma associated with congenital nevi
NAM: nevus-associated melanoma
NC-NAM: melanomas associated with acquired nevi

35%), terminal hairs (4 cases, 5%), and overall size (2 cases, 2.5%). The associated nevus was flat in 33 cases (41.25%), papular in 22 (27.5%), nodular in 16 (20%), and papillomatous in 9 (11.25%). Fifty-five nevi (68.75%) were pigmented. Borders were sharply demarcated in 55 cases (68.75%) and ill-defined in 25 (31.25%).

Notably, the melanoma component arose adjacent (eccentric/peripheral) to the nevus in 45 (56.25%) cases, whereas it was located central within the nevus in 35 (43.75%) (Fig 2 and supplemental material; available via Mendeley at http://doi.org/10.17632/kt3vy2cd7y.1).

Dermoscopic features

Dermoscopy showed a nevus component in 89 cases (53.94%), whereas in 22 (13.33%), the nevus was considered likely; no dermoscopic evidence of nevus was present in 54 (32.73%) cases.

In the 111 (67.27%) cases where a nevus component was dermoscopically visible, the prevalent features were regular dots/clods (n = 31, 27.93%), structureless brown areas (n = 28, 25.23%), typical pigmented network (n = 22, 19.82%), hypopigmented structureless areas (n = 15, 14.41%), central hypopigmented/hyperpigmented structureless areas surrounded by peripheral reticular pattern (n = 9, 8.11%), hairs (n = 3, 2.7%), streaks (n = 1, 0.9%), and structureless blue areas (n = 1, 0.9%). Dermoscopically, the melanoma was eccentric/peripheral in 59 cases (53.15%) and central in 52 (46.85%) (Fig 2).

Melanoma identification in NAMs was based on various dermoscopic criteria, including atypical network, irregular dots/globules, streaks, regression, raised blue color, reticular depigmentation, melanoma-associated vascular structures, atypical blotches, and structureless brown and shiny white structures. In most cases (90/165, 54.5%), dermoscopy showed the simultaneous presence of 2 or more criteria in the same lesion (multicomponent lesions).

Histopathologic features

Histologically, the associated nevus was congenital in 47 cases (28.48%) and noncongenital in 118 (71.52%); this latter category included 59 (50%) compound nevi, 34 (28.81%) dysplastic nevi, 24 (20.34%) dermal nevi, and 1 blue nevus (0.85%).

The mean Breslow depth was 0.53 ± 0.70 mm (range, 0-5.3 mm); in detail, 55 melanomas (33.3%) were in situ, 89 (53.9%) were less than 1 mm thick, and 15 (9.1%) were 1 to 2 mm thick. Only 6 (3.6%) were greater than 2 mm thick.

Comparison of melanomas arising in nevi with congenital features versus nevi without congenital features

We compared the demographics and lesion characteristics of patients with nevi with congenital features (C-NAMs) and nevi without congenital features (NC-NAMs). No differences between the 2 groups were seen for sex (23 male and 24 female patients with C-NAMs vs 71 male and 47 female patients with NC-NAMs; P = .19), location of the melanomas (P = .95), or mean size (15.13 ± 21.33 mm for C-NAM vs 10.31 ± 4.53 mm for NC-NAM; P = .19). Patients with histopathologic C-NAM were significantly younger than those with NC-NAM (39.02 ± 17.63 vs 51.08 ± 15.84 years; P = .0001). Breslow depth was significantly greater (P = .047) in C-NAMs (0.70 ± 0.92 mm) than in NC-NAMs (0.46 ± 0.58 mm).

