Received: 6 June 2018 | Revised: 31 October 2018 | Accepted: 17 November 2018

DOI: 10.1111/exd.13853

ORIGINAL ARTICLE

WILEY Experimental Dermatology

Pigmented skin lesions displaying regression features: Dermoscopy and reflectance confocal microscopy criteria for diagnosis

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Funding Information
"This research was kindly supported by Italian Ministry of Health (Project Code: NET-2011-02347213)."

Abstract

Melanomas and nevi displaying regression features can be difficult to differentiate. To describe reflectance confocal microscopy features in benign and malignant pigmented skin lesions characterized by regression features in dermoscopy. Observational retrospective study. Inclusion criteria were presence of dermoscopic features of regression; availability of clinical, dermoscopic and RCM imaging; definite histopathologic diagnosis. The study sample comprised 217 lesions; 108 (49.8%) melanomas and 109 were benign lesions, of which 102 (47.0%) nevi and 7 (3.2%) lichen planus-like keratosis (lplk). Patients with melanoma were significantly older than those with benign lesions (61.9 ± 15.4 vs 46.1 ± 14.8; $P < 0.001$) and a higher proportion of melanomas displayed dermoscopic regression structures in more than 50% of lesion surface (n = 83/108; 76.9%; $P < 0.001$). On RCM examination, pagetoid cells were significantly more reported in melanoma group, than in benign lesions (86.1% vs 59.6%; $P < 0.001$) and were more frequently widespread distributed (65.6% vs 20.0%; $P < 0.001$) and both dendritic and roundish (36.6% vs 15.4%; $P < 0.001$) in shape. Aspecific architecture at the dermo-epidermal junction (DEJ) was more commonly seen among melanomas than benign lesions (23.1% vs 11.9%; $P = 0.002$) with higher presence of dendritic and both dendritic and roundish atypical cells at the DEJ (28.7% vs 18.3% and 19.4% vs 3.7%; $P < 0.001$, respectively). Focal pagetoid infiltration and ringed or clod patterns were more commonly seen in benign lesion. In conclusion, the correct interpretation of regressing lesions remains a challenge, assessing carefully the extent and characteristics of architectural and cytologic atypia on RCM is an additional piece of the complex puzzle of melanoma diagnosis.

KEYWORDS
dermoscopy, reflectance confocal microscopy, regression

1 | INTRODUCTION

Dermoscopy and reflectance confocal microscopy (RCM) are non-invasive imaging tools that have been demonstrated to improve diagnostic accuracy in skin cancer detection.[1,2] A recent prospective study outlined the best indications for RCM use in clinical setting.[3] Interestingly, a high diagnostic accuracy was achieved for lesions characterized by the presence of dermoscopic regression.[3]

Regression is a controversial phenomenon that can occur in both melanocytic and non-melanocytic lesions, benign and malignant.[4] Histopathologically, an infiltrate of lymphocytes admixed with pigment-laden macrophages is seen, underlying an atrophic epidermis with flattened rete ridges. Dermal collagen may have a linear arrangement similar to that seen in a scar and increased blood vessels are also present.[4] Dermoscopically, regression is a challenging feature, characterized by the so-called blue-white scar-like areas (BWS).[5–9] BWS appear as white scar-like depigmentation and can be variably admixed with granularity or peppering. The presence of white and blue colour with variable arrangement corresponds to fibrosis and melanophages, respectively, in histopathology. Additional dermoscopic descriptors of regression are reticular grey-blue areas, usually seen in early melanomas as a coarse blue-grey net, with thick grey-blue lines (reticular blue areas) with large holes that correspond to pink-coloured regression areas.[6] The fading of dermoscopic structures results in areas of structureless light brown pigmentation.[5–9]

Zalaudek et al.[5] proposed a flow chart to manage melanocytic lesions exhibiting dermoscopic features of regression. This simple method takes into consideration the extension and location of BWS. They suggest that the presence of a combination of BWS, especially irregularly distributed within the lesion, covering more than 50% of the lesion surface, favours the diagnosis of melanoma. Whereas, nevi tend to reveal only blue areas, in a central location, involving less than 50% of lesion surface.

