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Digital dermoscopic changes during follow-up of *de-novo* and nevus-associated melanoma: a cohort study

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Abstract

Background Nevus-associated melanoma (NAM) has been regarded as a distinct biological entity from *de-novo* melanoma (DNM); however, static dermoscopy often fails in differentiating these entities. Digital dermoscopic monitoring allows to identify dynamic changes occurring during follow-up; this may improve diagnostic accuracy and potentially our knowledge on NAM biology. We aimed to define main independent factors associated with NAM diagnosis and those influencing follow-up time in a population of melanomas excised at follow-up.

Methods A cohort of melanomas excised at follow-up was retrospectively and consecutively selected. NAMs and DNMs were compared according to baseline features and main dermoscopic changes occurring during follow-up. Univariate and multivariable logistic and Cox's regression analysis were performed to respectively define factors associated with NAM diagnosis and those influencing the risk for excision.

Results Eighty-six melanomas were enrolled, of which 21 (24.4%) were nevus-associated. During follow-up NAMs mainly underwent atypical network modifications (47.6%), followed by inverse network (28.6%) and dermoscopic island (23.8%) worsening or appearance. DNMs were also mainly characterized by atypical network modifications (47.7%), however, a significant proportion of cases underwent irregular pigmentation/dots/globules or regression changes (29.2%), which were rarely seen among NAMs. Furthermore, both multivariable logistic and Cox's regression analysis demonstrated a significant association between NAM and a longer follow-up.

Conclusions We demonstrated that among melanomas excised at follow-up, different patterns of dermoscopic changes may be found between NAMs and DNMs. This finding, together with the association of NAM with a longer follow-up time, supports the hypothesis of different biological behavior of these two entities.

Introduction

Nevus-associated melanoma (NAM) represents a peculiar entity within the melanoma family, defined by the coexistence of nevus and melanoma components on histopathologic examination.[1] NAM accounts for almost one-third of all melanomas and has been regarded as a model to investigate melanoma origin.[2,3] A growing body of evidence supports the classification of NAM as a distinct biological entity from *de-novo* melanoma (DNM). In fact, NAM is more frequently seen on the trunk of younger patients with multiple atypical nevi, is generally a superficial spreading melanoma histologic subtype, more frequently harbors BRAF mutation,[4–7] and has a lower Breslow's thickness and better prognosis compared to DNM.[8–12] Specific dermoscopic differences between NAM and DNM have been scarcely described.[13,14] Besides static analysis, dermoscopy also offers the possibility to observe morphological changes over time through digital monitoring; only one study has explored this application for NAM.[15] Defining the main clinical and dermoscopic changes occurring in NAM and the time interval in which these occur could improve diagnostic accuracy and potentially shed light on NAM biology.

In this study we aimed to: (i) define the number of NAM excised at digital dermoscopic follow-up; (ii) assess clinical and

dermoscopic factors independently associated with the diagnosis of NAM excised at follow-up; and (iii) define factors independently influencing the follow-up time.

Materials and methods

In this cohort study, we retrospectively and consecutively enrolled melanoma cases excised after digital dermoscopic follow-up in our unit from April 2007 to January 2019. Only cases for which dermoscopic pictures were available at baseline and the last visit before surgical excision were enrolled. Special site melanomas were excluded. Lesions for which the time interval between the last and the previous visit was longer than 15 months were also excluded as it is considered as temporarily lost to follow-up, since in our service digital dermoscopy monitoring visits are scheduled at a maximum of 12-month interval. For the same reason, lesions with a time interval longer more than 24 months between two consecutive visits were also excluded. Finally, in cases of multiple lesions belonging to the same patients, we defined as the index case the first scheduled for excision, and in cases of synchronous melanomas, we selected the case with the longest follow-up. Demographic and clinical information were registered, such as body site, maximum diameter, photo-type, number of nevi, and personal and family history of melanoma. Follow-up interval was the time between the first visit (baseline) and the last in which excision was scheduled. Histopathological information, such as Breslow's thickness, ulceration, regression, nevus-association status, and the type of nevus associated were recorded. Histopathological slides were jointly reassessed to confirm melanoma diagnosis by two pathologists with experience in skin cancers (S.P. and M.R.). All clinical and dermoscopic pictures were jointly evaluated by two physicians (R.P. and V.M.), blinded for demographic information, in order to define clinical and dermoscopic features at baseline, and the major dermoscopic changes occurred during follow-up. In case of disagreement, a third experienced physician was asked to solve the issue (C.L.). Clinical pigmentation, palpability, and diameter modifications (symmetry and ratio [low: $\leq$25%; moderate: 25–50%; high: $\geq$50%]) were evaluated from clinical pictures, while criteria of the 7-point checklist together with inverse network and dermoscopic island were evaluated from dermoscopic images.[16] Furthermore, the main dermoscopic modification was also defined together with its distribution (focal vs. diffuse) and type (appearance vs. worsening). Major dermoscopic change was defined as most representative dermoscopic feature and/or the feature covering more than 40% of the lesion surface.[17] The institutional review board of Reggio Emilia (protocol number 2014/20976) approved this study.

