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ORIGINAL ARTICLE

Lentigo maligna and lentigo maligna melanoma in vivo differentiation with dermoscopy and reflectance confocal microscopy: A retrospective, multicentre study

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Abstract

Introduction: Dermoscopic predictors of lentigo maligna (LM) and lentigo maligna melanoma (LMM) have been recently reported, but these have not been reported in reflectance confocal microscopy (RCM).

Objectives: (i) To validate dermoscopic predictors for LM/LMM, (ii) to identify RCM patterns in LM and LMM, and (iii) correlations between dermoscopic and RCM features in LM and LMM.

Materials and Methods: A retrospective, multicentre study of consecutive lesions with histologically proven LM or LMM subtypes of the head and face, with complete sets of dermoscopic and RCM images.

Results: A total of 180 lesions were included ($n = 40$ LMM). Previously reported differential dermoscopic features for LM subtypes were confirmed. Other features significantly associated with LMM diagnosis included irregular hyperpigmented areas, shiny white streaks, atypical vessels and light brown colour at dermoscopy and medusa head-like structures, dermal nests and nucleated cells within the papillae at RCM ($p < 0.05$). Correlations among LM lesions between dermoscopic and RCM features included brown to-grey dots and atypical cells (epidermis), grey colour and inflammation and obliterated follicles and medusa head-like structures. Among LMM lesions, significant correlations included obliterated follicles with folliculotropism, both irregular hyperpigmented areas and irregular blotches with widespread atypical cell distribution (epidermis), dermal nests and nucleated cells within the papillae (dermis). Irregular blotches were also associated with medusa head-like structures (dermal epidermal junction [DEJ]).

Conclusions: Dermoscopic and RCM features can assist in the in vivo identification of LM and LMM and many are correlated. RCM three-dimensional analysis of skin layers allows the identification of invasive components in the DEJ and dermis.

INTRODUCTION

Lentigo maligna (LM) is the most common subtype of melanoma occurring in chronically sun-exposed areas,[1] such as the face. Due to the increase in cumulative exposure to ultraviolet radiation (UV) and to rising awareness of skin cancers, its diagnosis has been growing in recent decades.[2,3]

Several studies have been performed to identify dermoscopic predictors for LM diagnosis[4–6] but few have distinguished between features indicative of early and invasive

disease.[7] The use of dermoscopy, through the identification of distinctive features, can assist in the correct diagnosis of early and invasive disease; LM and lentigo maligna melanoma (LMM), respectively.[7] General dermoscopic criteria identified include grey dots, grey circle/semicircles, target-like pattern-circle within a circle, angulated lines, rhomboid structures, obliterated follicles, irregular hyperpigmented areas, irregular blotch, shiny white streaks, atypical vessels and erased areas.[6–8] Peruilh-Bagolini et al.[7] refined these criteria differentiating LM and LMM and highlighting that obliterated follicles, irregular blotches and black colour were positive predictors for invasive disease.

Other non-invasive diagnostic tools have been applied to improve the identification accuracy of malignant lesions, including reflectance confocal microscopy (RCM).[9–11] RCM patterns for LM/LMM include atypical cells at different skin layers, folliculotropism, medusa head-like structures, sheet-like structures, bulging around the follicle, junctional or dermal nests, nucleated cells within the papillae and inflammation (melanophages).[12–15]

However, non-invasive diagnostic criteria to differentiate LM from LMM have been rarely reported for dermoscopy[7] and are currently lacking for RCM.[16,17] As partial or incisional biopsies may be preferred in these aesthetically sensitive areas, identifying non-invasive predictors of invasive disease can assist in determining an adequate biopsy strategy for the correct final histopathological diagnosis.[7]

We aim to (i) validate dermoscopic predictors for LM/LMM as described by Peruilh-Bagolini et al., (ii) identify RCM patterns in LM and LMM and (iii) correlate dermoscopic and RCM features in a consecutive series of cases with histopathological diagnoses of LM or LMM.

