SHORT REPORT

Vemurafenib-associated Dupuytren- and Ledderhose palmoplantar fibromatosis in metastatic melanoma patients

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Abstract

Background The BRAF-inhibitor vemurafenib, used in patients with metastatic melanoma, induces multiple cutaneous side-effects.

Objective The aim of this work was to evaluate the development of palmoplantar fibromatosis in a population of patients treated with the BRAF inhibitor vemurafenib.

Methods Between April 2011 and February 2013, we initiated a treatment with vemurafenib in 53 patients with an unresectable stage IIIC or stage IV melanoma. The patients were followed-up on a regular base to monitor possible side-effects.

Results A plantar or palmar fibromatosis was observed in five of 53 patients treated with vemurafenib. In four of these patients other risk factors for the development of palmoplantar fibromatosis were absent.

Conclusion The BRAF-inhibitor vemurafenib might induce palmoplantar fibromatosis.

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Conflict of Interest

None declared.

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Introduction

Vemurafenib was the first BRAF-inhibitor offering an improvement in overall survival compared to dacarbazine chemotherapy in patients with metastatic melanoma harbouring a BRAF V600 codon mutation. Besides liver toxicity and arthralgia, vemurafenib is associated with cutaneous side-effects, including photosensitivity to UVA-light and skin tumours of squamous-cell origin (e.g. papilloma, keratoacanthoma, squamous-cell carcinoma).

Dupuytren's and Ledderhose's disease are fibromatoses, characterized by non-malignant proliferation of fibroblasts, with palmar or plantar thickening of the deep connective tissues (including fasciae). Clinical signs are firm nodules or cords on the palmar and/or plantar tendons that can cause impaired functionality of hands or feet. Well-established risk factors for fibromatoses are genetic predispositions involving intra-cellular signalling pathways (e.g. TGFβ[1] and Wnt-pathway[2]) or upstream regulating factors (e.g. Kruppel-like factor Zf9[3]), male gender, older age, diabetes mellitus, smoking, alcohol intake, frozen shoulder, trauma and exposure to vibration. While anticonvulsant drugs have been reported as potential elicitors numerous times, BRAF-inhibition has so far only once been suspected as a causal factor for the development of Dupuytrens disease.[4] When we search the Pubmed database for an association between metastatic melanoma and fibromatosis, none can be found.

Case reports

Between April 2011 and February 2013, vemurafenib treatment was initiated in 53 patients with an unresectable stage IIIC or stage IV V600-mutant melanoma. The median age of our population was 46 years (range 21–79 years), 24 were male and 29 were female patients. Within four to 17 months of vemurafenib treatment, five patients [three female and two male patients with a median age of 59 years (range 46–79 years)] developed palmar, plantar or palmoplantar fibromatosis, which are the first case-series of palmoplantar fibromatosis reported in patients treated with vemurafenib (Table 1).

Case 1

In April 2012, a 46-year old female with cutaneous and peri-renal lymph node melanoma metastases, obtained a complete remission after 2 months of vemurafenib treatment. In June 2012 she presented with a painless, firm nodule on the left planta (Fig. 1a). Excision biopsy of the nodule was performed to rule out melanoma metastasis. Histopathology showed proliferation of fusiform fibroblasts without mitotic activity on a background of collagen fibres (Fig. 1b). Immunohistochemistry for the melanocyte marker Melan-A was negative. Based on these findings, morbus Ledderhose was diagnosed. A conservative approach with orthopaedic insoles was adopted. After 16 months of treatment, the patient developed a corresponding nodule on the right planta. Following 25 months of uninterrupted vemurafenib treatment, trametinib (a small molecule MEK-inhibitor) was added to the treatment. Partial regression of the nodular fibromatosis of both soles was observed. After 3 years of uninterrupted BRAF-inhibitor therapy, treatment was stopped. At the latest follow-up in December 2014, complete remission of the melanoma was confirmed on PET-CT. The remaining nodular fibromatosis persisted.

Case 2

A 68-year-old female patient with lymph node, pulmonary, and omental melanoma metastases presented with morbus Ledderhose on the planta after 10 months of vemurafenib treatment. As the clinical presentation was typical, the nodule was not excised. Subsequently she developed a nodular fibromatosis of the hand, without flexion deformity or functional impairment (Tubiana score = 3 according to the Revised Tubiana Staging system[5]). There was no further evolution of her condition up to the time when vemurafenib treatment was stopped because of disease progression. The nodule-size decreased after stopping treatment.

Case 3

A 59-year-old male with unresectable lymph node metastases obtained a partial response after 2 months of vemurafenib treatment. Because of photosensitivity, treatment was switched to the