Statistical analysis

Quantitative variables were checked for normal distribution and then compared according to nevus-association status through *T* Student or Mann–Whitney *U* tests. Categorial variables were compared through Pearson's chi-square or Fisher exact test. To assess which factors were independently associated with nevus-association status (NAM vs. DNM), Spearman's rho coefficients were calculated in order to define significant correlations among demographic, clinical, dermoscopic, and histopathological variables, which were subsequently quantified via univariate logistic regression. Furthermore, a logistic multivariate regression model with backward stepwise variable selection was constructed to identify major independent factors. To define which variables independently influenced the time of follow-up, Kaplan–Meier survival curves were first constructed; both log rank and Tarone-Ware tests were used. Univariate logistic Cox regression analysis was then performed to assess the effects of covariates on the length of the interval, and a multivariable Cox model was constructed to determine which factors could independently affect follow-up time. Alpha level was set at 0.05, whereas an alpha level of 0.10 was used as cut-off for variable removal in the automated model selection for multivariate logistic and Cox's regression. All *P* values were derived from two-sided statistical tests. Statistical analysis was performed by STATA 15 (StataCorp. 2017, Stata Statistical Software: Release 15, College Station, TX, USA, StataCorp LLC).

Results

Study population

A total of 120 melanomas in 105 patients (mean age: 51.1 $\pm$ 13.4 years, 68 [64.8%] men) were initially retrieved. In particular, six patients had two melanomas, two had three, and one had six. Ninety-nine lesions (belonging to 86 patients) were selected after exclusions of cases for which time interval between the last and previous visit was longer than 15 months or with more than 24 months between two consecutive visits. A number of 86 index cases were finally included in the analysis (one for each patient), of which 21 (24.4%) were histopathologically associated with a nevus (Fig. 1). The associated nevus was compound in seven cases, dermal in six, and congenital in three, while this information was missing in five cases.

Demographics and clinical findings

Patients with DNMs were significantly older than those with NAMs (mean age: 57.7 $\pm$ 13.0 vs. 45.6 $\pm$ 12.7; $P = 0.032$, respectively), while no significant differences were found among groups concerning gender and body site, with more than half of lesions being located on the trunk in both groups. Also, groups were homogenous according to the main risk factors for melanoma development (nevus count, photo-type, personal and family history of melanoma). Considering lesion size, NAMs appeared to be significantly larger according to the baseline median diameter compared to DNMs {7.0 (interquartile range [IQR]: 5.0–9.0) vs. 4.0 mm (IQR: 4.0–6.0), respectively;