PATIENTS AND METHODS

Study design

We retrospectively examined dedicated databases of consecutive lesions, selecting histologically proven LM and LMM of the head and face with a complete set of dermoscopy and RCM images captured at the Department of Dermatology of the University of Modena and Reggio Emilia (January 2009–January 2020), University Hospital Saint-Etienne (January 2012–January 2018) and University Hospital Siena (January 2016–January 2021) This study was conducted according to the Declaration of Helsinki and approved by the Emilia Greater Northern Area Ethics Committee (Prot# 21282/22).

Patients

For each patient, basic demographic data (age and sex) and Breslow thickness (for LMM lesions) were retrieved from clinical and histopathological records.

Dermoscopy

Dermoscopy images were collected with DermLite Photo (3Gen) and were evaluated and described according to colours (grey, blue, red, light brown, dark brown and black) and recently reported dermoscopic criteria,[7,18] brown-to grey dots, grey circles/semi-circles, target-like pattern circles within a circle, angulated lines, rhomboid structures, obliterated follicles, irregular hyperpigmented areas, irregular blotches, shiny white streaks, atypical vessels and erased areas.

Reflectance confocal microscopy

Reflectance confocal microscopy images were collected with Vivascope 1500® and Vivascope 3000® (MAVIG GmbH). RCM criteria included previously described features at the epidermis: atypical cells (presence, type, shape [dendritic or roundish] and distribution [focal or widespread]), folliculotropism (presence or absence); at the dermal-epidermal junction (DEJ) atypical cells, medusa head-like structures, sheet-like structures, junctional nests, bulging around the follicle and polycyclic papillary contours; and at the dermis: dermal nests, nucleated cells within the papillae and inflammation.[9,11,12,16]

Image evaluation

Clinical, dermoscopic and RCM images were evaluated by three collaborating dematologists; one expert (>5-years experience) and two residents (<5-year experience). At the end of each lesion dermoscopic examination, RCM images were evaluated. Physicians were blinded to histopathologic LM/LMM subtype diagnosis.

Statistical analysis

Statistical evaluation was carried out with the STATA software (Stata/BE 17.0 for Mac).

Demographic, clinical, dermoscopic and RCM variables were included in the analysis. Absolute and relative frequencies of observations in LM and LMM were described. Student's *t*-test was used to assess the correlation between age and type of lesions. Chi-squared test or Fisher's exact test were used to describe the potential association between other clinical, dermoscopic and RCM criteria with different type of lesions.

Dermoscopy patterns were correlated with RCM patterns, $p \leq 0.05$ was considered significant.

RESULTS

A total of 180 lesions in 180 patients (45% women) with a mean age of 71 years (range 44–97) met the inclusion criteria.

TABLE 1 Significant dermoscopic features distinguishing LM and LMM.

LM	LMM
Grey circles/Semicircles	Obliterated follicles
Angulated lines	Irregular hyperpigmented areas
Light brown colour	Irregular blotch
	Shiny white streaks
	Atypical vessels
	Black colour

Abbreviations: LM, lentigo maligna; LMM, lentigo maligna melanoma.

TABLE 2 Significant reflectance confocal microscopy patterns distinguishing LM and LMM.

LM	LMM
	Medusa head-like structures
	Dermal nests
	Nucleated cells within the papillae

Abbreviations: LM, lentigo maligna; LMM, lentigo maligna melanoma.

Selected lesions, according to histopathological assessment, included 140 LM and 40 LMM. The mean Breslow index of LMMs was 0.68 mm.

Various associations between dermoscopy features and histopathological subtypes were identified. Grey circles/semi-circles, angulated lines and light brown colour were significantly associated with LM (Table 1, Table S1), while obliterated follicles, irregular hyperpigmented areas, irregular blotches, shiny white streaks, atypical vessels and black colour were significantly associated with LMM. According to RCM analysis, medusa head-like structures, dermal nests and nucleated cells within the papillae were significantly associated with LMM diagnoses (Table 2, Table S1).

