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DOI: <https://doi.org/10.1159/000322620>

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Journal Article

Published Version

Originally published at:

Kolm, I; Kamarashev, J; Kerl, K; Mainetti, C; Giovanoli, P; French, L E; Braun, R P (2011). Diagnostic pitfall: pigmented lesion of the nipple—correlation between dermoscopy, reflectance confocal microscopy and histopathology. *Dermatology*, 222(1):1-4.

DOI: <https://doi.org/10.1159/000322620>

Diagnostic Pitfall: Pigmented Lesion of the Nipple – Correlation between Dermoscopy, Reflectance Confocal Microscopy and Histopathology

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Key Words

Dermoscopy · Reflectance confocal microscopy · Nevus in special location · Nipple

Abstract

We present an unusual case of a nevus of the nipple changing during pregnancy which caused a diagnostic pitfall. Nevi on the nipple and areola are infrequent, and diagnostic criteria for clinical, dermoscopy or reflectance confocal microscopy examination for nevi in this 'special location' are still missing. We comment on the literature on dermoscopic findings in mammary lesions and their management during pregnancy, as well as the challenging histopathology of nevi along the milk line. Finally, we focus on two main limitations of reflectance confocal microscopy: the misinterpretation of dendritic cells and the limitation of the imaging depth.

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Case Report

We present a 27-year-old white woman, pregnant of 14 weeks, with a pigmented lesion involving her left nipple. The pigmentation had been present for years but increased in size and became darker during pregnancy. Clinically, we observed a dark brown pigmented asymmetric mac-

ule, 8 × 6 mm in size, involving the central lobules of the nipple (fig. 1, inset). Dermoscopy showed a rather unspecific pattern consisting of an irregular brown to gray-blue pigmentation of the lobules of the nipple forming an irregular cobblestone pattern. Additionally, at the periphery of some lobules the lesion displayed brown streaks, and few irregular dark brown dots were visible (fig. 1).

Examination of the lesion by reflectance confocal microscopy (RCM; VivaScope 1500; Lucid Inc., Rochester, N.Y., USA) was performed. Horizontal RCM cuts (mosaics or blocks) were recorded at different levels (epidermis, dermal-epidermal junction, upper dermis) to evaluate the general pattern of the epidermis, presence of pagetoid cells, dermal-epidermal architecture and pattern of melanocytic nests. RCM revealed a preserved honeycomb pattern throughout most of the epidermis interrupted by multiple refractile intraepidermal dendritic cells. Moreover, many individual monomorphic strong refractile round cells, as well as the formation of dense clusters, which appeared to be located above the dermal-epidermal junction, were observed (fig. 2). The dermoepidermal junction revealed a benign melanocytic pattern of edged papillae and clusters of dense cell nests (fig. 3).