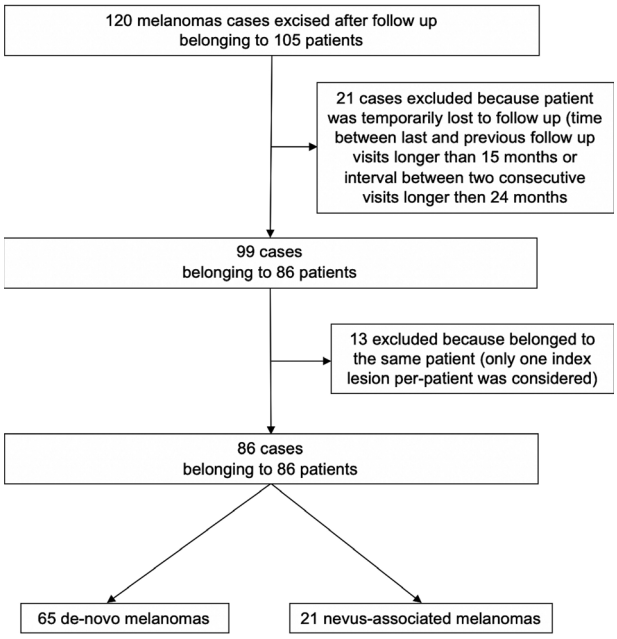

Figure 1 Flow-chart. Enrollment and selection process

$P < 0.001$}. There were no significant differences for clinical pigmentation and palpability at baseline. All melanomas were indeed flat, with the exception of one NAM that had both a papular and a flat component. The latter was kept in our cohort because of the absence of atypical features in the papular component at baseline. Concerning pigmentation, the majority of lesions had a brownish pigmentation in both groups, while the relative proportion of hypopigmented lesions was higher in NAM rather than in the DNM group (33.3% vs. 16.9%) (Table 1).

Baseline dermoscopic findings

Regarding baseline dermoscopic appearance, the majority of lesions were considered to be atypical (65/86, 75.6%) according to the 7-point checklist score, with a higher but not significant proportion in DNMs than in NAMs (80.0% vs. 61.9%; $P = 0.093$). No differences among groups were found, also according to the presence of inverse network and dermoscopic island, which were only found in 9 and 12 cases at baseline, respectively. The main dermoscopic criterion reported at baseline was atypical network in both groups (60.0% in DNM and 57.1% in NAM; $P = 0.817$), followed by regression and irregular dots/globules (Table 1).

Histopathologic findings

Concerning histopathological characteristics, all melanomas but one (1.2 mm) had a Breslow thickness ≤1 mm, with a median Breslow's thickness of 0.4 mm (IQR: 0.3–0.5) and no significant differences according to the nevus-association status ($P = 0.293$). *In situ* cases were (43.0%) 37/86 (26 DNMs and 11 NAMs; $P = 0.319$); ulceration was absent in all cases, while regression features were described in five DNM cases and were never reported among NAMs ($P = 0.328$).

Digital dermoscopic monitoring

When evaluating follow-up in the whole study population, we calculated a median time of 9.4 months (IQR: 6.2–19.1, range: 1.5–56.0 months) and a median number of visits of two (IQR: 1–3, range: 1–11). Interestingly, no differences were found in the mean follow-up time per visit between NAMs and DNMs (5.8 ± 2.0 vs. 6.0 ± 2.3 months; $P = 0.622$), also, follow-up time and number of visits were strongly correlated (Pearson's coefficient: 0.9; $P < 0.001$) and both were significantly higher in the NAM group as compared to DNM (follow-up: 18.6 [IQR: 11.2–28.5] vs. 8.0 [IQR: 6.0–13.9] months, $P = 0.001$; median number of visits 3 [IQR: 2–4.5] vs. 1 [IQR: 1–3]; $P = 0.001$ respectively). Moreover, more than one-third of melanomas were excised after only one follow-up visit (34/86, 39.5%), with significant differences between NAM and DNM (4.8% vs. 50.8%; $P < 0.001$ respectively). Concerning clinical changes during follow-up, pigmentation did not change in 69/86 (80.2%) cases, 16/86 (18.6%) lesions developed darker colors, while only 1/86 (1.2%) developed lighter colors. Palpability never changed during follow-up, while most of the enrolled lesions increased in diameter (72/86, 83.7%) and only a minority (16.3%) were stable, with no differences between NAMs and DNMs ($P > 0.99$). No significant differences were found concerning the type (symmetrical vs. asymmetrical) and the ratio of diameter increase. Nevertheless, most lesions only had a slight (≤25%) increase in diameter (Table 2).

Concerning the major dermoscopic change, we found five major modification patterns: (i) atypical network (47.7%), mainly seen as a worsening (70.3%); (ii) dermoscopic island (16.3%), already present at baseline in the majority of cases (78.6%); (iii) inverse network (14.0%) mainly appearing as a new criterion (58.3%); (iv) irregular dots/globules or irregular pigmentation (12.8%) only reported as the worsening of a pre-existing criterion; (v) regression (9.3%), mostly reported as a worsening (75.0%). We also found that the main dermoscopic change more frequently occurred diffusely within the lesion (DNM: 81.5% vs. NAM: 66.7%; $P = 0.224$, respectively) as a worsening of a pre-existing criterion (DNM: 76.9% vs. NAM: 57.1%; $P = 0.079$; respectively) (Table 2).

