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In vivo reflectance confocal microscopy: a useful non-invasive tool to assess the response to isolated limb perfusion for superficial pigmented melanoma in-transit metastatic disease. Report of a case

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ABSTRACT Complete response can be difficult to assess after isolated limb perfusion (ILP) for metastatic in-transit melanoma, especially when numerous and unresectable post-necrotic persisting pigmented lesions occur. These residual lesions are mainly seen in the more superficial and pigmented types of metastatic disease and correspond to the residual melanophage granuloma that persists after tumor tissues undergo complete necrosis. Reflectance confocal microscopy (RCM) is a non-invasive technique that allows the exploration of the superficial dermis. Here, we present the case of a patient in whom numerous post-ILP limb residual pigmented lesions were explored using combined RCM and histological examination of sample lesions and could be characterized as non-active. This approach allowed us to avoid additional excisions.

Case Presentation

A 57-year-old woman developed multiple (>20) melanoma in-transit metastatic nodules on her right thigh (Figure 1A), as confirmed by histological examination, after removal, six months earlier, of a primary 2.2 mm thick ulcerated nodular melanoma on her right leg for which the initial sentinel lymph node biopsy was negative. After completion of FDG PET-CT to exclude distant metastasis and assessment of the extent of limb metastasis, the patient was referred to a specialized center to receive, isolated limb perfusion (ILP) of melphalan under hyperthermia, TNF-α and interferon γ. Superficial and deep pelvic (ilioinguinal) lymphadenectomy was simultaneously performed and revealed two additional deep pelvic

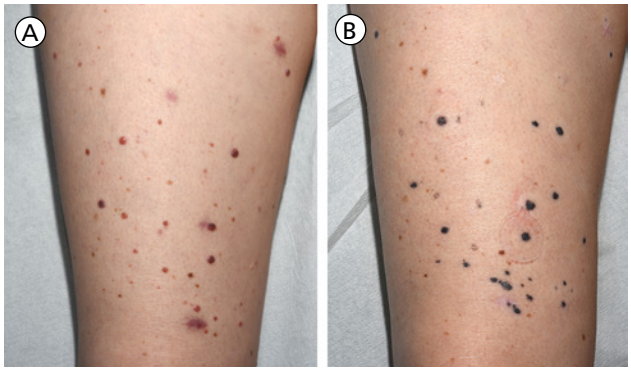

Figure 1. (A) In-transit metastatic nodules before ILP. (B) Persisting non-changing pigmented macules after ILP. The designated lesions (A, B) are the ones for which dermoscopy follow-up is shown in Figure 4. [Copyright: ©2017 Merat et al.]

