ORIGINAL ARTICLE

Amelanotic/hypomelanotic lentigo maligna: Dermoscopic and confocal features predicting diagnosis

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Abstract

Background: Amelanotic/hypomelanotic lentigo maligna and lentigo maligna melanoma (AHLM/LMM) may be very difficult to diagnose at an early stage.

Objectives: To quantify the predictive value of dermoscopic and reflectance confocal microscopy (RCM) features for AHLM/LMM.

Methods: Dermoscopic and RCM images of histopathologically diagnosed AHLM/LMM, amelanotic/hypomelanotic benign lesions (AHBL), and amelanotic/hypomelanotic basal and squamous cell carcinomas (AHBCC/AHSCC) of the head and neck from consecutive patients were retrospectively collected and blindly evaluated by three observers to assess presence or absence of dermoscopic and RCM criteria.

Results: Overall, 224 lesions in 216 patients including LM/LMM ($n = 55$, 24.6%), AHBL ($n = 107$, 47.8%) and AHBCC/AHSCC ($n = 62$, 27.7%) were analysed. Multivariable analysis showed that milky-red areas (OR = 5.46; 95% CI: 1.51–19.75), peripheral light brown structureless areas (OR = 19.10; 4.45–81.96), linear irregular vessels (OR = 5.44; 1.45–20.40), and asymmetric pigmented follicles (OR = 14.45; 2.77–75.44) at dermoscopy, and ≥3 atypical cells in five fields (OR = 10.12; 3.00–34.12) and focal follicular localization of atypical cells at dermo-epidermal junction (DEJ) (OR = 10.48; 1.10–99.81) at RCM were significantly independent diagnostic factors for AHLM/LMM vs. AHBL. In comparison with AHBCC/AHSCC, peripheral light brown structureless area (OR = 7.11; 1.53–32.96), pseudonetwork around hair follicles (OR = 16.69; 2.73–102.07), and annular granular structures (OR = 42.36; 3.51–511.16) at dermoscopy and large dendritic (OR = 6.86; 3.15–38.28) and round pagetoid cells (OR = 26.78; 3.15–227.98) at RCM led to a significantly increased risk of diagnosing AHLM/LMM.

Conclusions: Amelanotic/hypomelanotic lentigo maligna and lentigo maligna melanoma may have the same dermoscopic features of AHM on other body sites, such as milky red areas, peripheral light brown structureless areas and linear irregular vessels. These features, asymmetric pigmented follicles and at RCM ≥3 atypical cells in five fields and focal follicular extension of atypical cells at DEJ may help in recognizing AHLM/LMM even when LM conventional features (e.g., obliteration of hair follicles under dermoscopy and large pagetoid cells under RCM) are absent or present only in very small areas of the lesion.

INTRODUCTION

Lentigo maligna (LM) is an in situ melanoma arising on chronically sun-exposed skin, usually the face, in middle-aged and older patients, representing 79%–83% of all in situ melanomas.[1] LM is characterized by a variable long radial growth phase before progressing into invasive lentigo maligna melanoma (LMM) with a 3.5% annual risk of progression.[1] Clinically, LM presents as a slowly growing macule/patch with irregular, ill-defined borders, variable shades of brown and black, often as pseudonetwork with hypopigmented areas making a discontinuous appearance.[2] The dermoscopic diagnosis of LM may be difficult because it may show clinical and dermoscopic features of benign skin lesions and because of the frequent presence of collisions arising on sun-damaged skin.

Lentigo maligna may also be amelanotic or hypomelanotic presenting as ill-defined erythematous sometimes scaly macule/patch, mimicking eczematous dermatitis, Bowen's disease, inflamed solar lentigo, actinic keratosis, naevus depigmentosus and basal cell carcinoma (BCC), very difficult to diagnose in its early stage.[3–5] In amelanotic/hypomelanotic LM/LMM (AHLM/LMM), non-pigmented or hypopigmented areas extends beyond the visible margins of the lesion hindering the identification of the peripheral margin.[2]

Although several dermoscopic features have been described for pigmented LM/LMM, the literature on dermoscopy and AHLM/LMM is scanty.[6–7] Reflectance confocal microscopy (RCM) is an additional imaging technique that can help the diagnosis and definition of the margins of LM/LMM.[8–11]

Reflectance confocal microscopy resulted especially helpful for AHLM because in the latter, malignant melanocytes may appear very bright under RCM because they still have melanosomes, even if not dermoscopically visible.[11]

In this retrospective study, 224 amelanotic/hypomelanotic skin lesions of the head and neck were examined by dermoscopy and RCM to quantify by a multivariable analysis the predictive value of dermoscopic and RCM features for AHLM/LMM.