In patients with a clinically visible nevus component, significant differences were found for age (40.62 ± 18.3 years for patients with C-NAM vs 48.69 ± 14.65 years for patients with NC-NAM; P = .039), nevus-associated features (P = .048) (Table I), nevus pigmentation (25/26 pigmented C-NAMs vs 30/54 NC-NAMs; P = .00014), nevus borders (sharp in 22/26 C-NAMs vs 33/54 NC-NAMs; P = .03). A significant difference also concerned melanoma localization, which was central in the majority of C-NAMs (20/26, 76.92%) and eccentric/peripheral in the majority of NC-NAMs (39/54, 72.22%; P = .00003). No significant differences were seen for location (P = .79), size (P = .29), Breslow depth (P = .11), or morphology (P = .24) of lesions or sex distribution (P = .76).

Similarly, patients with a dermoscopically visible nevus component showed significant differences of age (35.92 ± 18.2 years for patients with C-NAM vs 48.79 ± 15.88 years for patients with NC-NAM; P = .0003) and dermoscopic pattern of the nevus component (P = .032) (Table I). In detail, C-NAMs showed significantly more frequent regular dots/globules (P = .007), whereas hypopigmented structureless areas were prevalent in NC-NAMs (P = .014). No differences were seen for location (P = .88), size (P = .38), and Breslow depth (P = .20) of lesions or sex (P = .39).

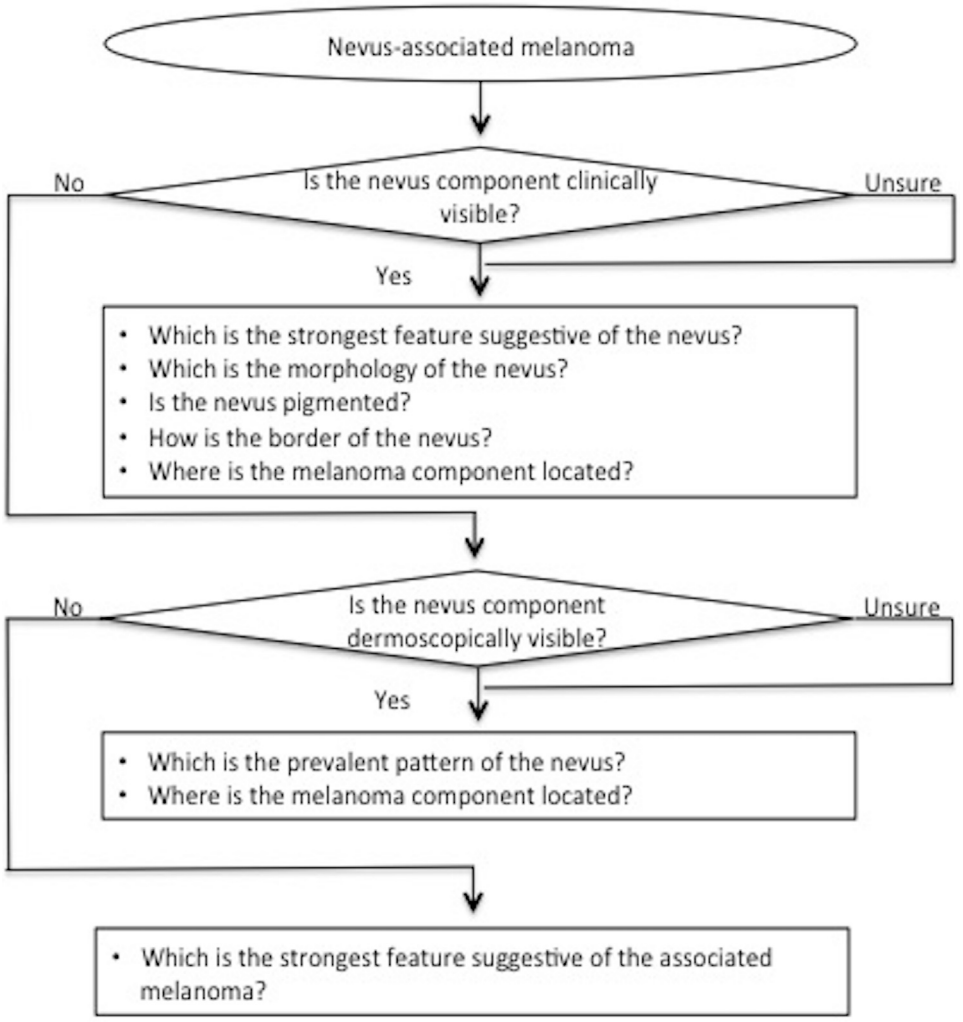

Fig 1. Schematic illustration of the 3 main funnel questions used for the clinical and dermoscopic evaluation of nevus-associated melanoma.