However, the only false-negative melanoma of their series was found in this latter group of lesions, being a thin melanoma, characterized mainly by blue areas, covering less than 50% of the lesion surface.[5] It appears evident that a grey zone exists. RCM showed the possibility to differentiate malignant and benign lesions characterized by blue colour, thanks to its capability to distinguish between tumor proliferation and melanophage infiltrate.[10,11] Recently, a retrospective study examined RCM features of 32 lesions characterized by high amount of regression features in dermoscopy (>30%), concluding that RCM and dermoscopy used together can improve diagnostic accuracy in this setting of lesions.[12] The aim of our study was to examine RCM features of a series of nevi, melanomas and other non-melanocytic tumors, excised and histopathologically diagnosed, exhibiting dermoscopic features of regression, in order to provide confocal microscopy descriptors of this phenomenon in benign and malignant lesions.

2 | METHODS

2.1 | Study population

All cases were retrospectively collected at the Skin Cancer Unit of the Arcispedale Santa Maria Nuova in Reggio Emilia, Italy. Ethics committee approval was obtained (Protocol 2011/1249). Inclusion criteria were presence of dermoscopic features of regression; availability of clinical, dermoscopic and RCM imaging; definite histopathologic diagnosis of nevus, melanoma and other non-melanocytic tumor. Dermoscopy, RCM and histologic examination were performed as standards of care in our centre. The pathologic examination was conducted following the routine procedures. Cases in which RCM images could not be evaluated because of poor image quality were excluded. Dermoscopic images were captured with DermlitePhoto equipment (3Gen, Dana Point, CA) at 10-fold magnification. RCM images were acquired by means of a Vivascope 1500 (Caliber ID, Rochester, NY), which uses an 830 nm laser beam with a maximum power of 20 mW. Instrument and acquisition procedures have been described elsewhere.[13–16]

Patient demographics and tumor characteristics were recorded, including age, sex, location. Two independent investigators (E.M. and C.B.) evaluated all clinical, dermoscopic and RCM images. Both were blinded to the histopathological diagnosis. If the two investigators failed to reach a consensus, a third investigator was involved (C.L.). Clinical, dermoscopic and RCM variables were selected on the basis of previously published data on melanoma and nevi and our preliminary observations (Table 1). The majority of lesions were pigmented (n 165; 76.1%); 50 (23.0%) were hypo-pigmented and 2 (0.9%) were non-pigmented.

2.2 | Statistical analysis

The analysis was conducted in order to assess if any dermoscopic or RCM criteria were independently associated to the diagnosis of melanoma or benign lesion (nevi and other non-melanocytic tumors). In the descriptive analysis, absolute and relative frequencies for demographic, dermoscopic and confocal variables were calculated for both groups and compared through Pearson's chi-squared test and Student's *T* test for qualitative and quantitative variables, respectively.

Spearman's correlation and univariate logistic regression analysis were used to assess and quantify which clinical, dermoscopic and confocal variables were significantly associated with melanoma diagnosis.

A multivariate backward logistic regression model was then constructed to identify independent positive and negative predictors of melanoma diagnosis, among those factors that showed a significant difference ($P < 0.10$) on univariate analysis, together with the notable intervariable interactions. Alpha level was set at 0.05.

Furthermore, a sub-analysis of lesions characterized by <50% of regression structures in dermoscopy was conducted. Sensitivity represented the proportion of melanomas in which a given feature was present, and specificity represented the proportion of benign lesions in which a given feature was absent. We then calculated positive predictive values to assess the probability that a lesion with a given

