Reflectance confocal microscopy features of labial melanotic macule: Report of three cases

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INTRODUCTION

The term *labial melanotic macule* of the lips (MML) is used to describe a flat-pigmented lesion on the vermilion border, with an estimated prevalence of up to 3% of the population. Most MMLs are located on the lower lip and are more common in female patients. MMLs are mostly associated with hyperpigmentation of the basal keratinocytes with normal to a slightly increased density of melanocytes; an infiltrate of melanophages in the superficial dermis can also contribute to the pigmented appearance of MMLs. These benign lesions may raise concern for melanoma or may be confused with other labial pigmentary disorders.[1-3]

Dermoscopy is widely used for the diagnosis of pigmented and nonpigmented lesions on the skin. In 2011, the International Dermoscopy Society published a multicenter study that evaluated the dermoscopic features of pigmented mucosal lesions. The study found that the presence of structureless zones inside the lesions with blue, gray, or white color had a 100% sensitivity for melanoma and 82.2% specificity for benign lesions.4 However, reaching a confident diagnosis of MML based on clinical and dermoscopic inspection can be quite challenging, requiring a lip biopsy or close monitoring of the lesion. Lip biopsies can be associated with discomfort and scarring.

Reflectance confocal microscopy (RCM) is an in vivo, noninvasive imaging technique that allows horizontal optical sectioning of skin at cellular-level resolution, from the surface to a depth of about 200 μm.[4] Although the lips are amenable for handheld RCM examination, publications about the RCM findings in MMLs are limited.[5,6] To improve the recognition of MML under RCM, we report on 3 cases of biopsy-proven MMLs.

Abbreviations used:

DEJ:	dermoepidermal junction
LCs:	Langerhans cells
MML:	melanotic macule of the lips
RCM:	reflectance confocal microscopy

CASE REPORTS

Case 1

A 43-year-old female patient had a superficial spreading melanoma, 1.1 mm in Breslow thickness, on her back, 1 year before the current visit. The patient presented with a new lesion on her lower lip, which was growing insidiously over 8 months. On clinical examination, the patient had Fitzpatrick skin phototype IV. She had a 3-mm symmetric, brownish macule on her lower lip. Dermoscopy found irregular parallel lines, circles, and a diffuse brownish pigmentation (Fig 1, *A*). RCM examination at the epidermal level found a regular honeycomb pattern, without pagetoid or dendritic cells; at the dermoepidermal junction (DEJ) level, there was a diffuse infiltration of dendritic cells in the interpapillary

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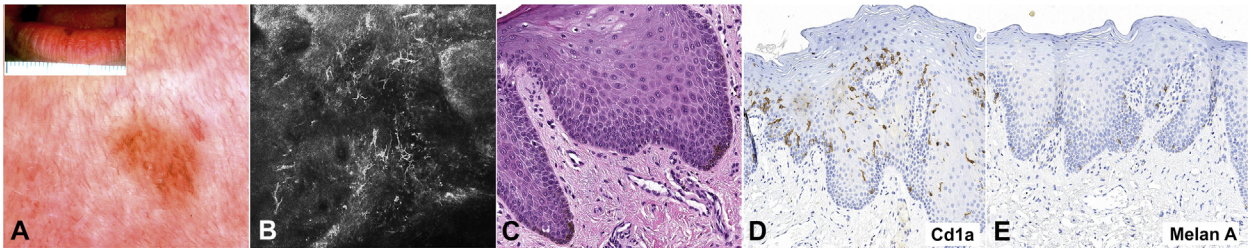

Fig 1. Labial melanotic macule: case 1. **A**, Dermoscopic image with irregular lines. **B**, RCM individual image (0.5 × 0.5 mm) shows at the DEJ level dendritic cells in the interpapillary spaces. **C**, H&E histopathologic panoramic view. Discrete acanthosis and hyperpigmentation of the basal keratinocytes. **D**, Immunohistochemistry profile shows $CD1a^{+}$, demonstrating that the dendritic cells seen under RCM are LCs. **E**, Melan-A immunostain shows a minimum increase in the melanocyte counts in the basal layer, with no atypia.

spaces (Fig 1, *B*). A biopsy was performed to rule out a melanoma. The histopathologic sections showed discrete acanthosis, parakeratosis, and hyperpigmentation of the basal keratinocytes with few melanophages in the papillary dermis (Fig 1, *C*) consistent with melanotic macule. CD1a was positive, showing that the dendritic cells seen under RCM were Langerhans cells (LCs) (Fig 1, *D*). Melan-A and S-100 immunostains showed a minimum increase in the melanocyte counts in the basal layer, with no atypia (Fig 1, *E*).