Correlations between dermoscopy and RCM patterns, according to histopathological subtypes revealed significant correlations. For LM lesions, correlation between brown-to-grey dots and dendritic cells ($p < 0.05$), obliterated follicles and medusa head-like structures ($p < 0.05$), grey colour and inflammation ($p < 0.05$) were identified. An additional potentially clinically relevant feature and pattern correlation, although not reaching significance, includes grey circles/semi-circles with medusa head-like structures. Both angulated lines and light brown colour were not significantly correlated with any specific RCM patterns, see Table 3.

Dermoscopic features and RCM pattern correlations in LMM lesions revealed significant correlations of obliterated follicles with folliculotropism. Both irregular blotches and irregular hyperpigmented areas were associated with widespread atypical cell distribution (epidermis) and dermal nests/nucleated cells within the papillae (dermis), while irregular blotches were also associated with medusa head-like structures (DEJ). Although less frequently observed in LMM compared to LM, the presence of grey circles/semi-circles was significantly associated with atypical cells (DEJ) and rhomboid structures with atypical cells (DEJ). Additionally, a significant correlation was observed between black colour and medusa-head like structures (DEJ) and dermal nests and nucleated cells within the papillae (dermis). Both shiny white streaks and atypical vessels were not significantly correlated with any specific RCM patterns, see Table 4.

DISCUSSION

For 20 years, the pivotal progression model proposed by Stolz[8] has shown the order of appearance of dermoscopic criteria in LM/LMM, without providing specific information about differential diagnosis between in situ and invasive disease. Diagnostic criteria to discriminate LM from LMM were recently explored in a dermoscopy study,[7] highlighting positive predictors for LM/LMM, but have not been investigated in RCM. Furthermore, the correspondence of LM/LMM dermoscopic and RCM criteria is unknown.

Our study validates grey circles\semi-circles, angulated lines as positive predictors of LM in dermoscopy, obliterated follicles, irregular hyperpigmented areas and irregular blotches as positive predictors of LMM in dermoscopy. In vivo RCM differential identification of more advanced disease has been revealed by this study, and include medusa head-like structures and dermal patterns. Our study also revealed significant differences in previously unreported dermoscopy feature distribution, including light brown colour for early LM and shiny white streaks and atypical vessels for more advanced disease (LMM). Further, dermoscopy features and RCM pattern correlations highlight the correlation of grey colour/structures with early disease (specifically, brown-to-grey dots with dendritic cells, grey colour with inflammation, a trend of correlation between grey circles/semi-circles with medusa head-like structures) and the progressive involvement of the follicular and dermal involvement in advanced disease.

Our study confirms that as LM disease progresses, grey circles/semi-circles, angulated lines and light brown colour become less evident, while obliterated follicles, irregular hyperpigmented areas, irregular blotches, shiny white streaks, atypical vessels and black colour are more frequently observed. Not all of these dermoscopy features have been previously identified among smaller cohorts.[6–8,19,20]

Statistical exploration of correlations between LM/LMM dermoscopy features described by Peruilh-Bagolini et al.[7] and RCM patterns revealed correlations between brown-to-grey dots and dendritic cells at the epidermis in early LM, which has also been reported by other studies using either RCM or histopathology.[5,21,22] Grey dots have been described as an important criterion for early signs of LM and have been associated with small aggregates of melanophages around the vessels, with overlying atypical melanocytes at the epidermal level, in histopathology.[4,18,22] Brown dots were significantly associated with LM diagnosis, compared to non-melanocytic skin neoplasms, and were described at RCM as resulting in pagetoid, atypical and inflammatory cells and melanocytic nests.[10]

TABLE 3 Correlations between selected dermoscopy features and RCM patterns in lentigo maligna.