Since the lesion had a reported history of recent change during pregnancy and

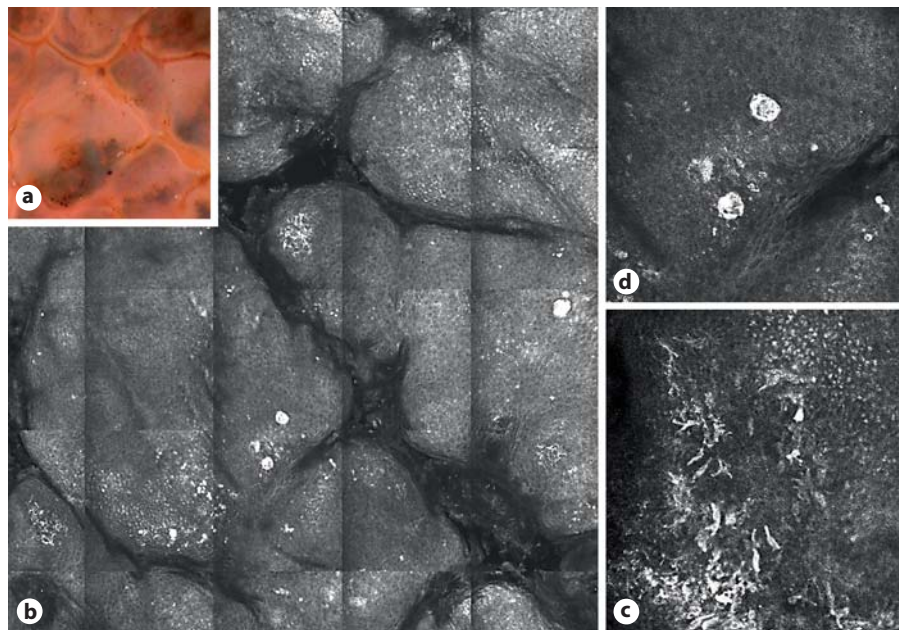
the dermoscopy and confocal microscopy findings were inconsistent with the diagnosis of a nevus, we opted for an excisional biopsy under local anesthesia during the 18th week of pregnancy. Histology revealed a sharply demarcated, relatively symmetrical compound melanocytic lesion. Pigmented parakeratosis was focally present as a sign of irritation. Worrisome features reminiscent of melanoma were observed in the intraepidermal compartment of the lesion and included the combination of nests of irregular shape and size and focal suprabasal pagetoid spreading of single cells. Most of the junctional melanocytes were heavily pigmented and had long, prominent dendrites; moreover, some melanocytes had hyperchromatic large nuclei and an abundant cytoplasm.

These findings in the epidermis are usually consistent with the diagnosis of a malignant melanocytic proliferation and are usually not in favor of benign growth. However, regarding the dermal component of the lesion, histopathology showed nests and cords of morphologically inconspicuous mature melanocytes without mitoses. Overall, from the histopathology findings and the clinical information on the special localization of the lesion, the final diagnosis was consistent with an irritated compound nevus of the milk line with signs of dysplasia and fibrosis (fig. 4).



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Fig. 1. Clinical (inset) and dermoscopy image. Dark brown macule, 8 × 6 mm in size, involving the central lobules of the nipple. Unspecific dermoscopy pattern: irregular brown to gray-blue pigmentation of the lobules with some brown streaks at the periphery of some lobules and few dark brown dots.



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Fig. 2. Dermoscopy (a) and correspondent RCM image of a lobule (b). c, d Optic sections (0.5 × 0.5 mm; Vivascope 1500, Lucid Inc.). Multiple dendritic cells in the suprabasal layer of the epidermis (c) and individual monomorphic strong refractile round cells and dense cell nests above the dermal-epidermal junction (d).

Discussion

We present an unusual case of a changing nevus of the nipple during pregnancy which caused a diagnostic pitfall.

Nevi on the nipple and areola are infrequent, and diagnostic criteria whether for clinical, dermoscopy or confocal microscopy examination for nevi in this 'special location' have not yet been established.

Only a few cases of melanoses of the areola are reported in the literature [1–3]. Blum et al. [3] described the dermoscopic findings in a case of melanosis of the areola. They found that the hyperpigmentation was arranged in a cobblestone pattern due to the anatomy of the normal skin of the areola. Interestingly, the change in color and size of the lesion reported by Blum et al. coincided also with pregnancy of the patient. So far there are only 2 reports in the literature dealing with the correlation of dermoscopy, histopathology and *in vivo* RCM findings in mammary lesions: one on mammary Paget's disease [4] and another – recently published by Zrinjka et al. [5] – on findings in a congenital nevus of the nipple. As in our case, dermoscopy showed an irregular black globular pat-

tern. Zrinjka et al. [5] nicely correlate their findings: RCM revealed irregular dense junctional nests, multiple melanophages in the upper dermis and the absence of pagetoid spreading. The final diagnosis of congenital nevus was therefore made by histopathology, especially with the positive immunostaining for melanophages; clinical findings alone were not conclusive either [5].

