Langerhans Cells as Morphologic Mimickers of Atypical Melanocytes on Reflectance Confocal Microscopy: A Case Report and Review of the Literature

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ABSTRACT

Pagetoid spread of melanocytes in the epidermis is a common indicator of melanocytic atypia, both histopathologically and with reflectance confocal microscopy (RCM). Specifically on RCM, large, bright, atypical dendritic and/or roundish cells are characteristic of melanoma. However, intraepidermal Langerhans cells (ILC) create the potential for diagnostic ambiguity on RCM. We describe one case of a pigmented facial lesion that was initially diagnosed as lentigo maligna (LM) due to numerous atypical perifollicular dendritic cells on RCM. Additionally, we present the findings of a literature review for similar reported cases conducted by searching the following terms on PubMed: reflectance confocal microscopy, RCM, lentigo maligna, melanoma, Langerhans cells, dendritic cells, and atypical cells. In our case, the lesion was determined to be a solar lentigo on histopathology. Immunohistochemistry (IHC) with CD1a identified the atypical-appearing cells as ILC, as it did in 54 reported cases of benign lesions (benign melanocytic nevus, Sutton/halo nevus, labial melanotic macule, and solar lentigo) misdiagnosed as malignant on RCM (melanoma, lip melanoma, lentigo maligna, and LM melanoma). According to our case and the literature, both ILC and atypical melanocytes can present with atypical-appearing dendritic and/or roundish cells under RCM. Currently, there is no method to distinguish the two without IHC. Therefore, the presence of pagetoid cells should continue to alert the confocalist of a potential neoplastic process, prompting biopsy, histopathologic diagnosis, and IHC differentiation.
Introduction

Reflectance confocal microscopy (RCM) is a technique that acquires en face images of the epidermis and papillary dermis in vivo, using a non-invasive laser device (830 nm). Confocal images have a resolution comparable to traditional histopathology [1]. This enables high accuracy diagnosis without the use of biopsy, particularly for pigmented lesions, in which melanin provides strong endogenous contrast [2]. Melanocytic cytologic atypia is suggested by the presence of large (>20 µm), bright, dendritic, or roundish cells [3]. Pagetoid melanocytosis observed in RCM has been histopathologically correlated to melanoma [4-7]. While not specific for malignancy, the presence of pagetoid spread on RCM of a pigmented lesion carries 11 to 22 [7,8] times greater risk of melanoma, with odds ratios of 4 to 9 for dendritic cells [4,6,8] and 9.7 to 108 [4-6,8] for roundish cells.

Suspicion for melanoma on RCM increases when atypical cells are densely distributed (>5 cells/mm²), pleomorphic with large and unusual morphology (triangular, star-shaped), roundish, diffuse, and extend to the stratum corneum [3,5,6]. Atypical dendritic or roundish pagetoid cells with folliculotropism are characteristic of lentigo maligna (LM) [9,10]. We describe a case in which a benign pigmented lesion on the cheek resembled LM on confocal images, owing to dendritic intraepidermal Langerhans cells (ILC) misinterpreted as atypical melanocytes. We present a literature review of additional cases in which the presence of ILC resulted in erroneous diagnosis of melanoma on RCM.

Case Report

A 64-year-old Caucasian woman presented with a 5 mm light brown papule on the left cheek that had been present for several months and was growing in size. She had a history of blistering sunburns in childhood and basal cell carcinoma of the right hand 13 years prior to presentation. Family history was significant for ocular melanoma in the patient’s mother. Dermoscopic examination of the lesion showed blue-gray granularity and crescent-shaped perifollicular pigmentation, which are considered indicative of melanophages in the dermis and atypical melanocytes extending down hair follicles (Figure 1A) [11,12]. The patient was referred for RCM due to provider suspicion for malignancy and patient preference for a non-invasive procedure (Figure 1B).

