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Comparative dermoscopy assessment of nevus-associated versus *de novo in situ* melanoma

Background: Dermoscopic features differentiating *in situ* nevus-associated melanoma (NAM) versus *in situ de novo* melanoma (DNM) are inconclusive. *Objectives*: The aim of the study was to investigate the dermoscopic features associated with *in situ* NAM versus DNM. *Materials & Methods*: This was a retrospective observational study. All consecutive *in situ* melanomas diagnosed in adult patients were retrieved and stratified as NAM vs DNM, and clinical and dermoscopic data were compared between the two. *Results*: A total of 183 patients with *in situ* melanoma were collected, of whom 98 (54%) were male with a mean age of 64±14 years. For 129 patients, standardized dermoscopic images were collected (51 for NAM and 78 for *de novo* MM). The most common dermoscopic features were an atypical pigment network (85%), atypical globules (63%) and regression (42%). No significant differences were found except for regression, which was detected in 54.9% NAM vs 33.3% DNM (p=0.016). Multivariate logistic regression confirmed the association between dermoscopic regression and NAM (OR=2.34, 95% CI: 1.15-4.91). *Conclusion:* Currently, the use of dermoscopy to determine whether a melanoma is associated with a nevus is unreliable, however, the presence of regression adjacent to atypical lesions may raise suspicion of *in situ* NAM.

Key words: *in situ* melanoma, nevus-associated melanoma, *de novo* melanoma, *in situ* nevus-associated melanoma dermoscopy, *in situ de novo* melanoma dermoscopy

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The presence of multiple nevi has been shown to be associated with a greater risk of cutaneous malignant melanoma, nonetheless there is general agreement that most melanomas develop *de novo*. Approximatively 70% of melanomas do not show an associated benign melanocytic nevus component on histopathological evaluation, and only a minority show the coexistence of a nevus, defined as nevus-associated melanoma (NAM) [1]. Two types of NAM are recognized, namely acquired and congenital NAM [2]. The clinicopathological features and prognosis of primary cutaneous melanoma with benign melanocytic naevus components (*i.e*. NAMs) are still under debate. Benign and atypical nevi have been shown to exist in histological contiguity with melanomas, suggesting that this melanocytic proliferation is also susceptible to malignant transformation [3, 4]. While large congenital melanocytic nevi are associated with the greatest risk of melanoma development, the role of small congenital and acquired nevi in NAM has been rarely defined. According to some authors, the nevus component of a melanoma arising on a nevus generally has similar characteristics to those of congenital nevus and does not show dysplastic alterations [5, 6]. Recent strategies have focused on early detection and continuous follow-up of nevi for malignant degeneration. Dermoscopy can help recognizing MM in its earliest stages (*i.e. in situ*) [7] but specific dermoscopic features differentiating NAM versus *in situ de novo* melanoma (DNM) are inconclusive. The early identification of melanomas arising on nevus may be of significant relevance, particularly when a patient is unreliable in reporting whether suspicious lesions arose *de novo* or on a pre-existing nevus. The aim of the study was to investigate the dermoscopic features associated with *in situ* NAM compared to DNM.

Materials and methods

A retrospective observational cross-sectional study was undertaken. Consecutive patients were collected from the electronic database of the Dermatology and Venereology Unit of the University Hospital of Verona (Italy) from 1st January 2006 to 30th April 2022. The inclusion criterion was diagnosis of *in situ* melanoma in adult patients. Exclusion criteria were: (1) genetic syndromes predisposing to melanoma (*e.g.* xeroderma pigmentosum); (2) melanomas arising on congenital nevus; and (3) acral, mucosal, nail, polypoid, nevoid and

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spitzoid melanomas. The patients were categorized by the presence or absence of an associated acquired nevus, as documented in the standardized histopathological report. Clinical and demographic features were collected, including age at diagnosis, sex, family history of melanoma, total number of nevi (with diameter >2 mm) as well as atypical nevi, Fitzpatrick phototype, hair and eye colour, presence of freckles, site of excision, number of cherry angiomas, presence of precancerous lesions (*i.e.* actinic keratoses) and solar lentigo, personal history of non-melanocytic skin cancers, and personal history of other non-skin cancers. Standardized dermoscopic images were retrieved and evaluated blindly by two dermatologists trained in dermoscopy. In the case of disagreement, a third dermatologist was consulted. The different features, as defined by the consensus meeting on dermoscopy pigmented lesions [8], were investigated. In detail, typical pigment vs atypical pigment network, dermoscopic island, cobblestone / homogeneously distributed globule pattern, atypical globules, peripheral globules, blotch, peripheral streaks / pseudopods, negative pigment network, tan structureless area, scar-like depigmentation, peppering, shiny white structures/lines, areas without a defined structure, blue-white veil, number of colours within the lesion, regression, atypical vessels and lesion size (mm) were assessed. The phenotypic and dermoscopic data of patients were recovered from the video-dermoscopic archive and NAM vs DNM were compared.