Notably, the most evident difference concerned the localization of melanomas with regard to the nevus. Although the majority of C-NAMs (28/36, 77.78%) exhibited a central melanoma component, 51 of 75 NC-NAMs (68%) displayed an eccentric/peripheral melanoma component (P = .000006).

However, we noticed that the melanoma component of any NAM, independent from the subgroup, tended to be more frequently central in patients younger than 40 years and eccentric/peripheral in those older than 40 years. Data from clinical observation showed such a trend close to significance (P = .06), which was confirmed at dermoscopic examination (P = .0017).

We also compared the frequency of dermoscopic features of C-NAMs and NC-NAMs (Table II).

Finally, a subgroup analysis of the characteristics of invasive vs in situ melanomas showed no significant differences.

DISCUSSION

Our study confirms current data about the epidemiology of NAMs and opens novel insights into their morphologic variability, suggesting different pathways to melanoma formation in nevi.

In line with previous studies,[10] NAMs in our study were associated with an average age of approximately 50 years, slightly more frequent in male patients (57%), and mainly located on upper to mid-lower portions of the back and upper extremities and rarely on the head/neck area or lower extremities. Also, in agreement with the literature, the most frequently reported nevus types associated with NAM were congenital, compound, and dermal nevi with or without dysplasia,[3,4] whereas junctional or lentiginous nevi are rarely associated with NAM. This might be related to the histopathologic difficulties of accurately differentiating the junctional component of nevi from that of associated

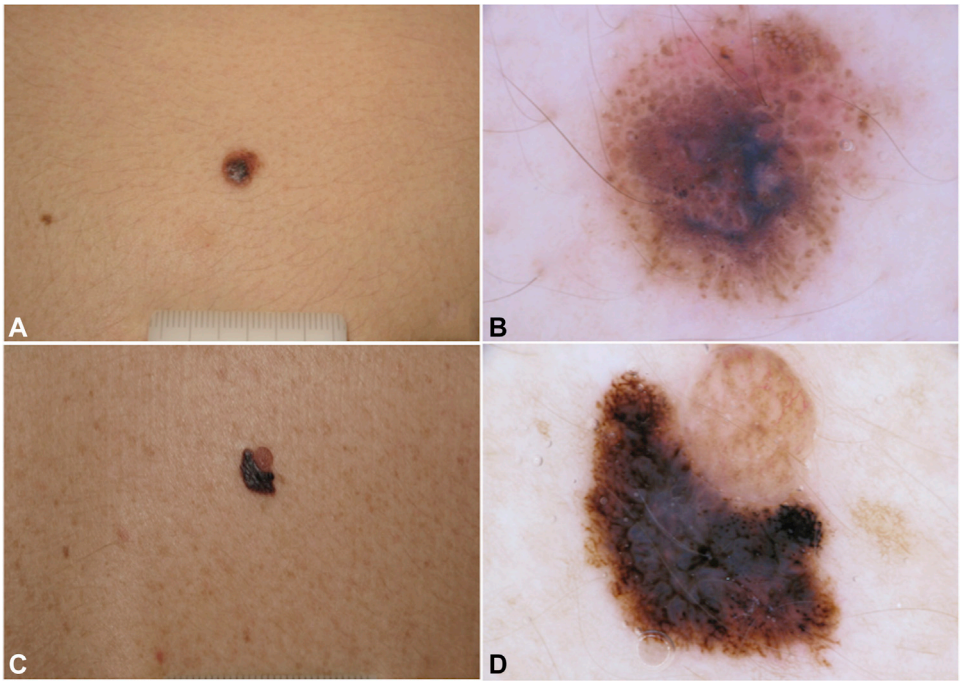

Fig 2. Clinical and dermoscopic appearance of 2 nevus-associated melanomas. Melanoma arising (**A, B**) within a nevus of the congenital type and (**C, D**) adjacent to an acquired nevus.

