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Clinical observation of panniculitis in two patients with BRAF-mutated metastatic melanoma treated with a combination of a BRAF inhibitor and a MEK inhibitor

Background: Treatment with selective BRAF or MEK inhibitors is frequently associated with cutaneous toxicities, including squamous cell carcinoma (SCC), papillomas and rash. These cutaneous adverse effects are typically observed at a lower incidence during combined BRAF and MEK inhibitor therapy. *Patients and Methods:* Two male patients with stage IV metastatic BRAF-mutated melanoma were treated with a combination of a selective BRAF inhibitor and a selective MEK inhibitor (dabrafenib and trametinib, or encorafenib (LGX818) and binimetinib (MEK162)) within two different clinical trials. Ten and 150 days after treatment start respectively, the patients developed painful nodules on the legs. In addition, one patient developed symmetrical articulation pain and intermittent fever episodes. *Results:* Based on the clinical and histological presentation, erythema nodosum-like panniculitis was diagnosed in both cases. No other aetiology could be found. After receiving topical or oral steroid treatment and anti-inflammatory analgesics, the painful nodular lesions disappeared several weeks later. In one case, a rebound of the painful nodules was observed when the combination treatment (dabrafenib and trametinib) was resumed after a 1-week unscheduled treatment interruption. *Conclusions:* Panniculitis has previously been described in association with BRAF inhibitor treatment, but not MEK inhibitor treatment. Combination treatment is usually associated with a lower incidence of cutaneous adverse events (AEs), as compared to monotherapy. Panniculitis was observed in two patients during combined BRAF and MEK inhibitor treatment. These cases illustrate the need for further research in a larger patient population to identify a possible link between combined BRAF and MEK inhibitor treatment and the incidence of panniculitis.

Key words: melanoma, targeted therapy, BRAF inhibition, MEK inhibition, panniculitis, adverse event

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The effective treatment of patients with advanced melanoma has changed in the past decade due to advances in understanding the signalling pathways and genetic alterations involved in the pathogenesis and progression of melanoma. The discovery that melanoma has a high frequency of activating mutations in genes of the RAS/RAF/MEK/ERK pathway such as BRAF (~50% of melanomas) [1] and NRAS (~15-20% of melanomas) [2] and kinase inhibitors that target this pathway has led to a complete paradigm shift in melanoma therapy [3]. Several selective BRAF and MEK inhibitors have been investigated as monotherapy in clinical trials, demonstrating improvement in overall survival in patients with advanced BRAF-mutated melanoma [4-7]. Vemurafenib (ZELBORAF, Genentech/Roche, San Francisco, CA) and dabrafenib (TAFINLAR, GlaxoSmithKline, LLC) were the first FDA-approved BRAF inhibitors and trametinib (MEKINIST, GlaxoSmithKline, LLC) was the first FDA-approved MEK inhibitor for the treatment of unresectable or metastatic BRAFV600E/K–mutated melanoma.

Combination treatment of BRAF-mutated melanoma with BRAF or MEK inhibitors has shown to be more efficient than monotherapy [8-10]. Moreover, combination of selective BRAF and MEK inhibitors is a strategy to delay the development of resistance [11-14]. Dabrafenib in combination with trametinib, as well as vemurafenib combined with the selective MEK inhibitor cobimetinib, demonstrated improved overall survival and progression free survival as compared to selective BRAF inhibitor vemurafenib monotherapy [8, 9]. Based on these data, the FDA granted accelerated approval to this combination (dabrafenib/trametinib) to treat patients with advanced unresectable or metastatic BRAFV600E/K–mutant melanoma in January 2014.

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Skin toxicities such as skin papillomas, hand-foot skin reaction, keratosis pilaris-like rash, acantholytic dyskeratosis and cysts of the milia type are common adverse effects which are well described with BRAF inhibitor monotherapy treatment [15-17]. With selective MEK inhibitor treatment, skin toxicities such as papulopustular rash, xerosis, paronychia and fissured fingertips, as well as reduced pigmentation of hair and skin, have been reported [18]. Interestingly, the combination of BRAF and MEK inhibitors is usually associated with fewer skin-related adverse events, as compared to monotherapy [19, 20].