When dealing with NAMs, the three main dermoscopic changes were: atypical network (47.6% of cases), followed by inverse network (28.6%) and dermoscopic island (23.8%) (Fig. 2; Figure S1). However, among DNMs, 47.7% of lesions had atypical network, 29.2% irregular pigmentation/dots/globules (16.9%) or regression (12.3%), and 13.8% dermoscopic island changes (Fig. 3; Figure S2).

Table 1 Demographic, clinical, and dermoscopic baseline features

Variables			Nevus-associated status			
			No (DNM)	Yes (NAM)	Total	*P* value*
Demographics and clinical	Mean age at first visit		57.7 ± 13.0	45.6 ± 12.7	50.9 ± 13.2	0.032
	Gender	M	42	13	55	0.822
			64.6%	61.9%	64.0%	
		F	23	8	31	
			35.4%	38.1%	36.0%	
	Location	HN	3	2	5	0.301
			4.6%	9.5%	5.8%	
		Trunk	38	11	49	
			58.5%	52.4%	57.0%	
		Upper limbs	7	5	12	
			10.8%	23.8%	14.0%	
		Lower limbs	17	3	20	
			26.2%	14.3%	23.3%	
	Median max diameter (mm) at baseline (IQR)		4 (4–6)	7 (5–9)	5 (4–7)	<0.001[a]
	Median Breslow's thickness		0.4 (0.3–0.5)	0.4 (0.4–0.7)	0.4 (0.3–0.5)	0.293[a]
	Pigmentation baseline	Amelanotic	0	1	1	0.104
			0.0%	4.8%	1.2%	
		Hypopigmented	11	7	18	
			16.9%	33.3%	20.9%	
		Normal brownish	44	10	54	
			67.7%	47.6%	62.8%	
		Heavily pigmented	10	3	13	
			15.4%	14.3%	15.1%	
	Palpability baseline	Macule	65	20	85	0.244[b]
			100.0%	95.2%	98.8%	
		Papule	0	1	1	
			0.0%	4.8%	1.2%	
	Photo-type	1	1	0	1	0.597
			1.5%	0.0%	1.2%	
		2	21	9	30	
			32.3%	42.9%	34.9%	
		3	43	12	55	
			66.2%	57.1%	64.0%	
	Nevus count	≤50	31	7	38	0.257
			47.7%	33.3%	44.2%	
		50–100	25	8	33	
			38.5%	38.1%	38.4%	
		≥100	9	6	15	
			13.8%	28.6%	17.4%	
	Previous melanoma		29	9	38	0.888
			44.6%	42.9%	44.2%	
	Family history of melanoma[c]		3	1	4	>0.99[b]
			4.9%	5.0%	4.9%	
Dermoscopy	Atypical network		39	12	51	0.817
			60.0%	57.1%	59.3%	
	Atypical vessels		2	0	2	>0.99[b]
			3.1%	0.0%	2.3%	
	Irregular pigmentation		10	2	12	0.722[b]
			15.4%	9.5%	14.0%	
	Irregular dots/globules		11	3	14	>0.99[b]
			16.9%	14.3%	16.3%	
	Irregular streaks		0	0	0	n.a.
			0.0%	0.0%	0.0%	
	Regression		10	4	14	0.738[b]
			15.4%	19.0%	16.3%	

Table 1 Continued

Variables		Nevus-associated status			
		No (DNM)	Yes (NAM)	Total	*P* value*
	7-point checklist ≥1	52	13	65	0.093
		80.0%	61.9%	75.6%	
	Inverse network	6	3	9	0.682[b]
		9.2%	14.3%	10.5%	
	Dermoscopic island	9	3	12	>0.99[b]
		13.8%	14.3%	14.0%	
Total		65	21	86	
		100.0%	100.0%	100.0%	

DNM, *de-novo* melanoma; NAM, nevus-associated melanoma; HN, head and neck; IQR, interquartile range.
[a]Mann–Whitney *U* test.
[b]Fisher's exact test.
[c]5 missing cases (4 DNMs and 1 NAM); the dermoscopic criterion blue-white veil and the histopathologic criterion ulceration were absent in the whole study population; regression features were only reported on histopathology in 5 DNM cases.
*$P < 0.05$.