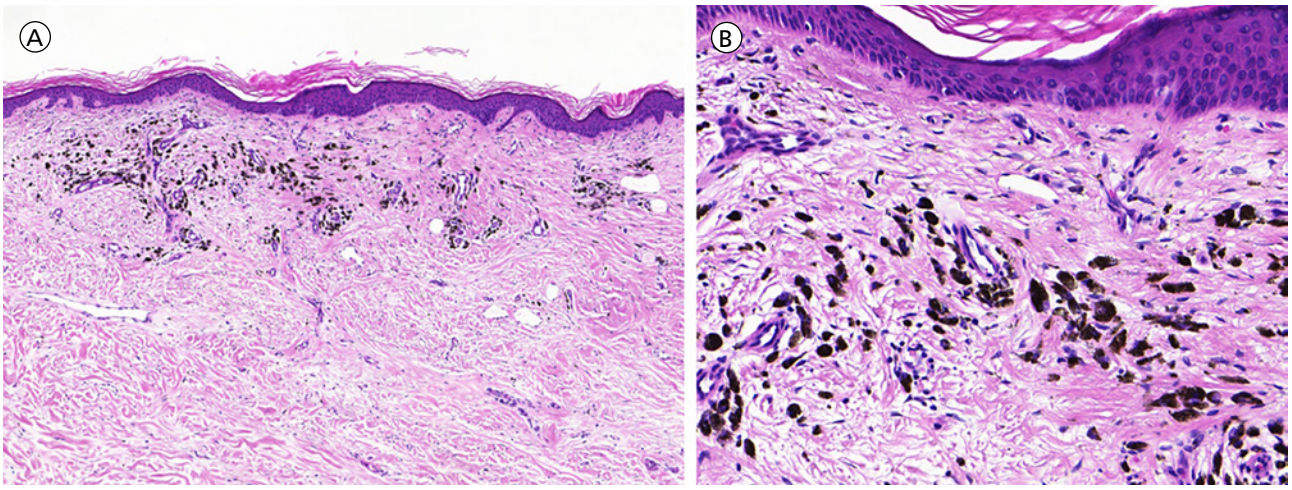

Figure 2. Histology (A) Persisting melanophage granuloma within areas of fibrosis in the upper dermis, original magnification x10. (B) Original magnification x20. Note the ring-shaped deposits as seen in RCM. [Copyright: ©2017 Merat et al.]

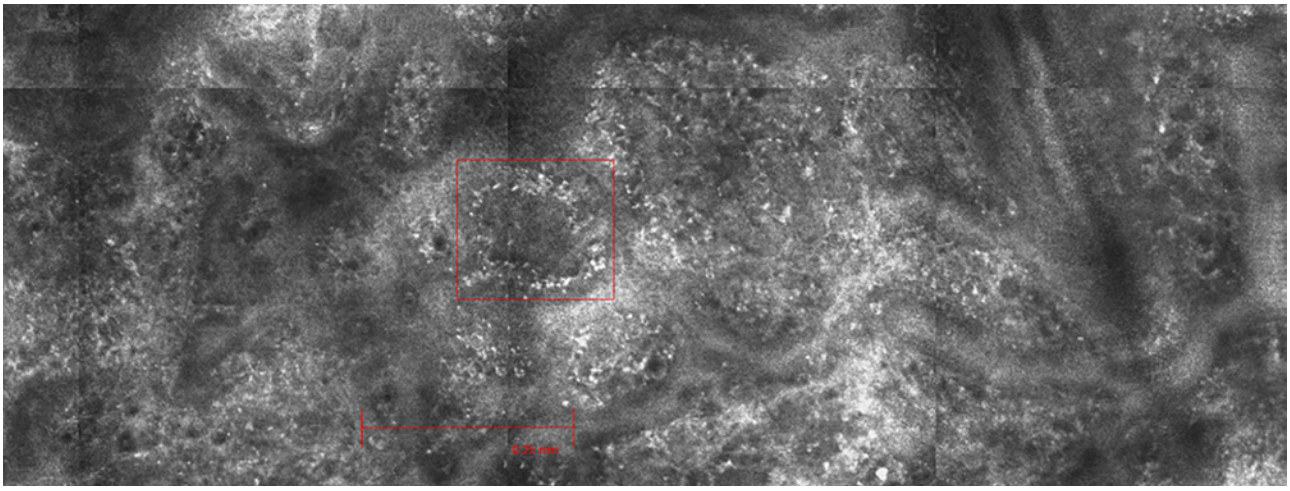

Figure 3. RCM mosaic from the upper dermis: ill-defined aggregates of dermal bright cells typical of melanophages and characteristic ring-shaped deposits within the network of collagen fibers. [Copyright: ©2017 Merat et al.]

lymph node metastases. One month after the end of this procedure, most in-transit lesions had undergone necrosis. Four months later, all lesions had healed and persisted as non-changing pigmented macules (Figure 1B) with no clinical or radiological (including FDG PET-CT) signs of relapse. In order to confirm that none of the residual pigmented macules was an active lesion, two of them were excised after being previously examined by RCM. Histological examination showed a persisting melanophage granuloma (nodular melanosis) within areas of fibrosis in the upper dermis with no sign of tumor infiltration (Figure 2A and 2B). RCM imaging, performed using the Vivascope 1500 (VivaScope Systems, Munich, Germany) showed ill-defined aggregates of dermal bright cells, typical of melanophages with almost no visible nuclei. Sometimes a characteristic ring-shaped deposit was seen within the network of bright collagen fibers and bundles (Figure 3). Such deposits could be seen in many areas of the excised lesions and correlated with the histological images. We then performed RCM imaging on 12 other main persisting pigmented lesions (Figure 1B) in which a similar characteristic image was consistently seen. This approach allowed us to avoid additional excision. The patient has now been followed for more than a year without any clinical or radiological sign of relapse and most lesions have slowly resolved (Figure 4).