RCM revealed an irregular honeycomb pattern with numerous large (>20 µm) atypical dendritic pagetoid cells, including some in a perifollicular distribution, consistent with LM (Figure 2). The dermo-epidermal junction (DEJ) contained focal areas of small bright and large bright inflammatory cells (Figure 3).

A shave biopsy was performed, and tissue sections were stained with hematoxylin and eosin (H&E) (Figure 4A, B). Histopathologic analysis revealed solar lentigo (SL) with underlying sebaceous hyperplasia. Immunohistochemistry (IHC) staining for the melanocyte-specific Melan-A showed a normal distribution of benign-appearing melanocytes in the epidermis, consistent with SL (Figure 4C). Staining for CD1a, a membrane glycoprotein specific for Langerhans...
cells and immature T cells, revealed numerous Langerhans cells throughout the epidermis (Figure 4D). Thus, the atypical dendritic cells visualized on RCM likely represented ILC, rather than atypical melanocytes.

Discussion

RCM is an accurate tool for non-invasive differentiation between benign and malignant melanocytic lesions. For the diagnosis of LM specifically, Guitera et al [10] isolated characteristic RCM features to develop an algorithmic “LM score,” resulting in a sensitivity of 85% and specificity of 76% for lesions with scores ≥2. Two major features earn +2 points each (nonedged papillae and large round pagetoid cells >20 µm), three minor features earn +1 point each (three or more atypical dendritic cells and immature T cells, revealed numerous Langerhans cells throughout the epidermis (Figure 4D). Thus, the atypical dendritic cells visualized on RCM likely represented ILC, rather than atypical melanocytes.

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Table 1. Reported cases of Langerhans cells presenting as atypical melanocytes in benign lesions on RCM.

| RCM Diagnosis | Reference | Case Composition | Clinical Features | RCM Cytologic Findings | Histopathologic Analysis |
|---------------|-----------|------------------|-------------------|-------------------------|--------------------------|
| Melanoma      | Hashemi et al.\(^{14}\) | 24 cases of BMN falsely diagnosed as melanoma | Pigmented lesions in various locations including shoulder, back, abdomen (others unspecified) | Bright cells in a pagetoid pattern: 5/24 roundish, 4/24 dendritic, 15/24 both | BMN, CD1a positive, 7/24 Melan-A positive, cytokeratin-20\(^{†}\) negative |
|               | Yelamos et al.\(^{18}\) | 1 case of recurrent nevus falsely diagnosed as melanoma | Pigmented macule on right knee | Pleomorphic, mostly dendritic cells throughout the epidermis, DEJ, and in the dermal nests | CMN with fibrosis suggestive of recurrent nevus; CD1a positive, SOX10 normal |
|               | Brugues et al.\(^{19}\) | 21 cases of clinically atypical Sutton (halo) nevi excised due to possibility of melanoma | Pigmented macules with atypical dermoscopic features such as: asymmetrical peripheral whitish halo, white/blue-gray regression, peppering | 13/21 atypical pagetoid cells (dendritic > roundish); atypical basal cells (roundish = dendritic); dermal atypical nucleated cells, plump cells, and bright particles | Sutton nevus, CD1a positive, Melan-A positive (large melanocytes) in the epidermis and DEJ |
| Lip melanoma  | Porto et al.\(^{20}\) | 3 cases of labial melanotic macule falsely diagnosed as lip melanoma | Pigmented macules on the lower lip | 3/3 bright dendritic cells at the DEJ, around and between dermal papillae | Labial melanotic macule, CD1a positive, Melan-A and S-100 negative (1/3) or normal (2/3) |
| LM/LMM        | Gomez-Martin et al.\(^{13}\) | 5 cases of pigmented facial macules falsely diagnosed as LM/ LMM | Clinically ambiguous pigmented facial macules | 5/5 abundant dendritic pagetoid cells; 4/5 round, large pagetoid cells; 3/5 atypical cells at the DEJ | CD1a positive, 2/5 showed both basal melanocyte hyperplasia and ILC secondary to postradiotherapy pigmentation |
| Current case  | 1 case of SL falsely diagnosed as LM | Pigmented facial papule with dermoscopic features concerning for LM | Large, atypical dendritic pagetoid cells in a perifollicular distribution | SL with underlying nodular sebaceous hyperplasia, CD1a positive, Melan-A normal |