PATIENTS AND METHODS

We collected consecutive cases of histopathologically confirmed AHLM/LMM, amelanotic/hypomelanotic melanoma (AHM) not of LM/LMM subtypes, amelanotic/hypomelanotic basal and squamous cell carcinoma (AHBCC), (AHSCC), and amelanotic/ hypomelanotic benign lesions (AHBL) of the head and neck evaluated with dermoscopy and RCM at four participating centres in Italy between January 2010 and December 2019. AHBL included both amelanotic/hypomelanotic benign melanocytic (e.g., melanocytic nevus) and non-melanocytic lesions (e.g., solar lentigo, actinic keratosis, seborrhoeic keratosis, liken-planus-like keratosis). In this study, only flat amelanotic/

hypomelanotic lesions were included, lacking any trace of melanin or partially pigmented (melanin pigmented area ≤25%) or lightly coloured showing only tan, light grey-blue pigmentation that occupied >25% of the lesion.[12]

Clinical, dermoscopic and RCM images (Vivascope 1500 or Vivascope 3000, for lesions localized on areas not accessible with the Vivascope 1500, Mavig, Munich, Germany), together with patients' clinical information and histopathological diagnosis were collected.

We assessed the lesions using dermoscopic and RCM features associated with LM/LMM, melanoma, BCC, SCC, melanocytic nevus, actinic keratosis, solar lentigo, seborrhoeic keratosis, and liken-planus-like keratosis.[6,7,11] Dermoscopic images were evaluated together with the RCM images by a panel of three blinded observers; the evaluation of the dermoscopic and RCM criteria was assessed when 3/3 or 2/3 observers agreed. LM score was also computed according to Guitera et al.[11]

In virtue of the Italian research regulations (D.Lgs. 101/2018), the approval by the Board of Ethics is waived for retrospective studies, as the patients give their consent to the use of clinical data for research purposes at hospitalization. The signed consent is stored, according to Italian regulations under the responsibility of the principal investigator of each participating centre.

Statistical analysis

Continuous variables were reported as median values and interquartile range (IQR); differences across groups were evaluated through Kruskal–Wallis test. The prevalence of dermoscopic and RMC features was reported as a percentage with corresponding 95% Clopper–Pearson confidence interval (CI); differences were tested through Fisher's exact test. For each dermoscopic feature, the univariate odds ratio (OR) and corresponding 95% CI of AHLM/LMM versus either AHBL and AHBCC/AHSCC were estimated through unconditional logistic regression models. To account for potential feature association, the independent effect of each factor was evaluated through a multivariable stepwise logistic regression model which included all dermoscopic and RCM features significantly associated with AHLM/LMM in the univariate analysis. Statistical significance was claimed for p-values < 0.05 (two-sided). The statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC) statistical software.

RESULTS

Patients demographics and classification of the lesions

The study evaluated 224 lesions in 216 patients (116 men, 100 women) with a median age of 67 years (range:19–96 years). The series included 55 melanomas (43 LMs, eight LMMs, two invasive melanomas, and two in situ melanomas), 62 non-melanocytic skin cancers (44 BCC, 15 in situ SCC, two invasive

SCC, and one case of metatypical carcinoma) and 107 benign lesions (51 actinic keratoses, 25 solar lentigines, 16 melanocytic nevi seven seborrhoeic keratoses and one lichen-planus-like keratosis). Regarding the histogenetic melanoma subtypes, the proportion of LM/LMM was enormously bigger than SMM. These results mirrored the literature data as LM/LMM was reported to be the most frequent histogenetic subtype (47.4%) of head and neck melanoma, followed by superficial spreading melanoma (34.5%), and nodular melanoma (15.8%) in a very large series of 5702 patients.[13] Compared with AHBL (Table 1), AHLM/LMM was more frequent in men ($N = 69$; 69%; 95% CI: 55–81%) and at an older age (median: 70 years; IQR: 61–78). Conversely, AHLM/LMM and AHBCC/AHSCC showed similar distribution by sex and similar median age. The three groups significantly differed according to site of presentation ($p = 0.03$). AHLM/LMM and AHBL was diagnosed more frequently on the cheek ($N = 22$, 40% [27–54%] and $N = 41$, 38% [29–48]%, respectively) and nose ($N = 15$, 27% [16–41%] and $N = 18$, 17% [10–25]%, respectively); conversely, AHBCC/AHSCC mainly occurred on frontal ($N = 15$, 24% [14–37%]) and nose ($N = 23$, 40% [13–35%]), (Table 1).

Multivariable analyses of dermoscopic and RCM features

Dermoscopic and RCM features significantly associated with LMM in the univariate analysis in comparison with AHBL and AHBCC/AHSCC were presented in Tables S1–S4. The independent effect of each feature was evaluated through a multivariable model, and significant associations with AHLM/LMM vs. AHBL and vs. AHBCC/AHSCC are reported in Table 2. Milky-red areas (OR = 5.46; 95% CI: 1.51–19.75), peripheral light brown structureless areas (OR = 19.10; 95% CI: 4.45–81.96), linear irregular vessels (OR = 5.44; 95% CI: 1.45–20.40) and asymmetric pigmented follicles (OR = 14.45; 95%: CI 2.77–75.44) at dermoscopy, and ≥3 atypical cells in five fields (OR = 10.12; 95% CI: 3.00–34.12) and focal follicular localization of atypical cells at DEJ (OR = 10.48; 95% CI: 1.10–99.81) at RCM led to a significantly increased risk of diagnosing AHLM/LMM vs. AHBL (Table 2).