TABLE 1 Clinical data and dermoscopy features of melanomas and benign lesions

Variables	Melanoma Total: 108 (%)	Nevi and other NMTs Total: 109 (%)	*P-value
Age (mean ± SD)	61.9 ± 15.4	46.1 ± 14.8	<0.001
Body site			
Back	51 (47.2)	57 (52.3)	**0.269**
Thorax	15 (13.9)	8 (7.3)	
Abdomen	5 (4.6)	10 (9.2)	
Head&neck	1 (0.9)[a]	0 (0.0)	
Limbs	36 (33.3)	34 (31.2)	
Dermoscopy features			
Atypical network	59 (54.6)	50 (45.9)	0.248
Inverse network	6 (5.6)	14 (12.8)	0.105
Irregular dots and globules	22 (20.4)	17 (15.6)	0.46
Irregular blotches	20 (18.5)	21 (19.3)	>0.99
Atypical vascular pattern	10 (9.3)	12 (11.0)	0.84
Blue-white veil	16 (14.8)	3 (2.8)	**0.004**
Irregular streaks	13 (12.0)	9 (8.3)	0.485
Blue-grey areas	36 (33.3)	57 (52.3)	**0.007**
White scar-like areas	58 (53.7)	14 (12.8)	**<0.001**
Peppering	35 (32.4)	7 (6.4)	**<0.001**
Blue-grey globules	11 (10.2)	26 (23.9)	**0.013**
Pink areas	11 (10.2)	19 (17.4)	0.177
Hypopigmented areas	19 (17.6)	30 (27.5)	0.113
Regression >50%	83 (76.9)	45 (41.3)	**<0.001**
Confocal features			
Pagetoid cells	93 (86.1)	65 (59.6)	**<0.001**
Pagetoid cell distribution			
Focal	32 (34.4)	52 (80.0)	**<0.001**
Widespread	61 (65.6)	13 (20.0)	
Pagetoid cells shape			
Roundish	18 (19.4)	27 (41.5)	**<0.001**
Dendritic	41 (44.1)	28 (43.1)	
Both	34 (36.6)	10 (15.4)	
Architecture			
Ringed	33 (30.6)	49 (45.0)	**0.002**
Meshwork	30 (27.8)	32 (29.4)	
Clod	7 (6.5)	14 (12.8)	
Aspecific	35 (23.1)	13 (11.9)	
Focal aspecific	52 (48.1)	56 (51.4)	0.734
Cytologic atypia at dermo-epidermal junction			
Roundish	37 (34.3)	39 (35.8)	**<0.001**
Dendritic	31 (28.7)	20 (18.3)	
Both	21 (19.4)	4 (3.7)	

(Continues)

TABLE 1 (Continued)

Variables	Melanoma Total: 108 (%)	Nevi and other NMTs Total: 109 (%)	*P-value
Nest type			
Dense	5 (4.6)	11 (10.1)	0.086
Dense and sparse	4 (3.7)	10 (9.2)	
Plump bright cells	45 (41.7)	33 (30.3)	0.108
Inflammatory cells	62 (57.4)	53 (48.6)	0.246

The values in bold are stastically significant or almost significant

NMT, Non-melanocytic tumors; SD, standard deviation.

[a]The lesion was located on the neck.

*$P < 0.05$.

dermoscopic or RCM feature would be melanoma, and negative predictive values to assess the probability that a lesion without a specific feature would be benign. Positive likelihood ratios and negative likelihood ratios were also calculated to assess how many more times a given feature was more or less likely, respectively, to be seen in a melanoma compared with benign lesions. The chi-square test was used to assess for statistical significance between dermoscopic features and a diagnosis of melanoma. $P < 0.05$ was considered statistically significant.

All statistical calculations were made with IBM SPSS 22.0 package (Statistical Package for Social Sciences, IBM SPSS Inc., version 22.0, Armonk, NY: IBM Corp).

3 | RESULTS

3.1 | Study population and descriptive analysis

The study sample comprised 217 lesions in as many patients (males = 55.3%; with a mean age of 53.8 ± 17.0); 108 (49.8%) were superficial spreading melanomas (48 in situ and 60 invasive melanomas); and 109 were benign lesions, of which 102 (47.0%) nevi (compound nevi n = 69, junctional nevi n = 16, spitzoid nevi n = 11, and sclerotic nevi n = 6) and 7 (3.2%) lichen planus-like keratosis (lplk). Mean Breslow thickness of invasive melanomas was 0.84 mm. Data about age, location, dermoscopy and RCM evaluation are listed in Table 1.