Driscoll and Grant-Kels [6] published a review on changes of nevi and melanoma during pregnancy. They concluded that a changing pigmented lesion in the pregnant woman should be approached in the same way as in any patient. Most dermoscopic changes are due to the physiological extension of the skin during pregnancy [7, 8]. Only pregnant women with dysplastic nevus syndrome require closer monitoring; their nevi tend to have a higher rate of clinical change during pregnancy [9]. Melanoma incidence is not higher during pregnancy; neither does pregnancy adversely affect survival or prognosis of melanoma [6]. Excisions under local anesthesia can be performed safely at any moment, especially after the third month of pregnancy [6].

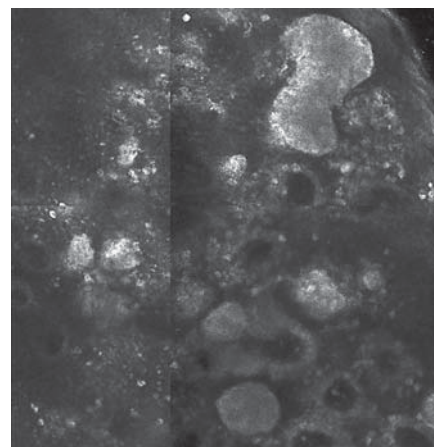
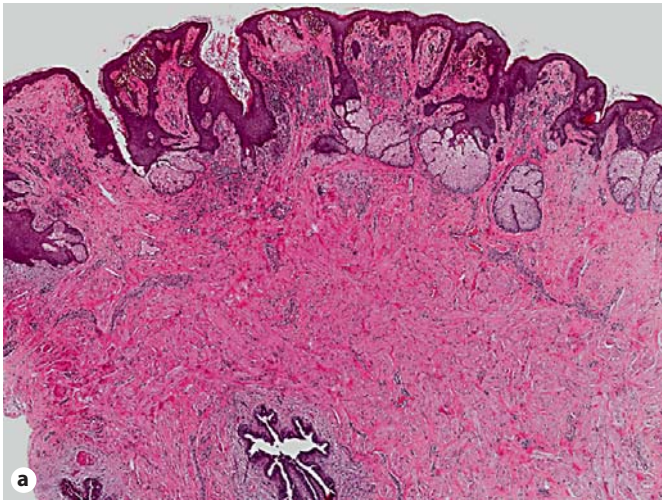


Fig. 3. RCM (Vivascope 1500, Lucid Inc.). Optic section (1 × 1 mm) at the dermal-epidermal junction with edged papillae and dense cell nests.

This case is interesting because it demonstrates two main problems of misinterpretation of RCM images of melanocytic lesions. Primarily we misinterpreted the single highly refractile dendritic cells in



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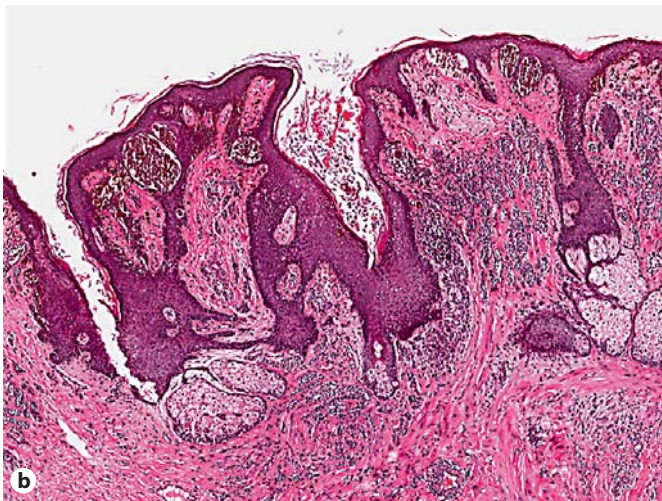
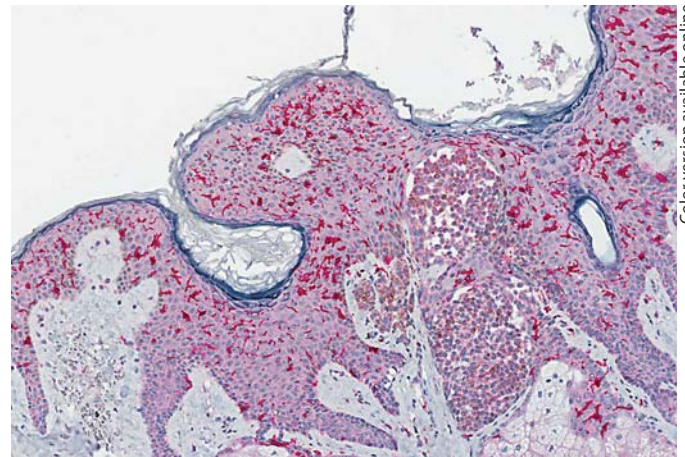