Clinical and dermoscopic factors associated with nevus-association melanoma status

Spearman's correlation highlighted significant correlations between nevus-association status and follow-up time, age at first visit, and maximum baseline diameter. Univariate and multivariable logistic regression analysis subsequently demonstrated that all these variables were independent predictors of nevus-association status. In particular, each mm of maximum diameter at baseline added gave 55% increased odds for a melanoma to be nevus-associated (AOR: 1.55; 95% CI: 1.17–2.06; $P = 0.002$), while each year of age added was associated with a 5% reduced odd to deal with a NAM (AOR: 0.95; 95% CI: 0.90–0.99; $P = 0.023$). Finally, NAMs were independently more associated with a longer follow-up than DNMs (AOR: 1.05; 95% CI: 1.00–1.09; $P = 0.041$) (Table 3).

Factors influencing the time of follow-up

Kaplan–Meier curves were constructed, and both the log rank and the Tarone-Ware tests were used to assess significant differences among groups concerning the time of follow-up. Both tests reported significant results for the following variables: nevus-association status, age at first visit, Breslow's thickness, dermoscopic regression, inverse network, dermoscopic island, maximum baseline diameter, diameter increase level, main dermoscopic modification criterion, and type. All variables were then quantified through univariate Cox regression analysis and were all associated with significant differences in follow-up time, with the exception of maximum baseline diameter. Subsequently, the multivariable Cox regression model demonstrated that nevus-association status, inverse network, dermoscopic island, and diameter increase level independently influenced the follow-up time. In particular DNMs had twice increased odds to be excised before NAMs (aHR: 0.47; 95% CI: 0.27–0.83; $P = 0.010$), while the presence of inverse network or dermoscopic island at baseline were, respectively, associated with 2.9 and 3.2 increased odds to be excised before lesions not displaying these criteria (aHR: 2.85; 95% CI: 1.26–6.46; $P = 0.012$; aHR: 3.18; 95% CI: 1.60–6.33; $P = 0.001$, respectively). Expectedly, lesions undergoing a moderate to high diameter increase during follow-up had a higher probability to be followed for a longer period than those with a low increase (Table 4).

Discussion

In this cohort retrospective study, we consecutively enrolled melanomas excised at digital dermoscopic follow-up. Interestingly, the ratio of NAMs (24.4%) was in line with a recently published meta-analysis reporting a prevalence of 29.1%.[3] However, it was significantly lower than the ratio of NAM excised at digital follow-up previously assessed by Haenssle *et al.* (60.7%)[7] and Alvarez Martinez *et al.* (62.5%).[15] This may be respectively explained by the higher number of common nevi reported and the exclusion of *in situ* melanomas as compared to our study, which may have led to underestimation of DNMs. Regarding demographic and clinical features, both univariate and multivariable analysis confirmed that patients with NAMs were significantly younger than those with DNMs, as reported in previous studies.[4–7] Also, the maximum baseline diameter was significantly larger in NAMs than DNMs, probably because of the coexistence of two adjacent components (benign and malignant) in the former. Notably, no significant differences were instead highlighted between NAM and DNM according to risk factors and histopathologic features. Concerning dermoscopic findings, most melanomas appeared to be atypical according to the 7-point check list score; however, no significant differences