Table I. Clinically and dermoscopically visible features of the nevus component of NAMs, C-NAMs, and NC-NAMs

	NAMs with the features indicated, n (%)		
Features	**C-NAM (n = 26)**	**NC-NAM (n = 54)**	***P***
Clinical			
Size	2 (7.69)	0 (0)	.051
Color	8 (30.77)	20 (37.04)	.58
Terminal hairs	3 (11.54)	1 (1.85)	.054
Two different components	13 (50)	33 (61.11)	.35
Overall			**.048**
	C-NAM (n = 36)	**NC-NAM (n = 75)**	
Dermoscopic			
Regular dots/globules	16 (44.44)	15 (20)	**.007**
Typical pigmented network	5 (13.89)	17 (22.67)	.28
Structureless brown	10 (27.78)	18 (24)	.67
Hypopigmented structureless	1 (2.78)	15 (20)	**.014**
Central structureless plus peripheral reticular	3 (8.33)	6 (8)	.86
Streaks	0 (0)	1 (1.33)	.66
Structureless blue	1 (2.78)	0 (0)	.16
Hairs	0 (0)	3 (4)	.4
Overall			**.032**

C-NAM, Melanoma associated with congenital nevi; *NAM,* nevus-associated melanoma; *NC-NAM,* melanoma associated with acquired nevi. Significant *P* values are in bold.

melanomas. However, this hypothesis does not explain why NAMs, according to the literature, occur at a younger age than de novo melanomas.[11] Although NAMs in our study presented an average diameter of 11.68 ± 12.12 mm (C-NAMs, 0.70 ± 21.33 mm; NC-NAMS, 10.31 ± 4.53 mm), an associated nevus was clinically recognizable in only approximately 48% of cases. The most suggestive criteria for associated nevi were different morphologic components and colors between the nevus and melanoma component, whereby the nevus showed a raised to nodular shape. Size difference was not

Table II. Frequency of dermoscopic features of NAMs, C-NAMs, and NC-NAMs

Dermoscopic features	Occurrences in C-NAMs, n			Occurrences in NC-NAMs, n			*P* values for occurrences in C-NAMS vs NC-NAMs		
	Single component	Multicomponent	Total	Single component	Multicomponent	Total	Single component	Multicomponent	Total
Atypical network	6	11	17	20	55	75	.09	**.036**	**.001**
Irregular dots/globules	1	10	11	3	30	33	.64	.57	.55
Streaks	0	2	2	2	11	13	.28	.52	.17
Regression	9	18	28	5	62	77	**.014**	.86	.94
Raised blue color	5	0	5	2	0	2	**.04**	N/A	**.01**
Reticular depigmentation	0	5	5	2	14	16	.28	.63	.61
Melanoma-associated vascular structures	1	3	4	4	20	24	.44	.22	.07
Atypical blotches	1	0	1	3	0	3	.64	N/A	.88
Structureless brown	3	0	3	7	0	7	.67	N/A	.91
Shiny white structures	1	6	7	0	20	20	.18	.90	.75
Overall							.07	.84	.12

C-NAM, Melanoma associated with congenital nevi; *N/A,* not applicable; *NAM,* nevus-associated melanoma; *NC-NAM,* melanoma associated with acquired nevi.
Significant *P* values are in bold.

significant, confirming this as the least important clinical diagnostic criterion of melanoma. Dermoscopy improved the recognition of associated nevi up to 67% of cases, whereby regular globules/clods, structureless brown areas, and regular network were the most frequent criteria associated with the nevus. Concerning melanoma-specific features in NAMs, Shitara et al[12] reported a negative pigment network (reticular depigmentation), globules, and streaks as surrogate diagnostic criteria of NAM. In our analysis, irregular globules were frequent in NAM, whereas reticular depigmentation and streaks were rare.