In addition, the multivariable analysis of the dermoscopic and RCM features of AHLM/LMM vs. AHBCC/AHSCC showed that a peripheral light brown structureless area (OR = 7.11; 95% CI: 1.53–32.96), pseudonetwork around hair follicles (OR = 16.69; 95% CI: 2.73–102.07) and annular granular structures (OR = 42.36; 95% CI: 3.51–511.16) at dermoscopy and large dendritic (OR = 6.86; 95% CI: 3.15–38.28) and large round (OR = 26.78; 95% CI: 3.15–227.98) pagetoid cells in the epidermis on RCM were significantly associated with an increased risk of AHLM/LMM (Table 2).

DISCUSSION

The most striking results of our study were that the only significant dermoscopic and RCM features discriminating

TABLE 1 Clinical characteristics of 224 amelanotic/hypomelanotic head and neck lesions by histopathological diagnosis

	AHLM/LMM		AHBL		AHBCC/AHSCC		
	No.	% (95% CI)	No.	(%)	No.	(%)	*p*
Total diagnoses	55		107		62		
Sex[a]							
Man	38	69 (55–81)	43	40 (31–50)	39	63 (50–75)	<0.001[b]
Woman	17	31 (19–45)	64	60 (50–69)	23	37 (25–50)	
Age (years)							
Median (IQR)		70 (61–78)		63 (53–74)		69 (56–75)	0.02[c]
Site[a]							
Cheek	22	40 (27–54)	41	38 (29–48)	10	16 (8–28)	0.03[b]
Nose	15	27 (16–41)	18	17 (10–25)	14	23 (13–35)	
Frontal	4	7 (2–18)	17	16 (10–24)	15	24 (14–37)	
Peri-auricular	1	2 (0–10)	3	3 (1–8)	4	6 (2–16)	
Peri-orbital	4	7 (2–18)	8	7 (3–14)	9	15 (7–26)	
Peri-oral	0	0 (0–6)	4	4 (1–9)	1	2 (0–9)	
Neck	2	4 (0–13)	3	3 (1–8)	1	2 (0–9)	
Scalp	1	2 (0–10)	5	5 (2–11)	6	10 (4–20)	
Other	6	11 (4–22)	8	7 (3–14)	2	3 (0–11)	

Abbreviations: AHBCC/AHSCC, amelanotic/hypomelanotic basal and squamous cell carcinoma; AHBL, amelanotic/hypomelanotic benign lesion; AHLM/LMM, amelanotic/hypomelanotic lentigo maligna/lentigo maligna melanoma; IQR, interquartile range.

[a]The sum does not add up to total because of some missing values.

[b]Estimated from Fisher's exact test.

[c]Estimated from Kruskal–Wallis test.

TABLE 2 Multivariable associations of dermoscopic and reflectance confocal microscopy features with AHLM/LMM in comparison with either AHBML/AHBNML or AHBCC/AHSCC

|	AHLM/LMM (No. = 55)		Comparison group	
			AHBL (No. = 107)	AHBCC/AHSCC (No. = 62)
	No.	% (95% CI)	OR (95% CI)[a]	OR (95% CI)[a]
Dermoscopic features				
Milky-red areas/>1 shade of pink	42	76 (63–87)	5.46 (1.51–19.75)	n.s.
Peripheral light brown structureless area	39	71 (57–82)	19.10 (4.45–81.96)	7.11 (1.53–32.96)
Pseudonetwork	33	60 (46–73)	n.s.	16.69 (2.73–102.07)
Annular granular structures	28	51 (37–65)	n.s.	42.36 (3.51–511.16)
Linear irregular vessels	27	49 (35–63)	5.44 (1.45–20.40)	n.s.
Asymmetric pigmented follicles	18	33 (21–47)	14.45 (2.77–75.44)	n.s.
Reflectance confocal microscopy features: epidermis				
Large dendritic pagetoid cells	34	62 (48–75)	n.s.	6.86 (3.15–38.28)
Large round pagetoid cells	18	33 (21–47)	n.s.	26.78 (3.15–227.98)
Reflectance confocal microscopy features: dermal/epidermal junction				
≥3 atypical cells in 5 fields	41	75 (61–85)	10.12 (3.00–34.12)	n.s.
Focal follicular localization of atypical cells	12	22 (12–35)	10.48 (1.10–99.81)	n.s.

Abbreviations: AHBCC/AHSCC, amelanotic/hypomelanotic basal and squamous cell carcinoma; AHBL, amelanotic/hypomelanotic benign lesion; AHLM/LMM, amelanotic/hypomelanotic lentigo maligna/lentigo maligna melanoma; CI, confidence interval; n.s., not significant (the feature was not selected by the stepwise regression model); OR, Odds ratio.