Panniculitis is a subcutaneous inflammation of the adipose tissue that has been described in association with BRAF-inhibitor monotherapy treatment, including both vemurafenib and dabrafenib [21-28]. It has not previously been described with MEK inhibitor treatment. Herein, two cases of panniculitis observed in male patients with metastatic BRAFV600E–mutated melanoma who received combined targeted therapy with a BRAF inhibitor and a MEK inhibitor are described.

Case 1

A 44-year-old male patient with metastatic BRAFV600E-mutated melanoma was treated with a combination of the selective BRAF inhibitor dabrafenib (75 mg BID) and the selective MEK inhibitor trametinib (2 mg QD) in a phase III clinical trial (NCT01597908). Ten days after the treatment started, the patient developed pressure sensitive nodules on the front sides of the legs *(figure 1)*.

Histology *(figure 2)* showed a mostly septal panniculitis with a widening of the fibrous septae of the subcutis and an inflammatory infiltrate dominated by lymphocytes and histiocytes with an admixture of some neutrophilic granulocytes.

The painful nodules disappeared within a few weeks when the patient was treated with a non-steroidal anti-inflammatory drug (NSAID) (mefenamic acid, 500 mg TID) and a topical steroid (betamethasone valerate). Medical history for other common causes of erythema nodosum-like panniculitis, such as infections, other drugs, sarcoidosis, enteropathies, Behçet syndrome or Sweet's syndrome, was negative. Four months later, after an unplanned 1-week treatment interruption, the patient developed the same erythema nodosum-like nodules ten days after treatment was restarted. The nodules resolved upon the same treatment with NSAID and a topical steroid. Since that time, the patient has been kept on treatment and has been asymptomatic without any new appearance of the painful nodules.

Case 2

A 43-year-old male patient with BRAFV600E-mutated metastatic melanoma was treated with a combination of the selective BRAF inhibitor encorafenib (LGX818, 450 mg QD) and the selective MEK inhibitor binimetinib (MEK162; 45 mg BID) in a phase Ib/II clinical trial (NCT01543698). After five months of treatment, the patient developed pressure sensitive nodules on the front of both legs and reported concomitant symmetric pain in ankle, knee and shoulder articulations, as well as intermittent fever episodes. Clinically, the lesions were consistent with an erythema nodosum–like panniculitis.

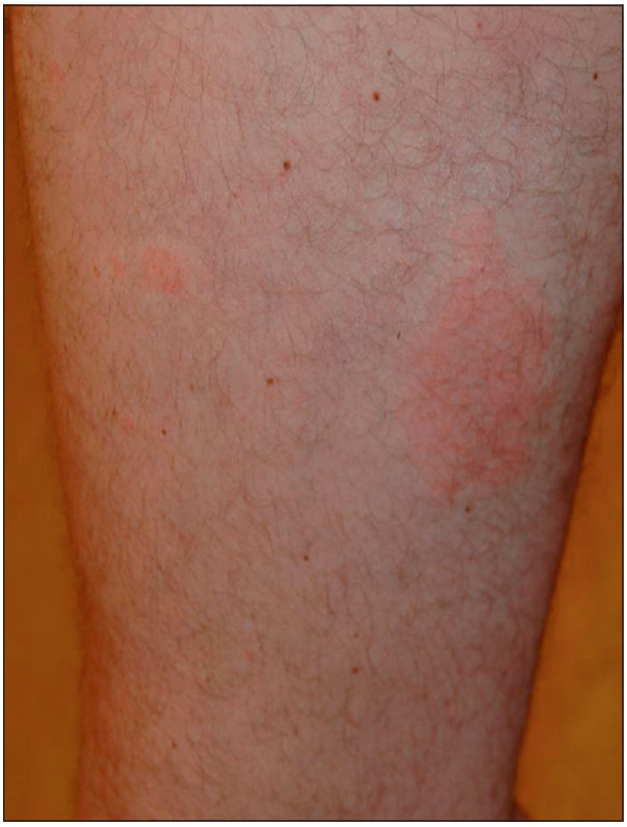

Figure 1. A pressure sensitive nodule on the front of the legs of a 44-year-old male patient.