Table 2 Diameter and main dermoscopic modification occurring during follow-up

Variables			Nevus-associated status			
			No (DNM)	Yes (NAM)	Total	*P* value*
Follow-up	Median time of follow-up in months (IQR)		8.0 (6.0–13.9)	18.6 (11.2–28.5)	9.4 (6.2–19.1)	0.001[a]
	N of follow-up visits	1	33	1	34	0.001
			50.8%	4.8%	39.5%	
		2	14	9	23	
			21.5%	42.9%	26.7%	
		>2	18	11	29	
			27.7%	52.4%	33.7%	
Main dermoscopic modification		Atypical network	31	10	41	0.045
			47.7%	47.6%	47.7%	
		Irregular pigmentation	5	0	5	
			7.7%	0.0%	5.8%	
		Irregular dots/globules	6	0	6	
			9.2%	0.0%	7.0%	
		Regression	8	0	8	
			12.3%	0.0%	9.3%	
		Inverse network	6	6	12	
			9.2%	28.6%	14.0%	
		Dermoscopic island	9	5	14	
			13.8%	23.8%	16.3%	
Main dermoscopic modification type		Appearance	15	9	24	0.079
			23.1%	42.9%	27.9%	
		Worsening	50	12	62	
			76.9%	57.1%	72.1%	
Main dermoscopic modification distribution		Focal	12	7	19	0.224[b]
			18.5%	33.3%	22.1%	
		Diffuse	53	14	67	
			81.5%	66.7%	77.9%	
Diameter modification		No	11	3	14	>0.99[b]
			16.9%	14.3%	16.3%	
		Increase	54	18	72	
			83.1%	85.7%	83.7%	
Total			65	21	86	
			100.0%	100.0%	100.0%	
Diameter increase level		Low (≤25%)	25	7	32	0.836
			46.3%	38.9%	44.4%	
		Moderate (25–50%)	17	6	23	
			31.5%	33.3%	31.9%	
		High (≥50%)	12	5	17	
			22.2%	27.8%	23.6%	
Diameter increase asymmetric		No	26	8	34	0.785
			48.1%	44.4%	47.2%	
		Yes	28	10	38	
			51.9%	55.6%	52.8%	
Total			54	18	72	
			100.0%	100.0%	100.0%	

IQR, interquartile range; DNM, *de-novo* melanoma; NAM, nevus-associated melanoma.
[a]Mann-Whitney *U* test
[b]Fisher's exact test.
*$P < 0.05$.

were highlighted at baseline between NAMs and DNMs. Significant differences were instead found when evaluating the main digital dermoscopic change during follow-up. More specifically, we identified five different modification patterns: atypical network, irregular pigmentation/dots/globules, regression, inverse network, and dermoscopic island. Both NAMs and DNMs more frequently (half of cases in both groups) underwent atypical network changes (appearance or worsening). This may

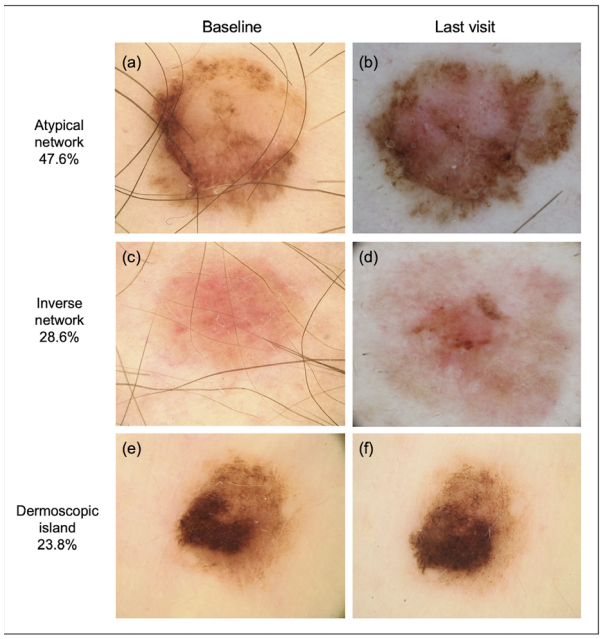

Figure 2 Main dermoscopic changes occurring among nevus-associated melanomas (NAMs). (a, b) Atypical network (47.6% of cases): a slightly palpable 8 mm *in-situ* NAM, located on the lower limbs of a 58-year-old man; excised after 49.0 months (5 follow-up visits) and developing atypical network and moderate asymmetric increase in diameter. (c, d) Inverse network (28.6%): an 8 mm NAM (Breslow's thickness: 0.8 mm) in a 43-year-old man, located on the back, excised after 37.0 months (6 follow-up visits), undergoing high symmetric increase in diameter and appearance of diffuse inverse network upon dermoscopy. (e, f) Dermoscopic island (23.8%): a 7 mm *in-situ* NAM, located on the back of a 30-year-old woman and excised after 7 months (2 follow-up visits), undergoing low asymmetric increase of hyperpigmented dermoscopic islands characterized by atypical network and developing irregular peripheral streaks