Statistical analysis

In the descriptive analysis, results were presented as mean and standard deviation or proportion when appropriate. NAM vs DNM were compared using the Pearson's Chi-squared test for categorical variables and the Mann-Whitney rank test for non-normally distributed continuous variables. A multiple logistic regression model was fitted to the data to estimate the dermoscopic features independently associated with NAM, adjusting for sex and age at diagnosis. *P* value < 0.05 was considered statistically significant. Statistical analyses were performed using Stata version 13 (Stata Corp, Texas, USA).

Results

A total of 183 patients with *in situ* melanoma were investigated, of whom 98 (54%) were male, with a mean age of 64±14 years. The locations of the lesions were the: upper back (22%), upper limbs (20%), lower limbs (20%), mid-lower back (11%), abdomen (11%), chest (10%) and head-neck (6%). The mean size of the lesions was 7.9 ± 3.7 mm (range: 3-20). The majority of the patients had type III Fitzpatrick phototype, with a total of 10 to 50 common nevi, without concomitant atypical lesions. The sample was stratified for 66 cases of (36%) NAM and 117 of (64%) DNM. Clinical and demographic characteristics of the patients are summarized in *table 1*. No significant differences were found among the clinical and demographic variables between NAM vs DNM, including phenotype risk factors for MM such as number of common and atypical nevi, cherry angiomas, solar lentigos, actinic keratoses and Fitzpatrick phototype. A total of 129 standardized dermoscopic images were collected (51 images of NAM and 78 of *de novo* MM).

Table 1. Clinical and demographic characteristics of consecutive patients with nevus-associated *in situ* melanoma vs *de novo in situ* melanoma.

	Nevus-associated *in situ* melanoma (*n*=66)	***De novo* *in situ* melanoma (*n*=117)**	*p*
Gender, male (%)	42 (63.6)	56 (47.8)	0.030
Age at diagnosis, years (mean±SD)	59.8 ± 14.5	59.0 ± 14.7	0.573
Excision site			0.714
Head-neck	5 (7.6)	7 (6)	
Chest	7 (10.6)	12 (10.2)	
Abdomen	9 (13.6)	11 (9.4)	
Back	23 (34.8)	37 (31.6)	
Upper limbs	13 (19.7)	23 (19.7)	
Lower limbs	9 (13.6)	27 (23.1)	
Average size (mm) ± SD	8.19 ± 3.41	7.74 ± 3.9	0.497
Total number of nevi*			
<10	7 (17.1)	23 (28)	
10-50	23 (56.1)	38 (46.3)	0.421
50-100	6 (14.6)	15 (18.3)	
≥100	5 (12.2)	6 (7.3)	
Number of atypical nevi*			
0	22 (53.7)	53 (64.6)	
1	7 (17.1)	8 (9.8)	0.580
2-5	8 (19.5)	15 (18.3)	
≥5	4 (9.8)	6 (7.3)	
Family history*	3 (7.3)	7 (8.5)	0.816
Excision of dysplastic nevi*	11 (26.8)	21 (25.6)	0.884
Fitzpatrick phototype*			
I	1 (2.4)	1 (1.2)	
II	17 (42.5)	35 (42.7)	0.845
III	23 (56.1)	45 (54.9)	
IV	0	1 (1.2)	
V	0	0 (0)	
Non-melanoma skin cancer	3 (7.3)	13 (15.8)	0.185
Non-skin cancer	6 (14.6)	12 (14.6)	1.000
Solar lentigo	25 (60.9)	45 (54.9)	0.723
Actinic keratoses	4 (9.8)	15 (18.3)	0.246
Hair colour			
Blonde	4 (9.8)	13 (15.8)	0.338
Brown	34 (82.9)	58 (70.7)	
Black	3 (7.3)	11 (13.4)	
Eye colour			0.798
Blue-green	21 (51.2)	35 (42.7)	
Brown-black	20 (48.8)	47 (57.3)	
Freckles	0	6 (7.3)	0.106
Number of cherry angiomas			
0	18 (43.9)	37 (45.1)	0.263
<10	7 (17)	23 (28.1)	
≥10	16 (39)	22 (26.8)	

*SD: standard deviation; * missing cases= 60 patients*

The most common dermoscopic features were atypical pigment network (85%), atypical globules (63%), regression (42%) and tan structureless area (30%). Among the different dermoscopic variables analysed, only regression was found to be more common in NAM compared to DNM (*figure 1*), and was detected in 28 out of 51 (54.9%) versus 26 out of 78 (33.3%) melanomas (p=0.016), respectively (*table 2*). Conversely, the presence of a dermoscopic island characterized by a different morphological pattern was not associated with NAM. Multivariate logistic regression, adjusting for age and sex, confirmed the association between dermoscopic regression and NAM (OR= 2.34, 95% CI: 1.15-4.91, p= 0.025) (*supplementary table 1*). Based on post-hoc analysis, we verified that dermoscopic regression corresponded to histopathological regression in all the cases and that the latter was absent on histological slides without such dermoscopic features.