[a]Estimated from stepwise unconditional logistic regression model including all dermoscopic and confocal features emerging from univariate analysis.

AHLM/LMM from AHBL at the multivariable analysis were milky-red areas, peripheral light brown structureless areas, linear irregular vessels and asymmetric pigmented follicles at dermoscopy and at RCM ≥ 3 atypical cells in five fields and focal follicular localization of the atypical cells at the DEJ.
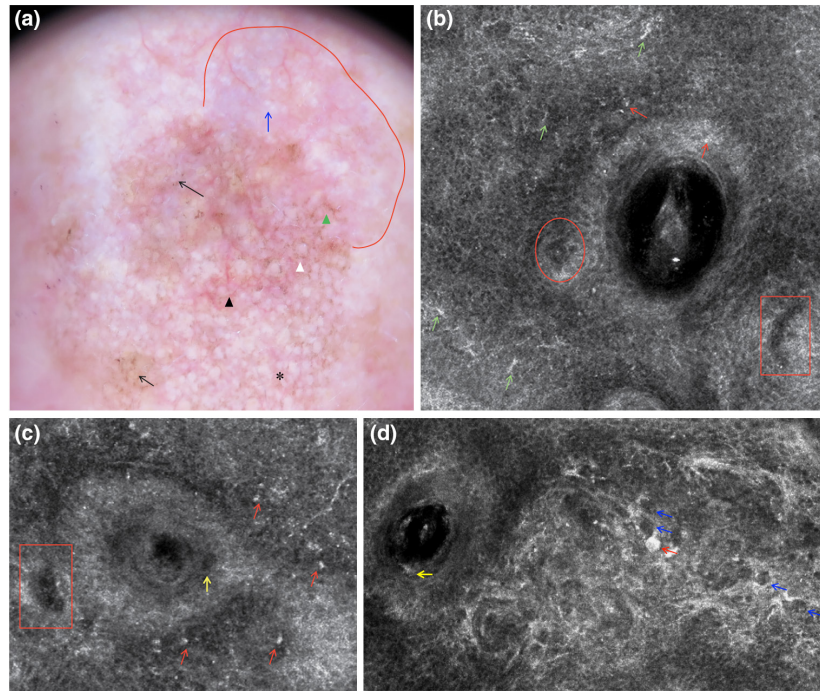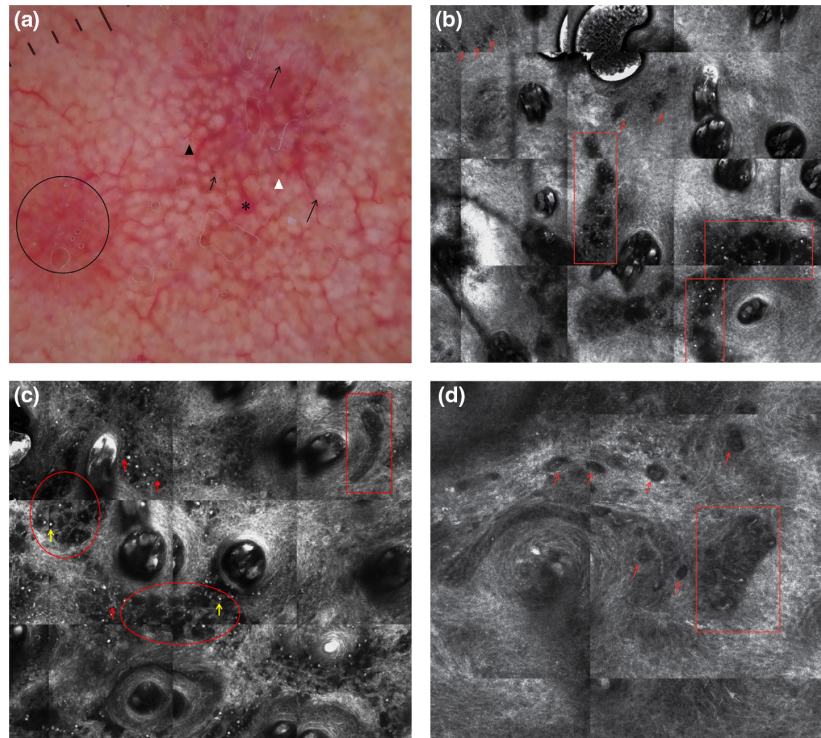
FIGURE 1 Dermoscopic and reflectance confocal microscopy (RCM) images of an hypomelanotic lentigo maligna on the nose of a 45-year-old man. (a) Dermoscopically, the lesion reveals asymmetric pigmented follicles (small black arrow), annular granular structures (white arrowhead), focal irregular brown dots (large black arrow) and pigmented rhomboidal structures (green arrowhead) intermixed with red rhomboidal structures (asterisk), and linear irregular vessels (black arrowhead); framed is the peripheral area with more than one shade of pink combined with shine white structures (circle) (10× magnification). (b) RCM performed with VivaScope 3000 (Mavig, Munich) reveals in the epidermis an irregular honey-combed pattern with few small hyper-reflective irregular roundish (red arrows) and dendritic cells (green arrows). Perifollicular roundish hyporeflective nests (red circle) and cord-like hyporeflective nests (red rectangle) were also visible. (c) Intrafollicular hyporeflective atypical cells in single unit (yellow arrow) or aggregated in cord-like nests (red rectangle) in perifollicular distribution can also be seen above dermo-epidermal junction (DEJ). (d) The DEJ displayed irregular large hyper-reflective dendritic and roundish cells (red arrows) and hyporeflective cells (blue arrows) among hair follicles probably correlating with pigmented rhomboidal structures seen at dermoscopy. In addition, focal follicular localization of irregular weakly reflective cells (yellow arrow) was also visible.