According to the descriptive analysis, patients with melanoma were significantly older than those with benign lesions (61.9 ± 15.4 vs 46.1 ± 14.8; $P < 0.001$) and a higher proportion of melanomas displayed dermoscopic regression structures in more than 50% of lesion surface (n = 83/108; 76.9%; $P < 0.001$). Furthermore, several dermoscopic features were significantly more represented in melanoma group than in benign lesions, including blue-white veil (14.8% vs 2.8%; $P = 0.004$), white scar-like areas (53.7% vs 12.8%; $P < 0.001$) and peppering (32.4% vs 6.4%; $P < 0.001$); while, blue-grey areas and blue-grey globules were more reported in benign lesions than in melanomas (33.3% vs 52.3%; $P = 0.007$ and 10.2% vs 17.4%; $P = 0.013$, respectively). (Table 1)

On RCM examination, pagetoid cells were significantly more reported in melanoma group, than in benign lesions (86.1% vs

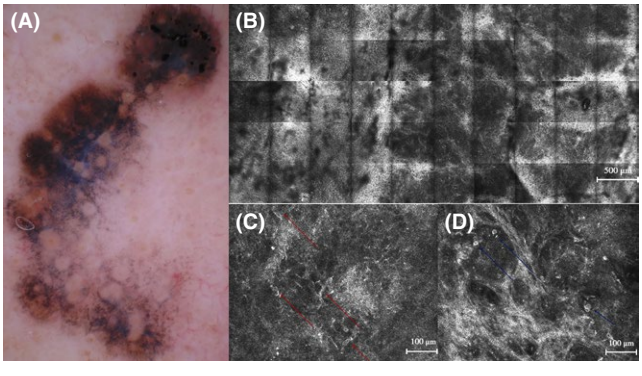

FIGURE 1 Dermoscopy and RCM of regressing melanoma, 1.1 mm Breslow thickness, located on the back of a 61-year-old man. (A) In dermoscopy, atypical network at the periphery and blue-white scar-like areas in the centre, involving more than 50% of lesion surface. (B) RCM mosaic (5 × 2.5 mm) taken at the level of the supra-basal layer and displaying an aspecific pattern. (C) RCM single image taken at the spinous/granular layer, showing multiple pagetoid cells, mainly dendritic (red arrows). (D) RCM single image at the level of the DEJ. A disarranged junction is visualized, with discohesive nests of atypical melanocytes (blue arrows)

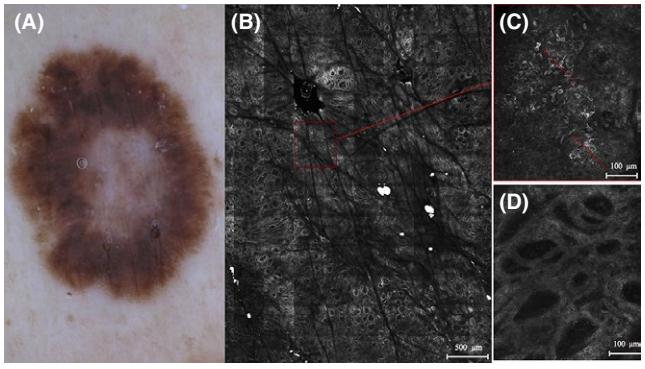

FIGURE 2 Dermoscopy and RCM of a compound nevus with regression, arising on the back of a 42-year-old woman. (A) Dermoscopy, with light and dark brown reticular pattern in the periphery and white scar-like areas in the centre involving less than 50% of lesion surface. (B) Mosaic image (5 × 3 mm) taken at the level of the DEJ, with meshwork and ringed pattern at the periphery, and a focal area in the centre of specific pattern. A cluster of atypical cells is seen (red square). (C) Close up of the red square area in figure b, highlighting the presence of a focal infiltration of pagetoid cells (red arrows). (D) RCM single image at the level of the DEJ, showing a regular meshwork pattern