		Selected dermoscopy features, *n* (%)									
	n (%)	Brown-to-grey dots	Grey circles semicircles	Target-like pattern circle within circle	Angulated lines	Rhomboid structures	Obliterated follicles	Erased areas	Grey	Light brown	Dark brown
RCM patterns		93 (66.4)	90 (64.3)	46 (32.8)	57 (40.7)	40 (28.6)	46 (32.9)	29 (20.7)	59 (42.1)	120 (85.7)	40 (28.6)
Epidermis											
Atypical cells	137 (97.9)	92 (98.9)	89 (98.9)	45 (97.8)	57 (100.0)	39 (97.5)	44 (95.7)	29 (100.0)	58 (98.3)	118 (98.3)	40 (100.0)
Atypical cells type	136 (97.1)										
Absent	4 (2.85)	1 (1.1)**	2 (2.2)	1 (2.2)	1 (1.8)	2 (5.0)	2 (4.3)	0 (0.0)	1 (1.7)	3 (2.5)	0 (0.0)
Roundish	3 (2.14)	2 (2.2)*	2 (2.2)	1 (2.2)	2 (3.5)	1 (2.5)	0 (0.0)	0 (0.0)	2 (3.4)	2 (1.7)	0 (0.0)
Dendritic	133 (95.0)	90 (96.8)*	86 (95.6)	44 (95.7)	54 (94.7)	37 (92.5)	44 (95.7)	29 (100.0)	56 (94.9)	115 (95.8)	40 (100.0)
Atypical cells distribution	136 (97.1)										
Absent	4 (2.85)	1 (1.1)	2 (2.2)	1 (2.2)	0 (0.0)	1 (2.5)	2 (4.3)	0 (0.0)	1 (1.7)	3 (2.5)	0 (0.0)
Focal	52 (37.14)	37 (39.8)	30 (33.3)	15 (32.6)	22 (38.6)	14 (35.0)	15 (32.6)	10 (34.5)	22 (37.3)	45 (37.5)	11 (27.5)
Widespread	84 (60.0)	55 (59.1)	58 (64.4)	30 (65.2)	35 (61.4)	25 (62.5)	29 (63.0)	19 (65.5)	36 (61.0)	72 (60.0)	29 (72.5)
Folliculotropism	106 (75.7)	70 (75.3)	72 (80.0)	38 (82.6)	42 (73.7)	28 (70.0)	32 (69.6)	21 (72.4)	48 (81.4)	92 (76.7)	29 (72.5)
DEJ											
Atypical cells DEJ	126 (90.0)	84 (90.3)	79 (87.8)	41 (89.1)	52 (91.2)	38 (95.0)	42 (91.3)	25 (86.2)	52 (88.1)	108 (90.0)	38 (95.0)
Medusa head-like structures	34 (24.3)	23 (24.7)	26 (28.9)**	15 (32.6)	13 (22.8)	11 (27.5)	16 (34.8)*	6 (20.7)	15 (25.4)	30 (25.0)	10 (25.0)
Sheet-like structures	8 (57.7)	5 (5.4)	6 (6.7)	5 (10.9)**	4 (7.0)	3 (7.5)	5 (10.9)**	4 (13.8)*	3 (5.1)	7 (5.8)	4 (10.0)
Junctional nests	110 (78.6)	72 (77.4)	72 (80.0)	37 (80.4)	45 (78.9)	30 (75.0)	40 (87.0)	23 (79.3)	45 (76.3)	95 (79.2)	35 (87.5)
Bulging around the follicle	65 (46.4)	44 (47.3)	39 (43.3)	21 (45.7)	24 (42.1)	19 (47.5)	25 (54.3)	14 (48.3)	22 (37.3)[a]	56 (46.7)	20 (50.0)
Polycyclic papillary contours	16 (15.7)	17 (18.3)	14 (15.6)	10 (21.7)	8 (14.0)	7 (17.5)	7 (15.2)	2 (6.9)	9 (15.3)	20 (16.7)	6 (15.0)
Dermis											
Dermal nests	0 (0.0)	-	-	-	-	-	-	-	-	-	-
Nucleated cells within the papillae	3 (2.14)	1 (1.1)	2 (2.2)	2 (4.3)	1 (1.8)	1 (2.5)	2 (4.3)	2 (6.9)*	1 (1.7)	2 (1.7)	2 (5.0)
Inflammation	77 (55.0)	54 (58.1)	51 (56.7)	25 (54.3)	30 (52.6)	19 (47.5)	27 (58.7)	17 (58.6)	38 (64.4)*	67 (55.8)	20 (50.0)

Abbreviations: DEJ, derma-epidermal junction; RCM, reflectance confocal microscopy.