Milky-red areas, also known as more than one shade of pink, probably corresponding to areas with increased vascularity[14] (Figures 1a and 2a), and the peripheral light brown structureless areas[15] (Figure 3a) have already been associated with AHM on other body sites.[12,16] The peripheral light brown structureless areas seemed to occur in the early phases of the neoplastic invasion in both melanoma on other body sites[17,18] and AHLM. Linear vessels, significantly found in our cases of AHLM/LMM (Figures 1a, 2a and 3a), have also been reported in some cases of AHLM[6] as well as in AHM.[12,19] Therefore, milky-red areas, peripheral light brown structureless areas and linear irregular vessels can be useful to identify not only AHM on other body sites but also AHLM/LMM. Asymmetric pigmented follicles are considered a first sign of invasion/outgrow[20] of the follicular unit still respecting the basement membrane,[7,21] which seem to characterize not only pigmented LM but also AHLM/LMM; this feature is due to neoplastic melanocytes surrounding follicular openings and to their uneven descent within hair follicles.[22,23] It is interesting to note that hyporeflective and weakly reflective atypical cells in a single unit or aggregated in dense and sparse nests and/or cord-like nests (Figures 1b–d, 2b and 3c,d) among follicles as well as in the follicular adnexa and/or perifollicular distribution in the epidermis and at DEJ were found in our cases of AHLM.

Hyporeflective atypical cells in the epidermis correlated with pagetoid infiltration of hypomelanotic/amelanotic malignant melanocytes were also reported in AHM.[24]

Notably, hyporeflective atypical cells in single unit and aggregated in cord-like nests among follicles, in follicular and perifollicular distribution in the epidermis and at DEJ, have not yet been described and could be a clue for the diagnosis of AHLM. In agreement with Guitera et al.,[11] we found also that ≥3 atypical cells, including both hyper-reflective and hyporeflective ones, in five fields at DEJ (Figures 1d, 2d and 3d) were significantly associated with the diagnosis of AHLM/LMM. At the DEJ, large hyper-reflective dendritic and roundish cells as well as hyporeflective atypical cells among hair follicles were visible in our AHLM cases (Figures 1d and 3c). Hyper-reflective dendritic and roundish cells could be probably correlated with pigmented rhomboidal structures since hyper-reflective dendritic and roundish cells were found in 66.7% of cases having pigmented rhomboidal structures and in 20.2% of cases without pigmented rhomboidal structures ($p < 0.0001$). Likewise, weakly and hyporeflective atypical cells among hair follicles could be probably correlated with red rhomboidal structures because of a significant association between these structures and atypical cells among hair follicles; red rhomboidal structures were found in 11.1% of cases with atypical cells among

FIGURE 2 Dermoscopic and reflectance confocal microscopy (RCM) images of an amelanotic lentigo maligna on the cheek of a 75-year-old man. (a) At dermoscopic examination, the lesion was characterized by an unfocused area of milky red colour (circle) and by a red pseudonetwork-like area revealing asymmetric pigmented follicles (small black arrow), annular granular structures (white arrowhead), shiny withe structures (large black arrows), linear irregular vessels (black arrowheads) and red rhomboidal structures (asterisk). (b) Upon RCM examination, hyporeflective atypical cells in single unit (red arrows) and arranged in cord-like nests with scattered hyper-reflective cells (red rectangle) among follicles as well as in perifollicular distribution in the epidermis. (c) A completely disarranged pattern with large aggregated irregular dense and sparse nests of different shapes and sizes composed of medium reflective and hyporeflective atypical cells (red circle), cord-like hyporeflective nests (red rectangle) and small weakly reflective atypical cells with hypopigmented nucleus (red arrows) can be seen above DEJ. In addition, small hyper-reflective cells corresponding to inflammatory cells were also present (yellow arrows). (d) Atypical hyporeflective cells (red arrows) and hyporeflective cord-like nests in perifollicular distribution (red rectangle) were detectable at DEJ.

hair follicles, and in only 2.2% of cases without atypical cells among hair follicle ($p = 0.018$). Although Pralong et al.,[7] have found that red rhomboidal structures could be associated with invasive LM in their series,[7] we did not find red rhomboidal structures in any of our eight invasive LM cases.