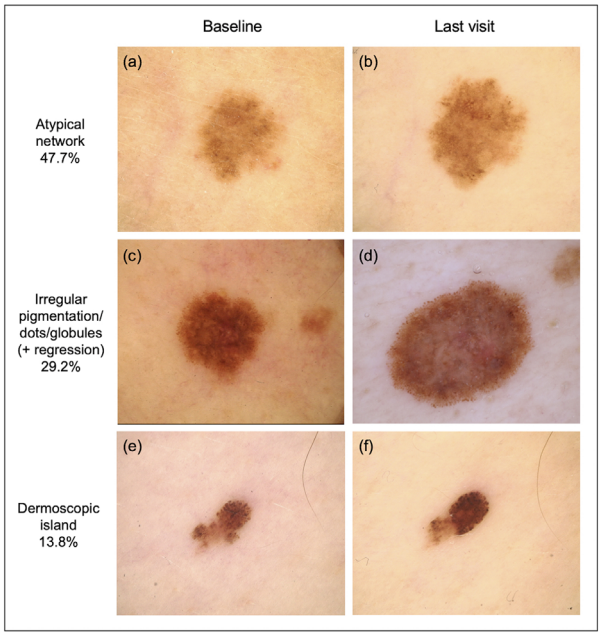

Figure 3 Main dermoscopic changes occurring among *de-novo* melanomas (DNMs). (a, b) Atypical network (47.7% of cases): a flat 4 mm *in-situ* DNM in a 63-year-old woman, located on the lower limbs, excised after 6.0 months (1 follow-up visit) and developing spotted atypical network appearance and low symmetric increase in diameter. (c, d) Irregular pigmentation/dots/globules or regression (29.2%): a 5 mm DNM (Breslow's thickness 0.5 mm), in a 56-year-old man, located on the back and excised after 9.7 months (3 follow-up visits), undergoing high asymmetric increase in diameter and worsening of irregular peripheral globules; regression features also become visible in the central part of the lesion. (e, f) Dermoscopic island (13.8%): a 3 mm DNM (Breslow's thickness 0.4 mm), located on the chest of a 46-year-old man, excised after 5.0 months (1 follow-up visit), undergoing a moderate asymmetric increase of a globular dermoscopic island

be explained by the tendency to select flat junctional lesion for digital dermoscopic monitoring in our unit.[18] The second main dermoscopic changes seen among DNMs regarded irregular pigmentation/dots/globules or regression, which were instead never reported among NAMs and almost exclusively derived from the worsening of a pre-existing criterion. Indeed, as expected lesions harboring such dermoscopic criteria are commonly scheduled for digital monitoring.[18] However, since no differences in the distribution of irregular pigmentation/dots/globules or regression were found at baseline between NAMs and DNMs, it appears that only DNMs tend to undergo a worsening of these criteria. Finally, the third and fourth main dermoscopic changes reported for DNMs regarded dermoscopic island and inverse network, respectively. Conversely, among NAMs, inverse network and dermoscopic islands were more frequently seen, representing the second and third main dermoscopic changes. This is in line with previous studies describing a significant association between the presence of dermoscopic island or inverse network and the diagnosis of NAM[14,19]; moreover, Alvarez Martinez et al. reported a tendency towards appearance or worsening of structureless brown-black areas or clods in DNMs and white lines in NAMs during follow-up.[15] One of the main findings of our study consisted of demonstrating that NAMs underwent a longer follow-up than DNMs. The median follow-up time for NAMs was indeed almost one year longer than DNMs. Both multivariable logistic and Cox's regression analysis confirmed that NAMs were associated with a higher risk to be excised later than DNMs. In this scenario, the coexistent nevus may play the pivotal role in slowing down melanoma progression.[20] Concerning survival analysis, we also found a significant association between a longer follow-up and absence of inverse network or dermoscopic island at baseline. These findings demonstrate that inverse network and dermoscopic island are commonly perceived as more atypical than other