BMN= benign melanocytic nevus/nevi; CMN = compound melanocytic nevus; DEJ = dermo-epidermal junction; ILC= intraepidermal Langerhans cell(s); LM = lentigo maligna; LMM – lentigo maligna melanoma; RCM = reflectance confocal microscopy; SL= solar lentigo

\(^{†}\) marker for Merkel cells

...Dermal atypical nucleated cells, plump cells, and bright particles.
(LMM) and benign pigmented facial macules [13]. The bright appearance of Langerhans cells is likely due to their Birbeck granules, which have a high reflectivity index and thus appear light gray to white under RCM, similar to melanin [14]. Langerhans cells are normally present in the epidermis and serve as antigen-presenting cells for T lymphocytes [15]. Among benign lesions, they are more likely to be prominent around inflammation, such as traumatized benign melanocytic nevi (BMN), recent scars, or lichen planus-like keratosis (LPLK) [16,17]. When identified on RCM in high densities, ILC are more likely to result in a false diagnosis of melanoma [14]. While dendritic cells alone are not enough to diagnose LM, as demonstrated by Guitera et al [10] and Gomez-Martin et al [13], the follicular localization of atypical cells on RCM, correlating to asymmetric follicular pigmentations on dermoscopy, raised the level of suspicion for LM in our patient’s case.

In the literature, ILC presence has been confirmed in several cases of benign lesions that were perceived to be malignant under RCM. These include suspected cases of melanoma [14,18,19], lip melanoma [20], and LM/LMM [13] (Table 1). Comparatively high densities of Langerhans cells exist within the head, neck, trunk, and limbs [21], corresponding to the variety of locations reported. Most cases described RCM findings of roundish and dendritic pagetoid cells, although some cases found atypical cells at the DEJ and dermis, as well. As evidenced by our case, traditional H&E stain was not sufficient in identifying ILC on histopathology and CD1a was required for further classification. In some studies, dendritic pagetoid cells were identified by RCM in lesions that were ultimately benign, but staining for Langerhans cells was not pursued [10,22,23]. Thus, the prevalence of ILC in pigmented lesions, and its confounding effect on RCM diagnosis, may be even greater than reported. The inability to use special stains and IHC when conducting in vivo RCM makes such morphologic mimickers indistinguishable across several lesion types.

Some malignant and pre-malignant lesions, particularly pigmented basal cell carcinomas [17,24], in situ or early invasive melanomas [14,25,26], pigmented actinic keratosis [27], and pigmented squamous cell carcinoma (SCC) in situ [28], may also contain a high density of Langerhans cells. In a study classifying melanoma into distinct types, Pellacani et al [29] found that in situ and thin melanomas (<1 mm Breslow thickness) were characterized by dendritic cells on RCM. While the authors did not further identify the cells immunohistochemically to rule out the possibility of ILC, this study, and others like it, highlight a possible association of dendritic cells with thin, or early, melanomas. In cases of larger suspicious pigmented lesions, RCM has the added benefit of real-time biopsy guidance, increasing the sensitivity for histopathologic detection of malignancy [10]. Future studies would need to determine whether the identification of dendritic cells on RCM of a clinically ambiguous lesion would result in earlier detection of melanoma.

While atypical cells have been identified as ILC rather than atypical melanocytes across benign lesions including BMN, Sutton (halo) nevi, labial melanotic macules, and SL, the presence of dendritic pagetoid cells should continue to alert the confocalist of a potential neoplastic process, prompting biopsy, histopathologic diagnosis, and IHC differentiation.

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