A key finding of our study, not previously reported, is related to the location of melanomas developing in association with nevi. We observed 2 patterns of NAM: melanomas arising centrally and eccentrically in relation to the nevus. The first pattern was associated with younger age (<40 years) and nevi showing congenital-like features dermoscopically (globular pattern) and histopathologically. The second pattern occurred more frequently in older individuals in raised to nodular hypopigmented nevi (mainly compound or dermal) without reported congenital features. Moreover, NC-NAMs showed an atypical network more often than C-NAMs. This can be explained by the fact that NC-NAMs were, on average, thinner than C-NAMs (0.46 ± 0.58 mm vs 0.70 ± 0.92 mm). In turn, NC-NAMs may be related to an earlier recognition of melanomas developing adjacent to a nevus, which cause more pronounced clinical asymmetry of the overall gestalt than melanomas arising within a nevus without initially affecting its overall symmetric shape.

Epidemiologic, demographic, and morphologic differences between melanomas arising within and adjacent to the nevus further point toward 2 different pathways of melanoma development in nevi, namely, within congenital and adjacent to acquired nevi (Fig 3). This agrees with the current dermoscopic concept of nevogenesis, which postulates that nevi develop via a congenital and acquired pathway.[13-15] According to the dual concept of nevogenesis, the congenital pathway gives rise to nevi with a clod/globular or structureless brown pattern, present at birth (true small congenital nevi) or developing during early childhood (late small congenital nevi) and persisting throughout lifetime. Such nevi are particularly commonly observed on the upper portion of the torso of children with a fair pigmentary trait.[16] In line with this, clods/globules or structureless brown pigmentation were common in our series of C-NAMs. In C-NAMs, melanoma appears to develop centrally to the nevus.

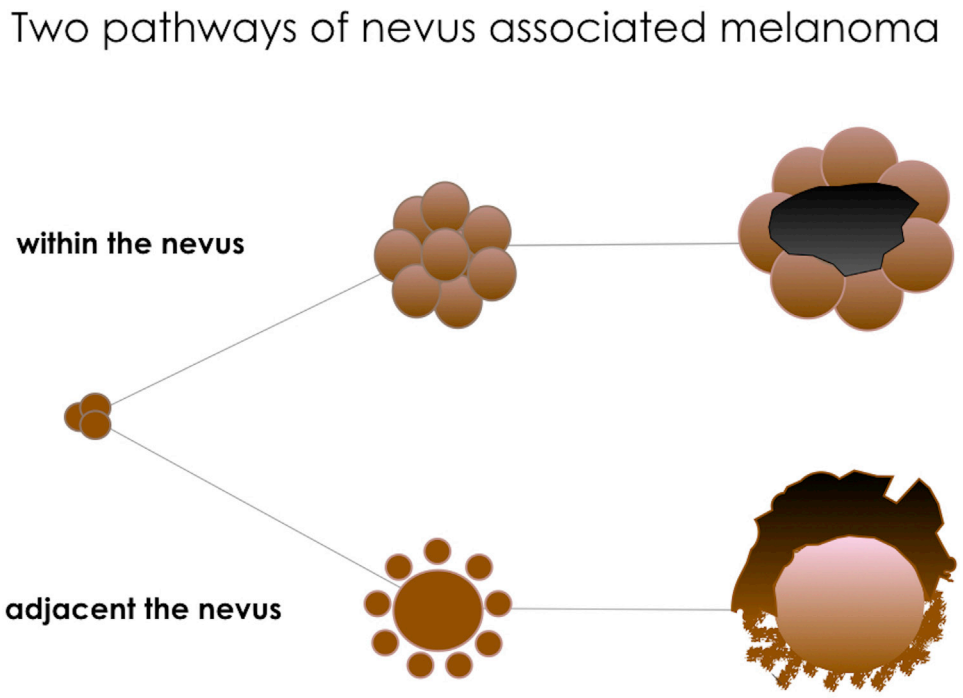

Fig 3. Model illustrating 2 different pathways of melanoma development in nevi, namely, within congenital and adjacent to acquired nevi.