Table 3 Factors associated with nevus-association status

	Spearman's correlation		Univariate logistic regression				Multivariable logistic regression			
				95% CI for OR				95% CI for aOR		
Variables	Rho coefficient	*P* value*	OR	Lower bound	Upper bound	*P* value*	AOR	Lower bound	Upper bound	*P* value*
Months between first and last visit	0.35	0.001	1.05	1.01	1.10	0.009	1.05	1.00	1.09	0.041
Age at first visit	−0.23	0.037	0.96	0.92	1.00	0.037	0.95	0.90	0.99	0.023
Maximum baseline diameter (mm)	0.42	<0.001	1.52	1.19	1.95	0.001	1.55	1.17	2.06	0.002

Variables at step 1: age at first visit, diameter, months between first and last visit.
AOR, adjusted odds ratio; CI, confidence interval
*$P < 0.05$.

Table 4 Factors influencing the time of follow-up

	Kaplan–Meier		Cox univariate				Cox multivariable			
				95% CI for HR				95% CI for aHR		
Variables	Log rank	Tarone-Ware	HR	Lower bound	Upper bound	*P* value*	aHR	Lower bound	Upper Bound	*P* value*
Nevus-association status (DNM vs. NAM)	0.013	0.003	0.54	0.33	0.89	0.015	0.47	0.27	0.83	0.010
Age at first visit	<0.001	<0.001	1.00	0.98	1.02	0.878				
Breslow's thickness	0.003	0.016	0.23	0.045	1.23	0.087				
Regression dermoscopic	0.011	0.007	2.08	1.16	3.74	0.014				
Inverse network	0.023	0.042	2.23	1.09	4.58	0.028	2.85	1.26	6.46	0.012
Dermoscopic island	0.006	0.009	2.33	1.24	4.39	0.009	3.18	1.60	6.33	0.001
Baseline maximum diameter	0.010	0.034	0.94	0.86	1.02	0.139				
Diameter increase level (low)	0.002	0.004	ref.				ref.			
Diameter increase level (moderate)			0.58	0.33	1.00	0.051	0.39	0.21	0.71	0.002
Diameter increase level (high)			0.34	0.18	0.65	0.001	0.30	0.16	0.59	<0.001
Main dermoscopic modification (atypical network)	0.015	0.023	ref.							
Main dermoscopic modification (irregular pigmentation)			1.33	0.52	3.40	0.554				
Main dermoscopic modification (irregular dots/globules)			1.97	0.82	4.70	0.128				
Main dermoscopic modification (regression)			3.20	1.45	7.07	0.004				
Main dermoscopic modification (inverse network)			0.91	0.47	1.78	0.784				
Main dermoscopic modification (dermoscopic island)			2.07	1.11	3.88	0.023				
Main dermoscopic modification type (appearance vs. worsening)	0.008	0.003	1.90	1.17	3.08	0.010				

Variables at step 1: nevus-association; inverse network; dermoscopic island; regression dermoscopic; main dermoscopic modification type (appearance vs. worsening); diameter increase level (low, moderate, high); main dermoscopic modification.
DNM, *de-novo* melanoma; NAM, nevus-associated melanoma; aHR, adjusted hazard ratio; CI, confidence interval
*$P < 0.05$.

dermoscopic criteria, inducing clinicians to schedule a shorter follow-up when already present at baseline.

The main limitation of this retrospective study is that we considered a very specific study population, which were melanomas excised at digital follow-up; thus, results can only be cautiously extended to the whole melanoma population. Another limitation consists in the high proportion of *in situ* melanomas enrolled. Indeed, it is more difficult to define, from a histopathological point of view, if an *in situ* melanoma is associated or not with an adjacent nevus. To overcome this issue, histopathological slides were jointly reassessed by two pathologists with expertise in skin tumors. Finally, further studies including a larger number of NAM cases are needed to confirm the results of our study.

To conclude, our study described different patterns of digital dermoscopic changes during follow-up, highlighting significant differences between NAMs and DNMs. It also demonstrated a slower growth for NAM as compared to DNM, which could be enhanced by the coexistence of the benign entity.[20]

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Supporting Information

Figure S1 Main dermoscopic changes occurring among nevus-associated melanomas (NAMs)

Figure S2 Main dermoscopic changes occurring among *de-novo* melanomas (DNMs)