59.6%; $P < 0.001$) and were more frequently widespread distributed (65.6% vs 20.0%; $P < 0.001$) and both dendritic and roundish (36.6% vs 15.4%; $P < 0.001$) in shape. Aspecific architecture at the dermo-epidermal junction (DEJ) was more commonly seen among melanomas than benign lesions (23.1% vs 11.9%; $P = 0.002$) with higher presence of dendritic and both dendritic and roundish atypical cells at the DEJ (28.7% vs 18.3% and 19.4% vs 3.7%; $P < 0.001$, respectively). (Figure 1) However, focal pagetoid infiltration (34.4% vs 80.0%; $P < 0.001$ in melanomas and benign lesions, respectively) and ringed or clod patterns (30.6% vs 45.0% and 6.5% vs 12.8%; $P = 0.002$ in melanomas and benign lesions, respectively) were more commonly seen in benign lesion (Table 1) (Figure 2).

3.2 | Spearman's correlation and logistic regression analysis

Spearman's correlation analysis highlighted significant correlations between histopathologic diagnosis and the following demographic, dermoscopic and RCM features: age (rho = 0.49; $P < 0.001$); regression >50% (rho = 0.36; $P < 0.001$); blue-white veil (rho = 0.21; $P = 0.002$); blue-grey areas (rho = −0.19; $P = 0.005$); white scar-like areas (rho = 0.43; $P < 0.001$); peppering (rho = 0.33; $P < 0.001$); blue-grey globules (rho = −0.18; $P = 0.007$); pagetoid cells presence, distribution and shape (rho = 0.30; 0.46; 0,38; $P < 0.001$, respectively); confocal architecture (rho = 0.18; $P = 0.009$), cytologic atypia (rho = 0.33; $P < 0.001$) and nest type (rho = −0.17; $P = 0.012$).

Univariate logistic regression analyses confirmed the association between all of these criteria and histopathologic diagnosis, with the exception of nest type. (data not shown)

Then, a multivariate logistic regression model was constructed to assess independent predictors of melanoma diagnosis. In particular, increasing age was only slightly associated with melanoma diagnosis (OR = 1.06; 95% CI 1.03-1.09); while, upon dermoscopy, the presence of regression features in more than 50% of lesion surface was confirmed as an independent predictor of melanoma diagnosis. (OR = 3.44; 95% CI 1.19-9.96), as well as the presence of blue-white veil and white scar-like areas (OR = 19.37; 95% CI 3.61-103.96 and OR = 9.16; 95% CI 3.20-26.22, respectively) (Table S1).

On RCM examination, the presence of pagetoid spread and cytologic atypia at the DEJ (OR = 9.02; 95% CI 2.64-30.82), with dendritic (OR = 6.32; 95% CI 1.67-23.91) or both roundish and dendritic cells (OR = 9.97; 95% CI 2.01-49.55), were from 6 to 9 times independently more associated with melanoma diagnosis. Conversely, a focal distribution of pagetoid cells was in favour of the diagnosis of benign lesion (OR = 0.18; 95% CI 0.06-0.54) (Table S1).

3.3 | Sub-analysis on lesions with <50% regression

Regarding the sub-analysis of lesions with <50% regression, most criteria demonstrated low to moderate sensitivities for melanoma diagnosis.