In the study by Guitera et al.,[11] other positive correlating LM features were found at multivariate analysis, such as large pagetoid cells >20 μm in diameter in the epidermis and non-edged papillae at DEJ, which we found significantly associated with AHLM/LMM only at univariate analysis.

The differences between the two studies could depend on the fact that the study by Guitera et al.[11] also included pigmented LM in addition to different size and type of sample (81 LMs and 203 benign macules).

However, in the epidermis, large dendritic and round pagetoid cells were not found significantly associated with AHLM at multivariable analysis. As we have previously described in some cases of AHM not of lentigo maligna type,[25] RCM features for malignancy can be more difficult to identify because large hyper-reflective pagetoid cells could be less numerous and hyporeflective pagetoid cells could be difficult to identify; these cells were visible only by zooming the mosaic images and carefully examination, often missed at first glance.[25] In addition, few small dendritic cells can be challenging to

discriminate from Langherans dendritic cells seen in the epidermis of benign lesions such as actinic keratosis and liken-planus-like keratosis. Moreover, in the epidermis of AHLM/LMM, we found small hyper-reflective irregular cells without evident nucleus, difficult to discriminate from keratinocytes, probably corresponding to neoplastic melanocytes. This could explain why pagetoid cells did not allow to discriminate AHLM/LMM from AHBL and why the integration of dermoscopy with RCM could improve the diagnosis not only of pigmented lentigo maligna[8] but also of AHLM.

Atypical cells of different reflectivity aggregated in dense and sparse nests surrounding adnexal openings at the DEJ, and/or just under it were seen in our cases, which may be correlated with irregular brown and grey dots significantly associated with AHLM/LMM at univariate analysis. In agreement with our results, other authors found in LM/LMM dense and sparse nests of pleomorphic atypical cells surrounding the adnexal opening at the DEJ, correlated with brown dots/globules surrounding the adnexal opening observed at dermoscopy.[26,27]

At the multivariable analysis, peripheral light brown structureless area, pseudonetwork, annular granular structures, large dendritic and large round pagetoid cells were the significant features distinguishing AHLM/LMM from AHBCC/AHSCC. Pseudonetwork has also been reported
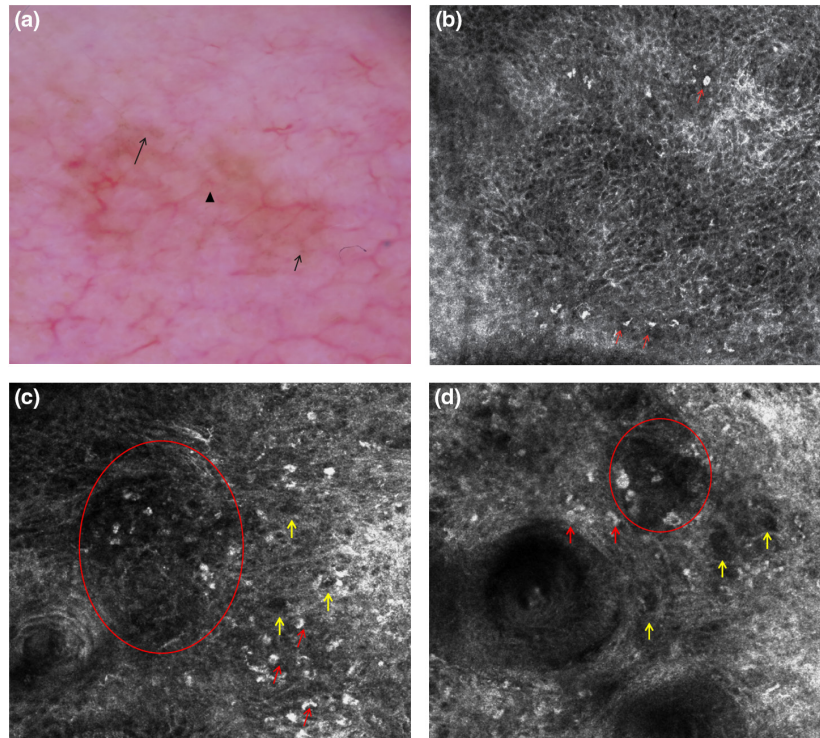
FIGURE 3 Dermoscopic and reflectance confocal microscopy (RCM) images of an hypomelanotic lentigo maligna on the cheek of a 41-year-old woman. (a) In the dermoscopic image, a peripheral irregular light brown pigmentation, focal small areas of depigmentation, initial annular granular structures around follicles (large arrows) linear irregular vessels (arrowhead) and focal irregular brown and grey dots (small arrows) can be seen. (b) RCM optical section at the epidermal level reveals irregular honey-combed pattern with small hyper-reflective irregular cells (red arrows) difficult to differentiate from keratinocytes. (c) Perifollicular roundish irregular dense and sparse nests with atypical cells of different reflectivity (red circle) and interfollicular hyper-reflective (red arrows) and hyporeflective (yellow arrows) atypical cells can also be seen above DEJ. (d) Perifollicular roundish irregular dense and sparse nests with atypical cells of different reflectivity (red circle) and single hyper-reflective (red arrows) and hyporeflective (yellow arrows) atypical cells can also be seen at DEJ.