*$p < 0.05$.; **Borderline ($p < 0.10$).

TABLE 4 Correlations between selected dermoscopy features and RCM patterns in lentigo maligna melanoma.

		Selected dermoscopy features, *n* (%)												
	n (%)	Brown-to-grey dots	Grey circles semicircles	Target-like pattern circle within circle	Rhomboid structures	Obliterated follicles	Irregular hyperpigmented areas	Irregular blotches	Shiny white streaks	Erased areas	Grey	Light brown	Dark brown	Black
RCM pattern		30 (75.0)	17 (42.5)	10 (25.0)	12 (30.0)	26 (65.0)	12 (30.0)	12 (30.0)	19 (47.5)	10 (25.0)	16 (40.0)	20 (50.0)	10 (25.0)	13 (32.5)
Epidermis														
Atypical cells	39 (97.5)	29 (96.7)	17 (100.0)	10 (100.0)	12 (100.0)	25 (96.2)	12 (100.0)	12 (100.0)	19 (100.0)	10 (100.0)	15 (93.8)	19 (95.0)	10 (100.0)	13 (100.0)
Atypical cells type	39 (97.5)													
Absent	1 (2.50)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (5.0)	0 (0.0)	0 (0.0)
Roundish	4 (10)	2 (6.7)	1 (5.9)	1 (10.0)	0 (0.0)	3 (11.5)	2 (16.7)	2 (16.7)	1 (5.3)	1 (10.0)	1 (6.3)	0 (0.0)	2 (20.0)	2 (15.4)
Dendritic	35 (87.50)	27 (90.0)	16 (94.1)	9 (90.0)	12 (100.0)	22 (84.6)	10 (83.3)	10 (83.3)	18 (94.7)	9 (90.0)	14 (87.5)	19 (95.0)	8 (80.0)	11 (84.6)
Atypical cells distribution	39 (97.50)													
Absent	1 (2.50)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)*	0 (0.0)	0 (0.0)	1 (6.3)	1 (5.0)	0 (0.0)	0 (0.0)
Focal	13 (32.50)	10 (33.3)	8 (47.1)	5 (50.0)	2 (16.7)	7 (26.9)	1 (8.3)*	0 (0.0)*	4 (21.1)	3 (30.0)	3 (18.8)	8 (40.0)	3 (30.0)	2 (15.4)
Widespread	26 (65.0)	19 (63.3)	9 (52.9)	5 (50.0)	10 (83.3)	18 (69.2)	11 (91.7)*	12 (100.0)*	15 (78.9)	7 (70.0)	12 (75.0)	11 (55.0)	7 (70.0)	11 (84.6)
Folliculotropism	33 (82.5)	25 (83.3)	15 (88.2)	9 (90.0)	12 (100)**	24 (92.3)*	11 (91.7)	11 (91.7)	18 (94.7)	9 (90.0)	11 (68.8)*	15 (75.0)	8 (80.0)	12 (92.3)
DEJ														
Atypical cells DEJ	35 (87.50)	27 (90.0)	12 (70.6)*	7 (70.0)**	8 (66.7)*	22 (84.6)	10 (83.3)	9 (75.0)	18 (94.7)	8 (80.0)	14 (87.5)	18 (90.0)	8 (80.0)	10 (76.9)
Medusa head-like structures	19 (47.50)	13 (43.3)	7 (41.2)	5 (50.0)	6 (50.0)	16 (61.5)*	8 (66.7)	9 (75.0)*	9 (47.4)	5 (50.0)	6 (37.5)	8 (40.0)	3 (30.0)	9 (69.2)**
Sheet-like structures	3 (7.50)	2 (6.7)	1 (5.9)	1 (10.0)	0 (0.0)	3 (11.5)	2 (16.7)	1 (8.3)	1 (5.3)	1 (10.0)	1 (6.3)	2 (10.0)	2 (20.0)	1 (7.7)
Junctional nests	27 (67.50)	21 (70.0)	11 (64.7)	7 (70.0)	9 (75.0)	18 (69.2)	7 (58.3)	8 (66.7)	15 (78.9)	4 (40.0)*	14 (87.5)*	12 (60.0)	5 (50.0)	10 (76.9)
Bulging around the follicle	16 (40.0)	12 (40.0)	7 (41.2)	3 (30.0)	5 (41.7)	10 (38.5)	5 (41.7)	5 (41.7)	7 (36.8)	2 (20.0)	7 (43.8)	9 (45.0)	5 (50.0)	5 (38.5)
Polycyclic papillary contours	3 (7.50)	2 (6.7)	1 (5.9)	1 (10.0)	1 (8.3)	3 (11.5)	1 (8.3)	1 (8.3)	1 (5.3)	0 (0.0)	1 (6.3)	1 (5.0)	2 (20.0)	1 (7.7)
Dermis														
Dermal nests	11 (27.50)	8 (26.7)	5 (29.4)	4 (40.0)	6 (50.0)*	9 (34.6)	6 (50.0)*	6 (50.0)*	7 (36.8)	3 (30)	5 (31.3)	4 (20.0)	3 (30.0)	6 (46.2)**
Nucleated cells within the papillae	6 (15.0)	4 (13.3)	3 (17.6)	2 (20.0)	3 (25.0)	6 (23.1)**	4 (33.3)*	4 (33.3)*	4 (21.1)	0 (0.0)	1 (6.3)	1 (5.0)	1 (10.0)	4 (30.8)**
Inflammation	21 (52.5)	17 (56.7)	10 (58.8)	7 (70.0)	7 (58.3)	13 (50.0)	6 (50.0)	6 (50.0)	9 (47.4)	6 (60.0)	10 (62.5)	11 (55.0)	8 (80.0)*	6 (46.2)