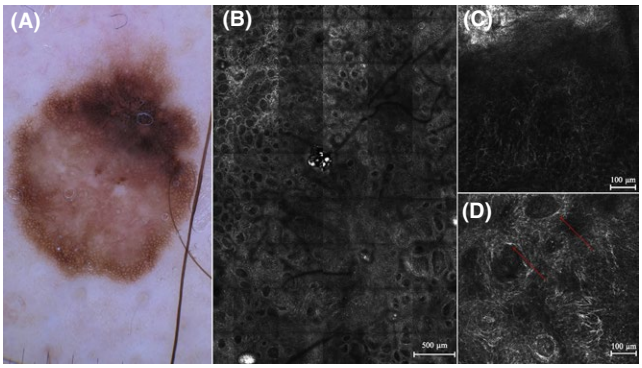

FIGURE 3 Dermoscopy and RCM of in situ melanoma with regression, located on the chest of a 41-year-old man. (A) In dermoscopy, atypical network at the periphery with areas of blue-grey reticular pattern and fading of the dermoscopic structures in the centre. Regression features involve more than 50% of lesion surface. (B) RCM mosaic (3 × 4 mm) taken at the level of the DEJ, a meshwork pattern is seen at the periphery of the lesion, while in the central area a aspecific pattern is detected. (C) RCM single image taken at the spinous/granular layer, showing multiple dendritic pagetoid cells. (D) RCM single image at the level of the DEJ highlighting dendritic atypical cells within an irregular meshwork pattern (red arrows)

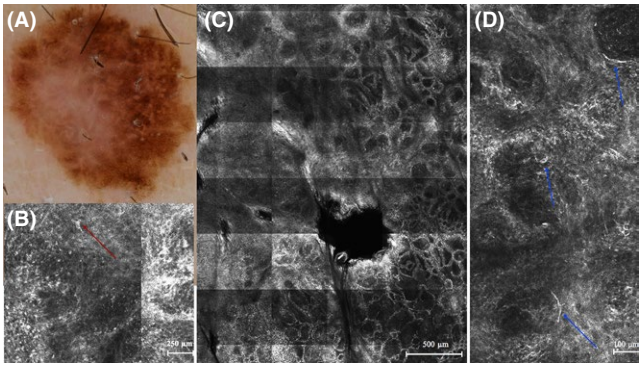

FIGURE 4 Dermoscopy and RCM of in situ melanoma with regression, located on the upper arm of a 70-year-old man. (A) In dermoscopy, atypical network is detected at the periphery, regression features involve less than 50% of lesion surface. (B) RCM single image at the level of the spinous-granular layer showing pagetoid infiltration of dendritic cells (red arrow). (C) RCM mosaic (2.5 × 3.5 mm) taken at the level of the DEJ, a ringed pattern is seen at the periphery of the lesion, while in the central area a aspecific pattern is detected. (D) RCM single image taken at the supra-basal layer, showing multiple dendritic cells infiltrating the papillae (blue arrows)

Age greater than 45 years old (median value) showed high-moderate sensitivity (76.0%) and moderate specificity (57.8%) for melanoma diagnosis.

Concerning dermoscopic examination, atypical network showed the highest sensitivity (84.0%), and was moderately specific (42.2%), while the presence of blue-white veil had a lower sensitivity (20.0%) but the highest specificity for the diagnosis of melanoma (96.9%).

According to RCM evaluation, the presence of pagetoid cells had the highest sensitivity (76.0%) and was moderately specific (48.4%).

Furthermore, a widespread pagetoid cells distribution and cytologic atypia had a lower sensitivity (56.0% and 12.0%, respectively), but higher specificity (92.2% and 96.9%, respectively).

Each of the considered features had high negative predictive value for melanoma diagnosis, while positive predictive value was higher than 60% for blue-white veil, white scar-like areas and widespread pagetoid cells distribution, which, respectively, resulted in 6.4-, 4.0- and 7.2-fold increase in likelihood for melanoma diagnosis (Table S2) (Figure 3 and Figure 4).

4 | DISCUSSION

The current study provides insights into dermoscopy and confocal features of benign and malignant tumors typified by regression on dermoscopy, analysing the largest series of cases up to know (217 lesions).

In line with previous findings, the amount of dermoscopic regression within a given lesion is a strong factor for the diagnosis of malignancy being present in 76.9% of melanomas, as well as the presence of other melanoma features, such as blue-white veil and white scar-like areas.[5,12]

Regarding confocal features, the strongest predictors of melanoma in our series were the presence of a widespread distribution of pagetoid cells and the presence of cytologic atypia at the level of DEJ, especially when composed of dendritic, or both roundish and dendritic cells. In fact, the association of pagetoid spread and cytologic atypia at the dermo-epidermal junction confer a 6 to 9 times likelihood of a given lesion to be a melanoma.