The second pathway leads to the formation of nevi developing after puberty, initially characterized by peripheric brown globules[17] and evolving into nevi with prevalent reticular (superficial compound) or reticular mixed pattern (deep compound).[18] Although most of these acquired nevi undergo spontaneous involution after the fourth or fifth decade,[19] it is plausible that in some deep compound nevi (often with a fried egg appearance), characterized by hypopigmented structureless elevated center (corresponding to the deep dermal component) and peripheral flat network (corresponding to the lateral junctional shoulders), the central dermal component persists for a longer period. In these nevi, melanoma apparently develops adjacent to the nevus.

Notably, Pandeya et al.[20] reported the association of NAMs with blue/green eyes, and nevi with a clod/globular pattern or central hypopigmentation were associated with a fair pigmentary trait.[21] Despite this, they found a higher frequency of *BRAF*^{V600E} compared to de novo melanomas, leading them to speculate whether *BRAF*^{V600E} plays a role in the pathogenesis of NAM. *BRAF*^{V600E} is widely considered an initial driver event in melanoma progression, whereas in nevi, it appears to play a role as a driver event only initially, later causing growth arrest via oncogene-driven senescence.[22] To our knowledge, our group was the first to show that the frequency of *BRAF*^{V600E} in nevi depends on clinical, dermoscopic, and histopathologic morphology and growth stage.[22] We found the highest mutational frequency among nevi with a dermoscopic globular/clod pattern, whereas the frequency in compound nevi (reticular, reticular mixed pattern) appeared growth dependent, that is, high during active growth and decreasing at growth arrest.[22] Tschandl et al[23] investigated the frequency of *BRAF*^{V600E} and *NRAS* mutations in the nevus and melanoma components of the same NAM but found no correlation between these components with regard to the mutational status. They concluded that *BRAF*^{V600E} seems to play no role in the progression of melanoma arising with a nevus; however, they did not mention whether melanomas arose within or adjacent to the nevus. Future studies investigating the frequency of *BRAF*^{V600E} considering the location of melanoma within the nevus and subtype of the nevus may shed more light on this.

Our study has several limitations. First, we retrospectively collected cases; hence, we have no information about additional patient characteristics (eg, nevus count, eye color, skin type). Second, we relied on the reported routine histopathologic diagnosis of the associated nevus, not reviewing the slides. Thus, no conclusions about interobserver agreement of the histopathologic characteristics of the associated nevus can be provided. Third, the evaluation of

specific criteria between the associated nevus and melanoma were based on clinical and dermoscopic assumptions of the associated components, not on clinical-histopathologic or dermoscopic-histopathologic correlation. However, assessment of whether a component was related to the nevus or the melanoma was performed in consensus and on the according dermoscopic criteria. Moreover, we did not assess the frequency of *BRAF* or *NRAS* mutations of the associated nevi and melanomas. Finally, a larger population would improve statistical power.

In summary, our study shows 2 types of NAMs, namely, melanomas arising within/overlying congenital nevi, characterized by a clod/globular or structureless brown pattern, and melanomas arising adjacent to acquired nevi, appearing more frequently as hypopigmented nodules/plaques. Persons developing the former type are generally younger. In the latter subtype, the adjacent location appears to facilitate the early recognition of melanoma. However, because no current method allows prediction of which nevus will develop melanoma, prophylactic excision of these common nevi is not recommended. This recommendation should also be seen in light of the considerably low overall risk of progression.

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