in both pigmented LM and solar lentigo/seborrhoeic keratosis and pigmented actinic keratosis.[28] Therefore, pseudonetwork did not allow to discriminate AHLM/LMM from AHBL, whereas this feature and annular granular structures, peripheral light brown structureless area, large dendritic and large round pagetoid cells were more frequent in AHLM/LMM than AHBCC/AHSCC. Pseudonetwork and annular granular structures are related to a folliculotropism of the LM without a complete invasion of the hair follicles, whereas AHBCC/AHSCC directly destroys hair follicles. As expected, large roundish and dendritic cells in the epidermis were found in LM/LMM and a few epithelial cancers because they are quite specific of malignant melanocytes in RCM.

Interestingly, LM score according to Guitera et al.[11] was reported significantly more frequently in LM than in AHBCC/AHSCC, and AHBL; LM score ≥2 was found in 89.1% of AHLM/LMM, in 58.1% of AHBCC/AHSCC, and in 29.0% of AHBL ($p \leq 0.001$; data not shown). Therefore, LM score may help in discriminating LM from head and neck malignant non-melanocytic and benign lesions. Nonetheless, diagnostic performance of LM score in AHBCC/AHSCC should be investigated.

Finally, our study found that AHLM/LMM may have the same dermoscopic features of AHM on other body sites, such as milky red areas, peripheral light brown structureless areas and linear irregular vessels. These features, asymmetric

pigmented follicles and at RCM≥3 atypical cells in five fields and focal follicular extension of atypical cells at DEJ may be useful in improving the detection of this difficult to diagnose subtype of melanoma even when LM conventional features (e.g., obliteration of hair follicles under dermoscopy and large pagetoid cells under RCM) are absent or present in very small areas of the lesion.

CONFLICT OF INTEREST
IZ reports consulting fees from Sanofi Genzyme and honoraria from MSD, Novartis, Sunpharm, Sanofi Genzyme, La Roche Posay, Philogen, Biogena, Almiral Hermal, outside the submitted work. FP reports grants from AstraZeneca, Eisai, Roche and honoraria from AstraZeneca Daiicki Sankyo, Eli Lilly, Novartis, Pfizer, Pierre Fabre, Gilead, Seagen, and Roche, outside the submitted work. All the remaining authors declared no conflict of interests.

DATA AVAILABILITY STATEMENT

The data are available upon reasonable request to the corresponding author.