Nevi revealing regressive dermoscopic features can present scattered pagetoid cells in the epidermis, but those cells have a focal distribution in the majority of cases (80%). Only 20% of nevi revealed a widespread pagetoid scattering and those might represent a real challenge in clinical practice because they simulate melanoma.

In the recent study by Agozzino et al.[12], the authors included only lesions with >30% of regression structures, and the total number of cases examined was 32 (9 melanomas).

In agreement with this previous study, our results also underline that the architecture of the lesion at the level of the DEJ is an important parameter. Not surprisingly, melanomas were typified by aspecific (also named disarranged) architecture, where it is not possible to recognize any of the usual patterns of melanocytic lesions (ringed, meshwork, cloud). Reasonably, it is due to the regression phenomenon in which flattening of the rete ridges is present along with dermal features on histopathology; those histologic aspects mirror aspecific architecture on confocal microscopy. On RCM, when analyzing at high power the disarrayed architecture, atypical melanocytes are usually found in melanomas and they are mainly of dendritic shape (Tables S1, S2).

Thus, combining clinical dermoscopic and RCM parameters, the diagnosis of melanoma is readily made in a lesion with >50% of regression structures, presenting blue-white veil, white scar-like areas and a widespread distribution of pagetoid cells in the epidermis, cytologic atypia at the DEJ and aspecific architecture.

However, since also in the original paper by Zalaudek et al.[5] the only false-negative melanoma was in the group of lesions with <50% of regression structures, we also conducted a sub-analysis of these lesions. The latter group seem to represent the real grey zone within lesions characterized by regression. In this subgroup, again well-known melanoma features in dermoscopy, such as atypical network, blue-white veil and white scar-like areas, had the highest likelihood ratio for the diagnosis of melanoma. In RCM, a widespread distribution of pagetoid cells was the only feature significantly associated with the diagnosis of melanoma ($P < 0.001$), with a 4.9-fold increase in likelihood. Thus, as a golden rule, all lesions with less than 50% of regression on dermoscopy but revealing a widespread pagetoid scattering should be promptly excised with high chance to detect a melanoma. Conversely, lesions with focal or absent pagetoid cells on RCM should be strictly monitored or excised if any other factors can be recognized.

Plump brigth cells (corresponding to melanophages) and inflammatory cells were almost equally represented in both benign and malignant lesions. Based on our results, they seem to have scarse value in discriminating between nevi and melanomas. They are expression of the inflammatory process co-existing with the regression phenomenon; however, we were not able to differentiate between "benign" and "malignant" inflammation (Table 1).

The current study has some limitations. First, the retrospective design of the study prevented us to investigate the stroma of the lesions. This would have been interesting in this setting of lesions, however, confocal imaging at the level of the dermis was only available in a minority of cases. Second, the high expertise of the RCM readers that might not reflect the common scenario in clinical practice.

However, the highest number of cases analyzed and the in deep analysis of the lesions strengthen this study.

In conclusion, the correct interpretation of regressing lesions remains a challenge, specially in those cases with regression structures in less than 50% of the lesion surface, that represent a real grey zone for dermoscopy and RCM evaluation. Assessing carefully the extent and characteristics of architectural and cytologic atypia on RCM is an additional piece of the complex puzzle of the melanoma diagnosis.

CONFLICTS OF INTEREST

None to declare.

AUTHOR CONTRIBUTION

EM and CL designed the research study and wrote the paper. CB analysed the data, performed the research. RP, AK, EB, SP and SB analysed the data. AL, GP and GA designed the research study. All authors have read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Multivariate logistic regression analysis.

Table S2. Sub-analysis on lesions with <50% regression.

How to cite this article: Moscarella E, Bombonato C, Pampena R, et al. Pigmented skin lesions displaying regression features: Dermoscopy and reflectance confocal microscopy criteria for diagnosis. *Exp Dermatol.* 2019;28:129–135. https://doi.org/10.1111/exd.13853