Fig. 4. Histopathological images. **a** Overview. Sharply demarcated, relatively symmetrical compound melanocytic lesion of the nipple with large, irregular, confluent junctional nests and single cells in a lentiginous pattern with a limited pagetoid scatter. **b** Detail of **a**. Heavily pigmented melanocytes in the superficial part of the lesion with long, prominent dendrites and some large hyperchromatic nuclei.

the lower epidermis to be of melanocytic origin. As mentioned before, pagetoid spreading is a hallmark criterion for melanoma [10]. Differentiation of dendritic melanocytes from activated Langerhans cells by RCM is difficult and often not possible. So far, the distinction between dendritic melanocytes and Langerhans cells is currently only possible by immunohistochemistry. CD1a staining of our case proved that the intraepidermal dendritic cells were in fact Langerhans cells (fig. 5). An explanation for the finding of multiple

Langerhans cells might be the pregnancy of our patient. It is estimated that only 3–5% of the epidermal cells are Langerhans cells, but it has been demonstrated that progesterone is able to increase the absolute number of Langerhans cells in different epithelial cells [11].

Secondly, RCM allows the examination of the skin at a quasi histological resolution to a depth of 200–250 μm depending on the level of keratinization of the skin. Therefore, RCM diagnosis is normally based on the findings in the epidermis,



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Fig. 5. CD1a immunohistochemical staining. Positive for Langerhans cells in the epidermis.

dermal-epidermal junction and upper dermis. In our case, the RCM findings of multiple dendritic cells in the suprabasal layer of the epidermis and single strong refractile round cells and dense cell nests above the dermal-epidermal junction led us to overdiagnose the lesion in favor of melanoma. Zrinjka et al. [5] mentioned that they also had to deal with the limitation in depth. Examination of the lower dermis was not accessible by RCM means, which may have changed our opinion towards benignity of the lesion.

Histopathologically the intraepidermal component of nevi situated along the milk line (nipple, areola, axilla, umbilicus and groin) often shows, similarly to genital nevi, architectural and cytological irregularities simulating melanoma; they are known in the dermatopathological literature as ‘special location’ nevi [12, 13]. Such lesions can be very challenging for the dermatopathologist.

The accurate evaluation of the maturation of cells in the dermal component and the consideration of the localization are essential for the correct histopathological diagnosis of these lesions.

With more reports in the literature on mammary lesions, patterns for this special anatomic site will be recognized, allowing us to have more confidence in *in vivo* diagnostic means, like dermoscopy and RCM.

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Erratum

In the article by Reich et al. [*Dermatology* 2010;221:172–178], entitled ‘Skin and nail responses after 1 year of infliximab therapy in patients with moderate-to-severe psoriasis: a retrospective analysis of the EXPRESS trial’, in table 3 on page 175, there was an unintentional error pertaining to median DLQI improvement percentages. Specifically, the mean DLQI improvement percentages for week 38 scores, i.e. 92.9% for all, 100.0% for PASI-75 responders and 100.0% for PASI-90 responders, should not have been included. The data points in the table should be replaced by dashes because there were no DLQI assessments at that time point in the EXPRESS study. The error did not affect the interpretation or conclusions of the study.