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REFERENCES

1. Collgros H, Rodriguez-Lomba E, Regio Pereira A, Lo SN, Scolyer RA, Guitera P. Lentiginous melanoma (lentigo maligna and lentigo maligna melanoma) in Australia: clinicopathological characteristics, management and recurrence rates after 10-year follow-up at a tertiary Centre. J Eur Acad Dermatol Venereol. 2021;35:1–8.
2. Menzies SW, Liyanarachchi S, Coates E, Smith A, Cooke-Yarborough C, Lo S, et al. Estimated risk of progression of lentigo maligna to lentigo maligna melanoma. Melanoma Res. 2020;30:193–7.
3. Cliff S, Otter M, Holden CA. Amelanotic lentigo maligna melanoma of the face: a case report and review of the literature. Clin Exper Dermatol. 1997;22:177–9.
4. Allan SJR, Dicker AJ, Tidman MJ, McLaren K, Hunter JA. Amelanotic lentigo maligna and amealnotic lentigo maligna melanoma: a report of three cases mimicking intraepidermal squamous carcinoma. JEADV. 1998;11:78–81.
5. Abdulla FR, Kerns MJ, Mutasim DF. Amelanotic lentigo maligna: a report of three cases and review of the literature. J Am Acad Dermatol. 2010;62:857–60.
6. Giacomel J, Lallas A, Zalaudek I, Argenziano G. Dermoscopic "signature" pattern of pigmented and nonpigmented lentigo maligna. J Am Acad Dermatol. 2014;70:33–5.
7. Pralong P, Bathelier E, Dalle S, Poulalhon N, Debarbieux S, Thomas L. Dermoscopy of lentigo maligna melanoma: report of 125 cases. Br J Dermatol. 2012;167:280–7.
8. Cinotti E, Fiorani D, Labeille B, Gonzalez S, Debarbieux S, Agozzino M, et al. The integration of dermoscopy and reflectance confocal microscopy improves the diagnosis of lentigo maligna. J Eur Acad Dermatol Venereol. 2019;33:e372–4.
9. Cinotti E, Labeille B, Debarbieux S, Carrera C, Lacarrubba F, Witkowski AM, et al. Dermoscopy vs. reflectance confocal microscopy for the diagnosis of lentigo maligna. J Eur Acad Dermatol Venereol. 2018;32:1284–91.
10. Couty E, Tognetti L, Labeille B, Douchet C, Habougit C, Couzan C, et al. In vivo reflectance confocal microscopy combined with the "spaghetti technique" for the identification of surgical margins of lentigo maligna. J Eur Acad Dermatol Venereol. 2018;32:e366–8.
11. Guitera P, Pellacani G, Crotty KA, Scolyer RA, Li LXL, Bassoli S, et al. The impact of in vivo reflectance confocal microscopy on the diagnostic accuracy of lentigo maligna and equivocal pigmented and nonpigmented macules of the face. J Invest Dermatol. 2010;130:2080–91.
12. Menzies SW, Kreusch J, Byth K, Pizzichetta MA, Marghoob A, Braun R, et al. Dermoscopic evaluation of amelanotic and hypomelanotic melanoma. Arch Dermatol. 2008;144:1120–7.
13. Hoersch B, Leiter U, Garbe C. Is head and neck melanoma a distinct entity? A clinical registry- based comparative study in 5702 patients with melanoma. Br J Dermatol. 2006;155:771–7.
14. Marghoob AA, Braun R. Proposal for a revised 2 step algorithm for the classification of lesions of the skin using dermoscopy. Arch Dermatol. 2010;146:426–8.
15. Marghoob NG, Liopyris K, Jaimes N. Dermoscopy: a review of the structures that facilitate melanoma detection. J Am Osteopath Assoc. 2019;119:380–90.
16. James N, Braun RP, Thomas L, Marghoob AA. Clinical and dermoscopic characteristics of amelanotic melanomas that are not of the nodular subtype. JEADV. 2012;26:591–6.
17. Filoni A, Lospalluti L, Zanframundo G, de Marco A, Argenziano G, Bonamonte D. Light brown structureless areas as a predictor of melanoma in situ. Br J Dermatol. 2020;183:158–92.
18. Annessi G, Bono R, Sampogna F, Faraggiana T, Abeni D. Sensitivity, specificity, and diagnostic accurac of three dermoscopic algorithmic methods in the diagnosis of doubtful melanocytic lesions. The importance of light brown structureless areas in differentiating atypical melanocytic nevi from thin melanoma. J Am Acad Dermatol. 2007;56:759–67.
19. Pizzichetta MA, Talamini R, Stanganelli I, Puddu P, Bono R, Argenziano G, et al. Amelanotic/hypomelanotic: clinical and dermoscopic features. Br J Dermatol. 2004;150:1117–24.
20. Zalaudek I, Marghoob AA, Scope A, Leinweber B, Ferrara G, Hofmann-Wellenhof R, et al. Three roots of melanoma. Arch Dermatol. 2008;144:1375–8.
21. Peruilh-Bagolini L, Apalla Z, Gonzalez-Cuevas R, Lallas K, Papageorgiou C, Bobos M, et al. Dermoscopic predictors to discriminate between in situ and early invasive lentigo maligna melanoma: a retrospective observational study. J Am Acad Dermatol. 2000;83:269–71.
22. Tiodorovic D, Argenziano G, Lallas A, Thomas L, Ignjatovic A, Rabinovitz H, et al. Age, gender, and topography influence the clinical and dermoscopic appearance of lentigo maligna. J Am Acad Dermatol. 2015;72:801–8.
23. Schiffner R, Schiffner-Rohe J, Vogt T, Landthaler M, Wlotzke U, Cognetta AB, et al. Improvement of early recognition of lentigo maligna using dermatoscopy. J Am Acad Dermatol. 2000;42:25–32.
24. Losi A, Longo C, Cesinaro AM, Benati E, Witkowski A, Guitera P, et al. Hyporeflective pagetoid cells: a new clue for amelanotic melanoma diagnosis by reflectance confocal microscopy. Br J Dermatol. 2014;171:48–54.
25. Pizzichetta MA, Canzonieri V, Rubegni P, Corneli P, Puglisi F, Zalaudek I, et al. Tips for difficult to diagnose hypomelanotic melanomas on reflectance confocal microscopy. J Dermatol. 2021;48:1–6.
26. De Carvalho N, Guida S, Cesinaro AM, Abraham LS, Ciardo S, Longo C, et al. Pigmented globules in dermoscopy as a clue for lentigo maligna mimicking non-melanocytic skin neoplasms: a lesson from reflectance confocal microscopy. J Eur Acad Dermatol Venereol. 2016;30:878–80.
27. Guida S, Farnetani F, De Pace B, Kaleci S, Chester J, Stanganelli I, et al. Flat pigmented facial lesions without highly specific melanocytic dermoscopy features: the role of dermoscopic globules and dots in differential diagnosis with corresponding reflectance confocal microscopy substrates. J Eur Acad Dermatol Venereol. 2020;34:1536.
28. Lallas A, Argenziano G, Moscarella E, Longo C, Simonetti V, Zalaudek I. Diagnosis and management of facial pigmented macules. Clin Dermatol. 2014;32:94–100.

SUPPORTING INFORMATION

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