Abbreviations: DEJ, derma-epidermal junction; RCM, reflectance confocal microscopy.

*$p < 0.05$.; **Borderline ($p > 0.05 < 0.06$).

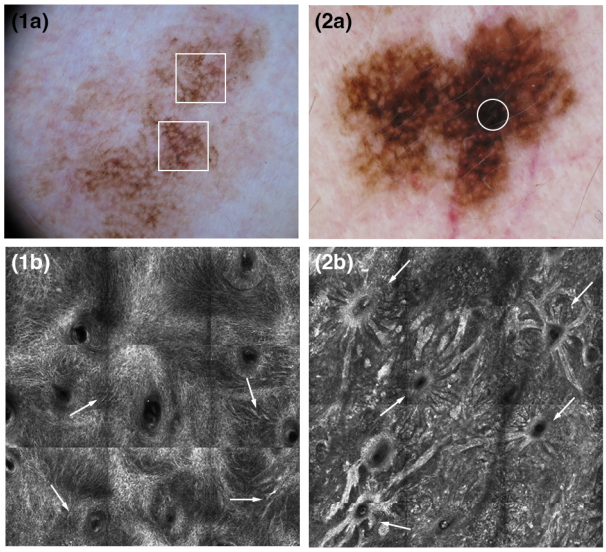

FIGURE 1 Lentigo maligna lesions. Brown-to-grey dots (square) in dermoscopy (1a) correlate with dendritic cells in epidermis, without any invasion of follicular openings (arrows) in reflectance confocal microscopy (RCM) (1b). Obliterated follicles in dermoscopy (2a) correlate with medusa head-like structures at the dermal–epidermal junction (arrows) in RCM (2b).

