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Letter to the editor

Abrupt development of Dupuytren's contractures with the BRAF inhibitor vemurafenib

ARTICLE INFO

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Vemurafenib, a serine-threonine kinase inhibitor, has recently been approved for the treatment of patients with metastatic melanoma harbouring a BRAF V600E mutation. While vemurafenib significantly improves overall survival of treated patients [1], it frequently induces skin toxicity, which affects more than 90% of patients [2]. It primarily involves phototoxicity, maculopapular rashes, the development of verrucal papillomas, squamous cell carcinomas, hand-foot syndrome and even *de novo* melanomas [2–4]. Rheumatological adverse events are also common, primarily in the form of inflammatory arthralgia, which is identified in 50% of cases, of grade 2 or 3 in more than 20% of cases [1]. We describe here the abrupt onset of Dupuytren's contractures after introduction of vemurafenib. This adverse event has never previously been reported.

A 66-year-old male patient was managed for melanoma with unresectable metastatic cervical lymph nodes. Lymph node metastases carried a V600E mutation and vemurafenib was started (Zelboraf®, 960 mg, twice daily orally). After 6 weeks of treatment, the patient noted the rapidly progressive development of fixed digital flexion contractures affecting the metacarpophalangeal joints of the small and ring fingers, with visible cords adhering to the skin (Fig. 1). The impairment was bilateral but asymmetrical. The diagnosis of Dupuytren's contractures was adopted, with a Tubiana score of 10 (left) and 7 (right), respectively. No associated nodules were identified and knuckle pads and Garrod's nodes as well as Ledderhose disease were not found either. The lesions rapidly worsened, considerably affecting certain activities of daily living. It was then decided to definitively discontinue the treatment. Three months later, the digital cords remained globally stable without worsening or improving (Fig. 2a and b).

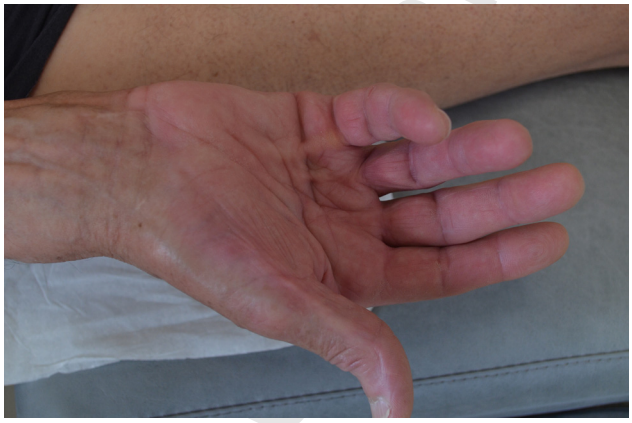

Fig. 1. Visible cords after 6 weeks of treatment.

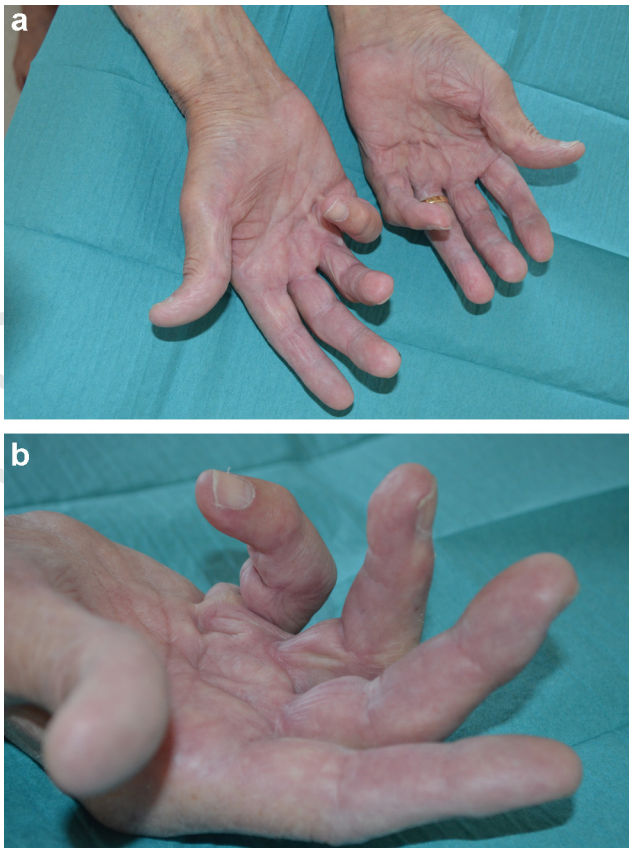

Fig. 2. a, b Persistent fixed digital flexions.

Dupuytren's disease usually occurs in isolation but can sometimes be associated with several risk factors, including genetic predisposition, diabetes, smoking, alcohol consumption, HIV infection, use of anticonvulsant drugs, and exposure to recurrent trauma [5–7]. It has also been very exceptionally reported in patients treated for advanced cancer with matrix metalloproteinase inhibitors [8]. Although Dupuytren's disease is more prevalent in Caucasian males over the age of 60 years [5,7], its onset in our patient seems to be no coincidence here. First, the patient displayed none of the known associated factors described above. Most

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importantly, the lesions developed very rapidly after the introduction of vemurafenib and became clearly symptomatic within just a few weeks, not following the conventional, slow, three-stage progression of Dupuytren's disease [5–7]. Lastly, a link between the development of Dupuytren's contractures and the use of BRAF inhibitor has been suggested very recently in a patient enrolled in a clinical trial [9]. The pathophysiology of Dupuytren's disease is still poorly understood and the cause of myofibroblast proliferation is a matter of speculation [5,6]. We can here hypothesize that vemurafenib induces a paradoxical proliferation in wild type-BRAF myofibroblasts, similar to the mechanism previously described in keratinocytes and melanocytes devoid of a BRAF mutation, leading to the development of skin tumours in treated patients [2–4].

Finally, we can suggest in this context that a local management with fasciotomy should be more appropriate than aponeurectomy [10].

Addendum: this adverse event has been reported to both Centre régional de pharmacovigilance and Pharmacovigilance department of Roche® (Ref AG/VY-LRN 2130961), and subsequently to the French Health Authorities.

Disclosure of interest

The authors have not supplied their declaration of conflict of interest. Q2

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