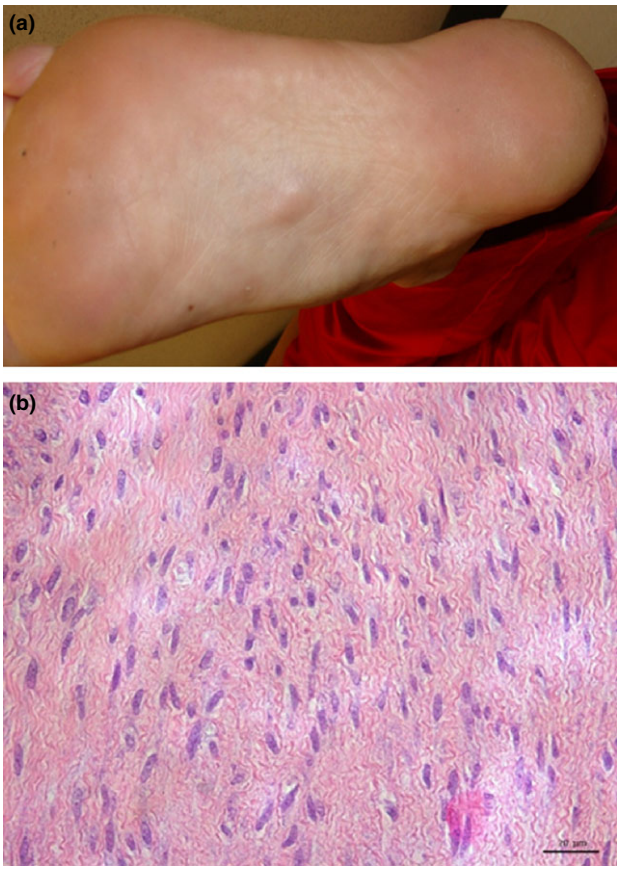

Figure 1 (a) Clinical presentation of plantar fibromatosis. (b) 40× enhancement of histopathology findings in plantar fibromatosis: fusiform fibroblasts without mitotic activity on a background of collagen fibres.

Table 1 Characteristics of the five patients who developed a fibromatosis during vemurafenib treatment

Patient	Age (years)	Gender	Type of fibromatosis	Occurence of fibromatosis after start therapy (months)	Evolution of fibromatosis after interuption of therapy
1	46	Female	Plantar	4	Regression
2	68	Female	Palmoplantar	10	Regression
3	59	Male	Palmar	Data missing†	Persistence
4	79	Male	Palmar	6	Persistence
5	55	Female	Palmar	17	Regression

†The patient could not recall exactly when the lesions occurred, after starting vemurafenib.

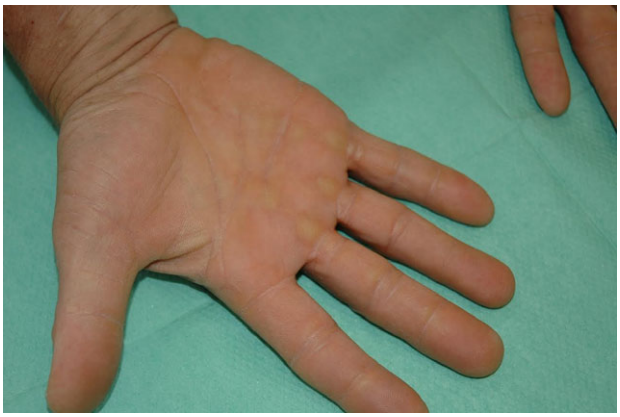

Figure 2 Clinical presentation of palmar fibromatosis.

BRAF-inhibitor dabrafenib. The patient recalled the appearance of painless nodules on the flexor tendons of both palms (Tubiana score = 4) shortly after the initiation of vemurafenib, persisting under dabrafenib-treatment (Fig. 2). This patient had a positive family history of Dupuytren's disease and did manual labour. Dupuytren's disease was unchanged 11 months after the end of vemurafenib treatment.

Case 4

A 79-year-old male with pulmonary and liver metastases obtained a partial response 2 months after initiation of vemurafenib treatment. Six months later, bilateral nodular palmar fibromatosis (Tubiana score = 4) was noticed. Family history or predisposing factors for Dupuytren's disease was negative. Vemurafenib was stopped due to progressive disease and the patient died briefly after.

Case 5

A 55-years old female with skin, lymph node, pulmonary and liver metastases, developed M. Dupuytren on her right hand (Tubiana score = 2) 17 months after initiation of vemurafenib. Again, no risk factors were present. The size of her fibromatosis decreased after interrupting the treatment.

Discussion

In our patient population, palmoplantar fibromatoses occurred in five of 53 (9.4%) patients who were treated with vemurafenib. The occurrence of the fibromatosis during vemurafenib treatment is highly suggestive for a causal link. In addition, there was the absence of known risk factors in four patients.

Vemurafenib inhibits the MAPK-pathway via BRAF in melanoma cells. However, it is not known to interact directly on the TGFβ or Wnt-pathways, or on transcription factor Zf9, (associated with Dupuytren's and Ledderhose's disease). In contrast, BRAF-inhibition induces a paradoxical activation of the MAPK-pathway in BRAF wild type cells, including fibroblasts (the originators of fibromatoses). Paradoxical MAPK-pathway activation in cells with activating mutations in other components of the MAPK-pathway (such as RAS-proteins) can induce cellular proliferation and increased survival, causing growth of squamous skin tumours.[6]

We suspect that paradoxical activation of the MAPK-pathway, potentially in combination with genetic predisposition, is responsible for the development of palmoplantar nodular fibromatosis under anti-BRAF-treatment.

Of note is the observation that the combination of a BRAF and MEK-inhibitor, which is a downstream inhibitor of the MAPK-pathway, (e.g. vemurafenib and cobimetinib) is less associated with hyperproliferative cutaneous adverse events.[7] So far, we have not diagnosed any case of fibromatosis in any of our patients treated upfront with BRAF plus MEK-inhibitor combination therapy.

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