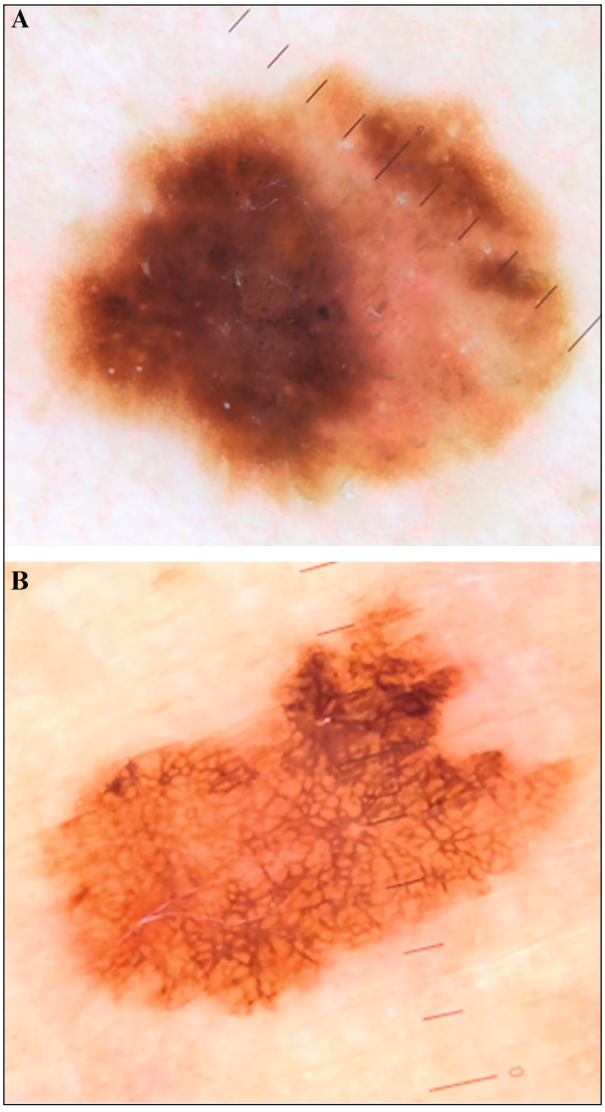

Figure 1. A) Dermoscopy of nevus-associated *in situ* melanoma displaying an atypical pigment network, atypical globules, peppering, regression and atypical vessels. **B**) Dermoscopy of a *de novo in situ* melanoma displaying an atypical pigment network.

Table 2. Dermoscopic characteristics of consecutive patients with nevus-associated *in situ* melanoma vs *de novo in situ* melanoma.

Dermoscopic features, *n* (%)	**Nevus-associated *in situ* melanoma (n=51)**	***De novo in situ* melanoma (*n*=78)**	***p****
Typical pigment network	3 (5.8)	8 (10.3)	0.390
Atypical pigment network	46 (90.2)	63 (80.8)	0.155
Dermoscopic island	8 (15.7)	10 (12.2)	0.647
Typical globules/ cobblestone	2 (3.9)	1 (1.3)	0.355
Atypical globules	27 (52.9)	42 (53.8)	0.451
Peripheral globules	7 (13.7)	15 (19.2)	0.418
Blotch	3 (5.9)	2 (2.6)	0.353
Streaks/pseudopods	9 (17.6)	10 (12.8)	0.451
Negative piment network	4 (7.8)	5 (6.4)	0.755
Tan structureless area	15 (29.4)	24 (30.8)	0.870
Scar-like depigmentation	10 (19.6)	12 (15.4)	0.534
Peppering	8 (15.7)	8 (10.3)	0.363
Shiny white structure/lines	3 (5.8)	6 (7.7)	0.694
Areas without a definable structure	9 (17.6)	19 (11.5)	0.368
Blue-white veil	10 (19.6)	8 (10.3)	0.641
Number of colours in the lesion			
1	1 (1.2)	9 (11.5)	0.164
2	25 (49)	34 (43.6)	
3	15 (29.4)	23 (29.5)	
4	7 (13.7)	10 (12.8)	
≥5	3 (5.9)	2 (2.6)	
Regression	28 (54.9)	26 (33.3)	**0.016**
Atypical vessels	13 (25.5)	16 (20.5)	0.509