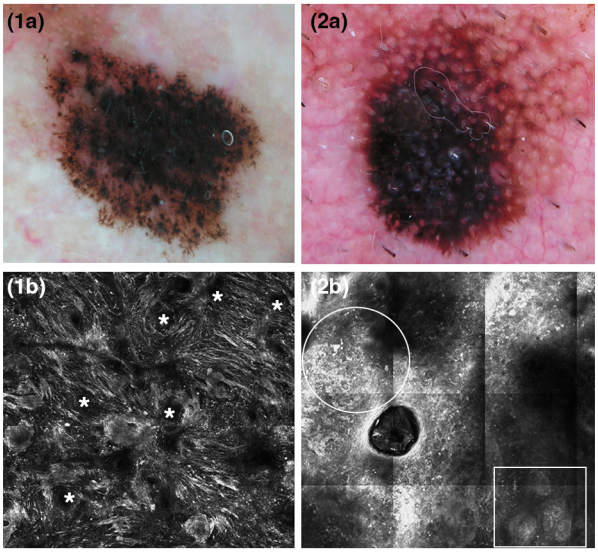

FIGURE 2 Lentigo maligna melanoma lesions. Obliterated follicles in dermoscopy (1a) correlate with folliculotropism; invasion of the follicules (stars) in reflectance confocal microscopy (RCM) (1b). Irregular hyperpigmentated areas in dermoscopy (2a) correlate with dermal nests (square) and nucleated cells in the dermis (circle) in RCM (2b).

Interestingly, some dermoscopy features have been correlated with different RCM patterns according to disease progression. Obliterated follicles in early disease have been associated with RCM medusa head-like structures but in advanced disease indicate folliculotropism. Medusa-like structures are considered an important criterion for the diagnosis of LM, as compared to other flat-pigmented lesions of the face.[9,18] Both medusa-head like structures and folliculotropism have been reported as RCM features describing different distribution of atypical cells around (partial) or infiltrating (complete) the hair follicle, respectively.[23] Therefore, the observation of obliterated follicles in both LM and LMM can be related to a differential progressive increase in follicular invasion (Figures 1 and 2).

Our study reveals the previously unreported differential RCM patterns for LMM. The increasing involvement of the dermal layer in disease progression[24] is evident with RCM analyses. Interestingly, dermal nests were observed exclusively among LMM lesions. Additionally, RCM dermal patterns, including dermal nests and nucleated cells within the papillae, have been significantly associated to the dermoscopic observation of irregular hyperpigmented areas and irregular blotches in more advanced disease. Black colour was independently associated with LMM diagnosis. Irregular hyperpigmented areas, irregular blotches and black colour can be referred to as 'darkening at dermoscopy' and have been associated with epidermal pigment[18] but also with dermal features.[25–27] Therefore, 'darkening' at dermoscopy, together with RCM patterns including dermal nests and nucleated cells within the papillae may also warrant a full biopsy for correct histopathological analysis. As a matter of fact, the proper management of LM/LMM encompasses the correct identification of the potential invasive component since estimates suggest that up to 50% of unguided biopsies may not include an existing lesion's invasive component.[28]

Overall, this study shows a progressive modification with tumour progression of the cytological pattern (Figure 3). In fact, early lesions show a predominant dendritic cell proliferation mostly concentrated in the hair follicle, which progressively increase in number and density (dense follicular infiltration and abundancy of dendritic cells in epidermis) and forms aggregates spreading out of hair follicles (medusa-head like structures). In a subsequent step roundish (epithelioid) atypical cells appear and clusters of atypical cells show up as nests at the DEJ and infiltrating the dermis. This progression pattern is aligned with previous dermoscopy based hypothesis[28] and RCM observations,[25] and corresponds to different aggressive melanoma behaviours, as recently shown by Marconi et al.[29] This justifies the slow progressive attitude of LM, which is capable to expand within the epidermis for several years, but also its malignant potential, with the unpredictable capability of the cellular component to transform into more aggressive subtype. Gérard et al.[30] have recently suggested that also the location of the lesion may be associated with a high risk of invasion; as a matter of fact they recently observed that lesions located in the peripheral zone (chin-mandibular area, temple, ears, neck, scalp, forehead and preauricular area) are more likely to be invasive as compared to those located in the central zone (cheeks and lower eyelids, inner canthus, nose, nasolabial fold, upper eyelids and eyebrows, perioral area).