Case 2

A 46-year-old woman, with no history of skin cancer, presented with a lesion on her lower lip of unknown duration or evolution. On clinical examination, the patient had Fitzpatrick skin phototype IV. On the lower lip, a 6-mm asymmetric, brownish macule was seen. Dermoscopy showed irregular parallel lines and a diffuse brownish pigmentation (Fig 2, *A*). RCM examination at the suprabasal epidermis showed a regular honeycomb pattern without pagetoid or dendritic cells. At the DEJ level, an infiltration of dendritic cells was seen around and between the dermal papillae and occasionally crossing the papillae (Fig 2, *B*). A biopsy found discrete acanthosis, parakeratosis, hyperpigmentation of the basal keratinocytes, and few melanophages in the papillary dermis (Fig 2, *C*) consistent with a melanotic macule. CD1a found the presence of numerous LCs throughout the epithelium (Fig 2, *D*), whereas Melan-A and S-100 immunostains found a normal density of melanocytes (Fig 2, *E*).

Case 3

An 84-year-old woman with no history of skin cancer presented to the skin cancer clinic for routine skin cancer screening. On physical examination, the patient had Fitzpatrick skin phototype III. A 2-mm irregular brownish macule was noted on the lower lip. Dermoscopy showed irregular brown parallel lines, gray dots/granules, and irregularly distributed dark globules (Fig 3, *A*). RCM examination found a regular honeycomb pattern at the spinous and granular layers; at the DEJ, sheets of dendritic cells were seen around and between the dermal papillae, whereas plump-bright cells, corresponding to melanophages, were seen within the dermal papillae (Fig 3, *B*). The histopathologic examination found epidermis with focal parakeratosis, hypergranulosis, epidermal hyperplasia, and increased pigmentation of the basal keratinocytes. There was a bandlike lymphohistiocytic infiltrate throughout the upper part of the dermis (Fig 3, *C*). CD1a confirmed numerous LCs throughout the epithelium (Fig 3, *D*). Immunostains for Melan-A and S-100 were negative. These findings were consistent with a melanotic macule.

DISCUSSION

MMLs are commonly seen in daily practice, and the differential diagnosis with melanoma can be challenging. To this end, handheld RCM examination can be used as a diagnostic additional tool to clinical and dermoscopic assessment.

Erfan et al[2] imaged with RCM 4 cases of MML and reported the abundance of dendritic cells at the DEJ, which correlated under histopathology with normal-appearing melanocytes; the authors noted that these RCM findings in MML may present a pitfall for the false-positive diagnosis of melanoma, based on previously published criteria for diagnosis of melanoma on sun-damaged skin.[2]

Debarbieux et al[7] retrospectively reviewed the RCM features of 56 cases of mucosal pigmented macules. They observed bright dendritic cells around papillae, which were often weakly reflective, in 86% of MMLs; roundish bright cells were not seen

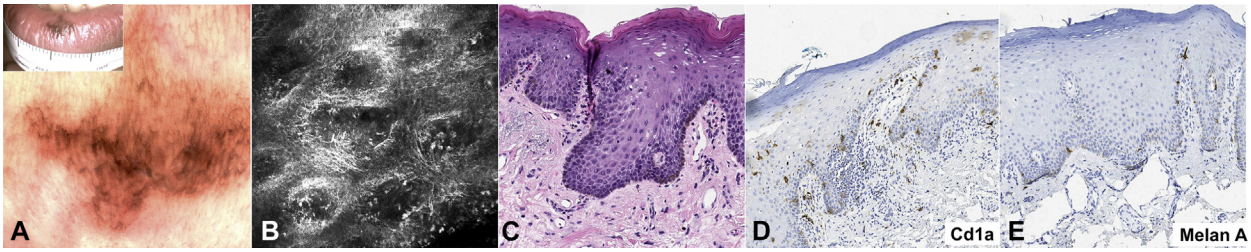

Fig 2. Labial melanotic macule: case 2. **A**, Dermoscopic image shows irregular lines and brownish pigmentation. **B**, RCM individual image (0.5 × 0.5 mm) shows at DEJ level dendritic cells around and between dermal-papillae. **C**, H&E histopathologic panoramic view. Acanthosis, parakeratosis, and hyperpigmentation of the basal keratinocytes. **D**, Immunohistochemistry profile for CD1a shows numerous LCs. **E**, Immunohistochemistry profile for Melan-A immunostain negative for melanocytic proliferation.