Discussion

In this study, dermoscopic differences between *in situ* NAMs and DNM were assessed. NAM accounted for approximatively one third of all *in situ* melanomas. Regression was found to be a relatively common feature, being reported in one third of the cases. Of relevance, dermoscopic regression was associated with the presence of an acquired nevus on histopathology, defining an acquired NAM. Our study confirms that the current data on the epidemiology of NAMs are generalizable to *in*

situ NAM. Consistent with the previous studies, we found that NAM generally develops on the upper back region with slightly higher prevalence in middle-aged male patients [2, 6, 9]. According to the literature, NAM occurs at a younger age than DNM and has a thicker Breslow index [10-12]. In this study, no differences in age at onset or Breslow thickness between NAM and DNM were found, probably reflecting the exclusion of congenital NAM from the sample.

With regards to dermoscopic features, *in situ* melanoma exhibited an atypical pigment network in more than three quarters of the cases, atypical globules in more than a half, and regression and a tan structureless area in one third. Of note, only dermoscopic regression was associated with acquired NAM (OR= 2.34, 95% CI: 1.15-4.91). Two specific types of dermoscopic regression have been defined: blue-grey granules, also known as peppering, and white depigmentation [13-15]. Dermoscopic regression has previously been reported to be associated with *in situ* melanoma, particularly when the amount of regression is greater than 50% (OR = 4.7, CI: 2,8-8.1) [16]. Zalaudeck *et al*. have suggested that the quality and quantity of dermoscopic regression differ between melanomas and nevi, with melanoma most frequently exhibiting extensive blue-grey and white regression [13]. Seidenari *et al*. also found that *in situ* melanoma exhibited a greater extent of areas with grey-blue regression located centrally or peripherally to the lesion, compared to atypical nevi [17]. Certain structures representing dermoscopic regression, such as peppering and scar-like depigmentation, were found more easily in invasive melanomas [18, 19]. More interestingly, Stante *et al*. found that regression was more common among NAM compared to DNM (60.0% vs 39.7%, $p<0.048$) [20]. According to a retrospective dermoscopic evaluation of 165 congenital vs non-congenital NAM, hypopigmented structureless areas were shown to be a feature associated with the latter, which in fact can be a common dermoscopic presentation of regression [2]. In a cross-sectional study of 160 NAM and 218 *de novo* melanomas, including both *in situ* and invasive forms, *in situ* NAM were 2.1-fold more likely to display a dermoscopic area without definable structures than *de novo* melanomas [21]. These findings slightly differ from those of our study and could be due to the different selection of samples, as invasive melanomas were also considered. As an example, Shitara *et al*. found that NAMs more frequently showed a negative pigmented network (OR: 9.9; 95% CI: 2.2-45.0), globules (OR: 2.4; 95% CI: 1.2-4.9) and streaks (OR: 2.4; 95% CI: 1.3-4.7), while the blue-white veil was significantly associated with *de novo* melanoma (OR: 0.520, 95% CI: 0.3-0.9) [22]. Di Stefani *et al*. reported that NAM presents three benign dermoscopic patterns more frequently than *de novo* melanoma, including a globular/cobblestone pattern (27.6% vs 9.4%), homogeneous pattern (27.6 vs 16.2%) and typical pigmented network (36.8% vs 23.6%) [23]. Zalaudek *et al*. hypothesized that, in acquired nevi, NAM develops adjacent to the nevus. Since most acquired nevi undergo spontaneous involution after the fourth or fifth decade, the dermoscopic findings of regression are not uncommon, presenting as a hypopigmented structureless elevated centre (corresponding to the deep dermal component) and peripheral flat network (corresponding to the lateral junctional shoulders) [2]. Dermoscopic regression may represent the remnants of the involved nevic component next to the associated melanoma [21].

This study is burdened by some limitations, including the retrospective design and monocentric recruitment. Nonetheless, the study has some strengths such as triple blind dermoscopic evaluation, standardized histopathological reports and the analysis of multiple clinical variables.

In conclusion, *in situ* NAM accounts for approximately 30% of all melanoma diagnoses. *In situ* NAM may occur at all ages, but middle-aged men seem to be more frequently affected. Among clinical, epidemiological and dermoscopic features, dermoscopic regression was found to be associated with *in situ* acquired NAM. Although currently it is not possible to judge whether a melanoma is associated or not with a nevus clinically or dermoscopically, the presence of regression adjacent to atypical nevi may raise suspicion of NAM. Further and larger studies are needed to confirm our results.

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Conflicts of interest: *none.*

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