This study is limited by a retrospective design which did not allow targeted correlations of dermoscopic features

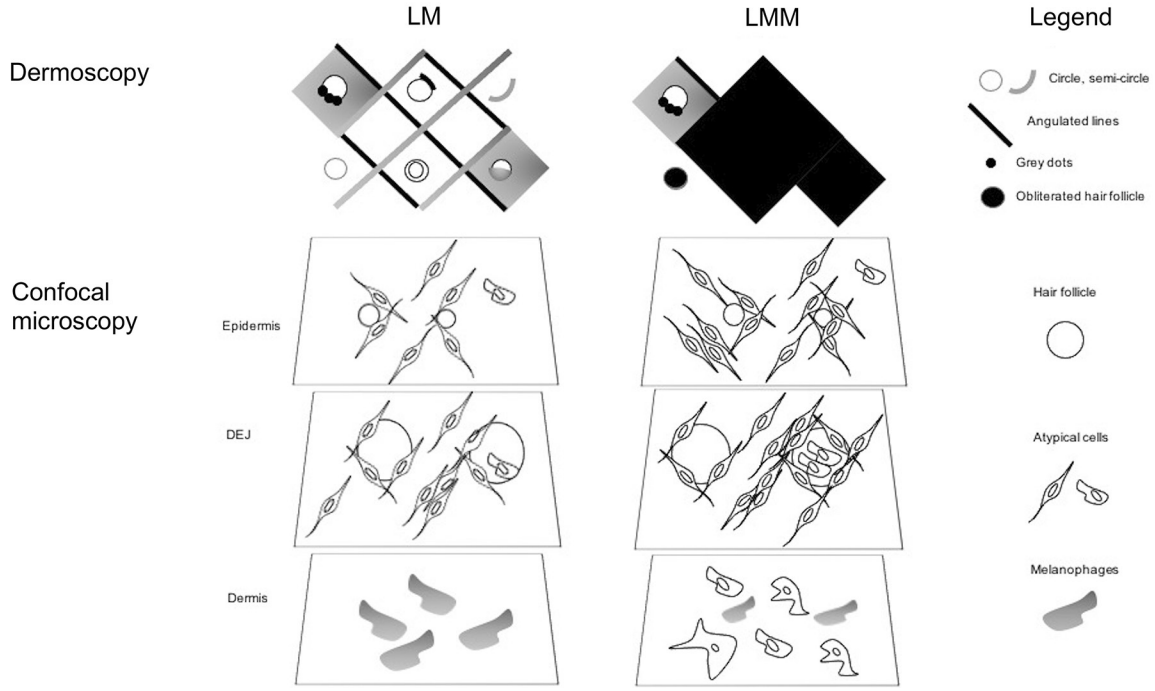

FIGURE 3 Progression model of lentigo maligna (LM)/lentigo maligna melanoma (LMM) progression with dermoscopy and confocal microscopy. The model shows dermoscopic patterns in LM and LMM and corresponding substrates in reflectance confocal microscopy.

and RCM structures, suggesting that our findings should be interpreted with caution, in particular for large lesions. Further, our study does not include any histopathological correlations. Future direct correlations between dermoscopy, RCM and histopathological features, with precise image overlaps, are necessary to confirm our results and extend findings to histopathological correlations.

CONCLUSIONS

Differential diagnosis of LM/LMM can be challenging. Specifically, differentially identifying invasive forms of disease is essential for prognostic reasons and can assist in optimising the area to be biopsied, in order to improve the recognition of LMM. Therefore, the identification of obliterated follicles, irregular hyperpigmented areas and irregular blotches and RCM patterns including folliculotropism, dermal nests and nucleated cells within the papillae is essential for the proper management of LM/LMM.

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CONFLICT OF INTEREST STATEMENT
Giovanni Pellacani received honoraria for seminars on confocal microscopy from MAVIG GmbH (Germany). All other authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

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

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