Discussion

Around 5-10% of patients with malignant melanoma develop lymphatic dissemination and in-transit metastasis. Even in the era of effective systemic therapies, isolated limb perfusion (ILP) with hyperthermia performed using various agents (melphalan, with addition of chemokines, i.e., TNF-α and/or other chemokines) is still a valuable therapeutic approach and is being used for patients who develop numerous limb lesions simultaneously and are therefore considered inoperable [1]. According to the literature, a 50% complete response rate can be obtained with ILP [2]. Nevertheless complete response can be difficult to assess if post-necrotic persisting pigmented

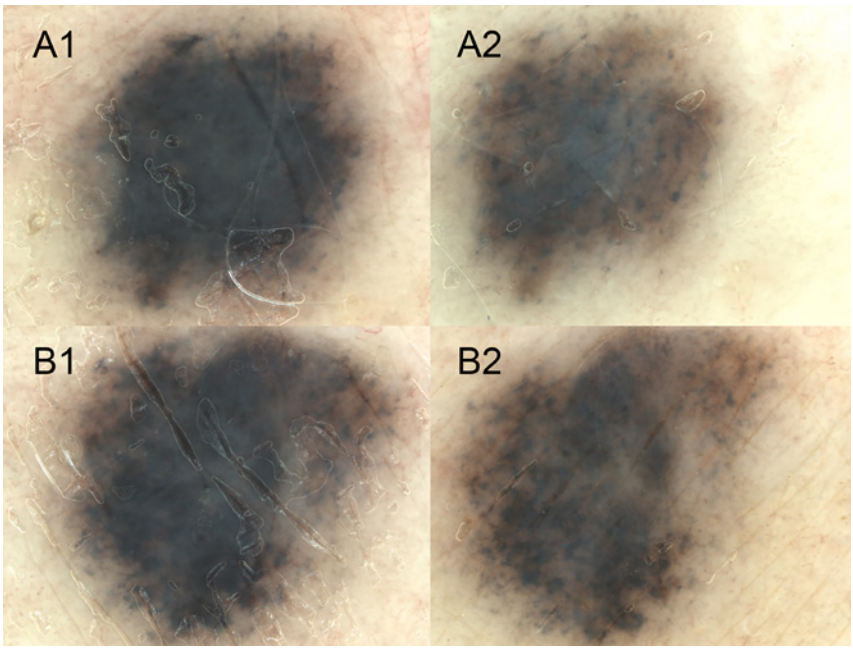

Figure 4. Examples of dermoscopy follow-up of pigmented macules after ILP (A1, B1) and one year later (A2, B2). Note the gradual pigment resorption. [Copyright: ©2017 Merat et al.]

lesions occur, especially if numerous and unresectable. These residual lesions occur mainly in the more superficial and pigmented types of metastatic disease. As it was the case with our patient, these lesions can often correspond to the residual melanophage granuloma (nodular melanosis) that persists after tumor tissues undergo complete necrosis and can be difficult to distinguish from partial response and persisting in-transit metastasis. RCM is a non-invasive technique that allows the exploration of the superficial dermis. Confocal-histopathological correlation has been shown to be possible for the visualization of some histologic features in the superficial dermis up to 300um deep [3-6] where, in the case of superficial in-transit metastasis, post-necrotic residual melanophage granuloma (nodular melanosis) might be localized. Morphologic features of melanophages under in vivo RCM have been well characterized, allowing their distinction from melanocytes [7,8]. Here, using combined RCM and histological examination of two sample lesions, numerous unresectable post-ILP limb residual pigmented lesions were considered by RCM to be non-active as confirmed by the subsequent dermoscopy follow-up. Although in the case presented here there was not any doubt at follow-up regarding the absence of residual disease, considering that the deeper reticular dermis cannot be explored with RCM, biopsy remains mandatory in case of doubt during the subsequent needed close follow-up.

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