LETTER TO THE EDITOR

Dermal fillers may induce late-onset adverse skin reactions in patients under BRAF inhibitors

Dear Editor,

Histiocytoses are disorders characterized by inflammation and the accumulation of cells derived from the monocyte and macrophage lineages, which results in tissue damage. Considerable advances in the understanding of their genetics have led to an increased clinical recognition of these conditions and fuelled further insights into their pathogenesis.[1] Almost 70% of patients affected by Erdheim–Chester disease (ECD), a rare non-Langerhans cell histiocytosis, have the somatic V600E mutation of the *BRAF* gene.[2] *BRAF* and MEK inhibitors can be efficacious for treating ECD, particularly in cases of life-threatening manifestations.[3] Granulomatous eruptions have been described during targeted therapies for cancers, although they are rather infrequent than with immune checkpoint inhibitors.[4] We report the case of a woman in her 80s with ECD and *BRAF* V600E mutation, who developed simultaneously cutaneous sarcoid-like lesions as well as foreign body granulomas in the lips after 8 months on dabrafenib treatment.

She presented with marked induration of oral lips (Fig. 1a) that significantly disrupted her regular speaking and breathing. On physical examination, three pink soft nodules were also found on her arms (Fig. 2a) and abdominal area.

High-resolution ultrasonography of lip induration demonstrated hyperechoic deposits with a 'snowstorm' pattern (Fig. 1b,c). Although she denied any previous aesthetical treatment of the lips, a biopsy was taken, showing foreign body granulomas due to silicone (Fig. 1d). With this result, the patient's daughter finally admitted having been injected this material 20 years ago. A skin biopsy showed non-necrotizing granulomatous dermatitis as well (Fig. 2b). Extracutaneous involvement was ruled out, and prednisone was started at 30 mg per day for 1 month, with mild improvement only on the skin lesions. Finally, dabrafenib was discontinued with cutaneous lesions resolution and progressively improvement of lip infiltration.

Sarcoidosis-like lesions are referred to those that not fulfil the typical sarcoidosis criteria. Although the development of sarcoidosis-like lesions seems to be a paradoxical adverse event of BRAF/MEK inhibitors, recent data confirm their immunomodulatory effect.[5] Three reported cases of sarcoidosis occurring during BRAF-inhibitor treatment for ECD have demonstrated an original intracellular mechanism of granuloma formation linked to paradoxical ERK expression.[2]

Contrary to Amoura *et al.*,[2] median duration of BRAF inhibition treatment before occurrence of sarcoidosis-like lesions was 8 months. As reported in the literature, cutaneous manifestations of sarcoidosis were also predominant in our patient. Although spontaneous resolution of the lesions has been reported, potent topical or systemic steroids, when severe systemic involvement, are the main treatment.[5,6] Foreign body granulomas may occur decades after the injection of silicone fluids, with a reported incidence of 0.1–1%.[7] Intralesional corticosteroid injections are the primary treatment. Systemic therapy can be used for recalcitrant foreign granulomas. Surgery is not a first choice therapy because the difficulty of removal all the granulomas.[8] In our patient, foreign body granulomas partially resolved after systemic corticosteroids and dabrafenib stopped, while cutaneous granulomas completely resolved. Ultrasound

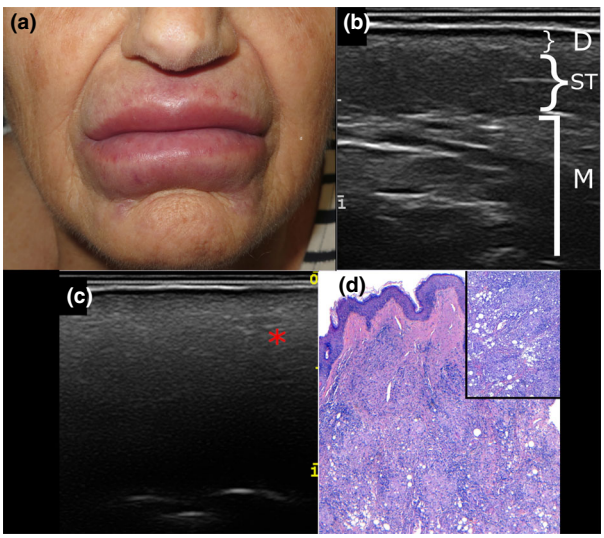

Figure 1 (a) Oedema and induration of lips due to foreign body granulomas formation after BRAF inhibition treatment. (b) High-frequency ultrasound image of normal skin layers and deeper structures. D, dermis; M, muscle; ST subcutaneous tissue. (c) High-frequency ultrasound image of silicone oil injection (longitudinal view). Hyperechoic deposits (*) with a 'snowstorm' pattern affecting the supra-labial skin. (d) Granulomatous reaction affecting the whole dermis and hypodermis (100× magnification). Prominent vacuolated histiocytes and giant multinucleated foreign body type cells (200× magnification).

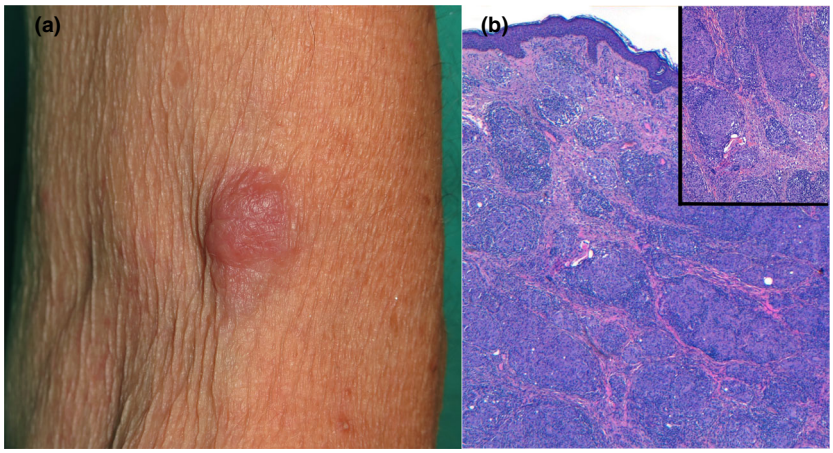

Figure 2 (a) Sarcoidosis-like nodule on the right arm. (b) Multiple granulomas consisting of epithelioid histiocytes with scarce lymphoid crown (100× magnification) and some giant multinucleated cells (200× magnification).

may be helpful not only in diagnosis but also in treatment monitoring.

Finally, it seems that the development of granulomatous/sarcoidosis-like lesions associated with BRAF/MEK inhibitors, as well as immune checkpoint inhibitors, could be associated with favourable therapeutic response in a subset of patients.[9–11]

To the best of our knowledge, this is the first case of foreign body granulomas formation during BRAF inhibitors. Present patient had received IFN-alpha several years earlier, with no sarcoid reaction. We hypothesize an immune-modulator role of BRAF inhibitor in addition to silicone as trigger. Beyond immunotherapy, physicians should be aware of this late-onset granulomatous complication in patients during BRAF inhibitors treatment.

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