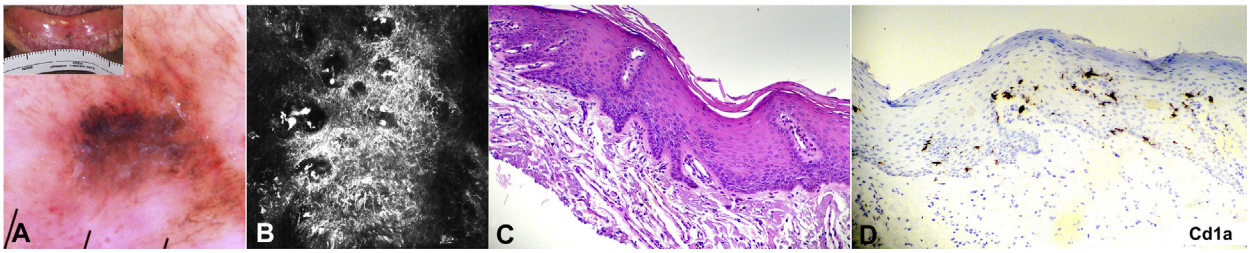

Fig 3. Labial melanotic macule: case 3. **A**, Dermoscopic image shows irregular gray and dark dots/granules. **B**, RCM individual image (0.5 × 0.5 mm) shows at DEJ level a sheet of dendritic cells around and between the dermal papillae. **C**, H&E histopathologic panoramic view. Epidermis with hypergranulosis, epidermal hyperplasia, and increased pigmentation of the basal keratinocytes of the third patient. **D**, Immunohistochemistry profile for CD1a immunostain is positive for numerous LCs cells into the squamous mucosa.

in the epidermis. Clues for melanoma included the presence of roundish cells, a high density of atypical dendritic cells, and focally dense intraepithelial bright dendritic or roundish cells.

Maher et al[8] prospectively evaluated 8 patients with suspicious pigmented lesions on the lips. Although the presence of dendritic cells at the DEJ raised concern for the diagnosis of mucosal melanoma, a low density of the dendritic cells was a reassuring finding. The authors also found RCM to be valuable for delimiting the area for surgical removal or for guiding incisional biopsies of the pigmented macules.

Recently, Uribe et al[5] retrospectively compared the RCM findings in 16 patients with MML, 5 patients with 6 lip melanomas, and 10 normal lip control patients. In normal lips, elongated polycyclic papillae with well-demarcated borders without dendritic cells were identified in all cases. Dendritic and/or roundish pagetoid infiltration was found in all melanomas, whereas among MML, pagetoid infiltration of only dendritic cells was seen in 25%. At the DEJ, an infiltration of dendritic cells was detected in 100% of MML and 83% of melanomas; however, significant differences between melanomas and MMLs included atypical round cells (83% vs 6%, respectively), marked cellular atypia (100% vs 19%), continuous (lentiginous) proliferation of atypical enlarged bright cells (83% vs 13%), infiltration involving the interpapillary spaces (100% vs 38%), and high density of cells (>20 dendritic cells per mm^2, 100% vs 40%, respectively). The presence of dendritic or roundish pagetoid cells were the strongest RCM feature for melanoma diagnosis.

Based on these findings, the authors proposed an RCM Lip Score for Diagnosis with a sensitivity of 100% and specificity of 88% for melanoma diagnosis for a score ≥ 4.[5] We retrospectively applied this score to our 3 cases. The first and the third patients scores were +1, whereas the second patient score was 0. According to the RCM Lip Score for Diagnosis, all 3 patients could have been monitored without a biopsy.

The RCM features in all 3 cases reported herein are consistent with those previously described in the literature. The presence of a regular honeycomb epidermal pattern and an infiltration of dendritic cells at the DEJ level, surrounding the dermal

papillae and the interpapillary space, were the key features of MML. Although the infiltration of dendritic cells was quite dense in our cases, the absence of roundish nucleated cells at the DEJ and of dendritic cells in pagetoid spread were reassuring findings.

An interesting and, to the best of our knowledge, novel finding in this study is that the dendritic cells seen under RCM in MML correlated mostly with LCs and not melanocytes. LCs are usually sited in the suprabasal and spinous layers of the epidermis; nevertheless, these cells may present important regional difference, for example, in the density and distribution in the oral mucosa. The lower lip is characterized by a rich content of immunoreactive cells. LCs in this location tend to be concentrated mainly along the papilla and tend to be highly dendritic.[9]

LCs are not evident in the epithelium by routine hematoxylin-eosin (H&E) staining. The presence of LCs has not been reported in the histopathologic description of LMM, which only includes hyperpigmentation of the basal keratinocytes, increased number of melanophages, and normal or slightly increased number of melanocytes.[1,3] There is also a difficulty in differentiating these cells from melanocytes under RCM. Up to now, there is no reproducible differences in cellular morphology that allows a clear distinction between these 2 cell types in RCM imaging.[10] Herein, immunohistochemistry staining confirmed a proliferation of $CD1a^{+}$ cells in the epidermis, whereas Melan-A staining showed the presence of sparse melanocytes.

LCs may be expected in labial melanotic macule, in a peculiar distribution. Notably, histopathologic review of a greater number of cases, using specific IHC-staining to identify LCs, will be necessary to confirm our findings. We highlight that RCM imaging of these benign lesions requires evaluation of additional criteria, as the presence of dendritic cells at the DEJ may be a sensitive, but not specific, RCM criterion for the diagnosis of melanoma.

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