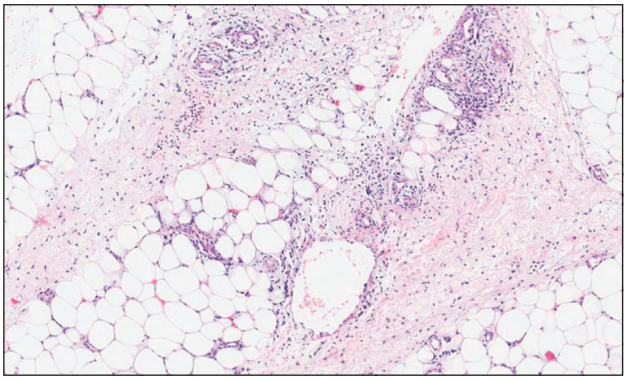

Figure 2. In the histology, a mostly septal panniculitis was identified with a mixture of some neutrophilic granulocytes.

Histology yielded a mostly septal panniculitis with a pronounced infiltration of the fibrous septae by lymphocytes and neutrophilic granulocytes. Several laboratory tests were performed, including antinuclear antibody titer, antistreptolysin titer, angiotensin-converting enzyme levels, rheumatoid factor, antibodies to neutrophil cytoplasmic antigens (ANCA), neupterin concentration and a quantiferon test. With the exception of a discrete elevation of the antistreptolysin titer without history of infection, all results were in the normal ranges.

Treatment with NSAIDs (mefenamic acid, 500 mg TID), topical and oral steroids (betamethasone valerate and 20 mg prednisone QD) was started and symptoms and lesions disappeared within one day. The patient remained on the combination treatment and has since been asymptomatic.

Discussion

Both patients developed painful erythematous nodular lesions while receiving combined BRAF inhibitor and MEK inhibitor treatment. Medical history and laboratory investigations did not detect any other cause for the development of these erythema nodosum-like panniculitis. These cases suggest some component of the combination treatment to be the cause for these painful nodular lesions.

BRAF and MEK inhibitors cause a specific spectrum of skin adverse reactions. Panniculitis is an adverse event previously reported in patients receiving either vemurafenib or dabrafenib monotherapy treatment [21-28]. The first case was reported by Zimmer, *et al*. in 2012 [21]. Further cases have since been reported [22-28]. The interval between the start of treatment and the appearance of panniculitis seems to vary from case to case and from treatment to treatment. So far, no panniculitis case has been reported under the treatment with selective MEK inhibitors. By contrast, very recently 3 cases during combined treatment have been described [29]. In most cases, all symptoms disappeared after several days with NSAIDs and topical or oral steroid treatment [21-28]. We report here two patients who developed panniculitis during combined treatment with a BRAF inhibitor and a MEK inhibitor. Histology showed a mostly septal panniculitis. This is in contrast to previously reported cases, where mainly lobular neutrophilic panniculitis were observed [21-28].

Skin adverse effects are typically observed less frequently in patients receiving combined BRAF and MEK inhibitor treatment than those receiving monotherapy, as evidenced from clinical practice and previous reports [19]. The rationale for the possible suppression effect has previously been described [30]. BRAF inhibition promotes cell proliferation via activation of the RAS/RAF/MEK/ERK pathway, with dimerization of BRAF and CRAF. As a consequence, this leads to a higher incidence of non-melanoma and melanoma tumours. On the other hand, the inhibition of MEK decreases Notch-I expression by blocking the epidermal growth factor receptor (EGFR) in the basal keratinocytes, which results in reduced proliferation. Therefore, the combination of BRAF and MEK inhibitors seems to reduce the paradoxical proliferative effect known with BRAF inhibition.

In conclusion, panniculitis is a newly described adverse effect observed with combined BRAF and MEK inhibitor treatment. Further research and clinical observations in a larger patient population are necessary to define the frequency of panniculitis and the exact mode of action. ■

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