

ONLINE FIRST

Panniculitis With Arthralgia in Patients With Melanoma Treated With Selective BRAF Inhibitors and Its Management

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Background: Painful lobular panniculitis appears to be a novel cutaneous adverse effect of selective BRAF inhibitors.

Observation: We report the clinical course and management in 2 women with metastatic melanomas harboring the *BRAF*^{V600E} mutation, who developed panniculitis with arthralgia during therapy with selective oral BRAF inhibitors. Panniculitis with arthralgia was the acute presenting adverse effect in both patients. Painful, red, nodular lesions were located on the upper and lower extremities. Biopsy specimens of the nodules showed a mild, predominantly lobular neutrophilic panniculitis. Analgesic and anti-inflammatory treatment improved pan-

niculitis and arthralgia in both cases. It was also necessary to reduce the BRAF inhibitor dose in 1 patient.

Conclusions: During therapy with selective BRAF inhibitors, panniculitis with arthralgia represents a new adverse effect that can require dose reduction. In case of this adverse effect, treatment with nonsteroidal anti-inflammatory drugs, such as etoricoxib, should be initiated early to keep patients on treatment and to avoid drug discontinuation and tumor progression.

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THE IDENTIFICATION OF *BRAF* point mutations in tumors and cell lines was first reported by Davies et al¹ in 2002. *BRAF* mutations occur in 40% to 60% of melanomas.² Particularly, melanomas developing in intermittently sun-exposed sites without chronic sun damage³ and melanomas in younger patients (age, 20-40 years)⁴ exhibit *BRAF* mutations. *BRAF* mutations have also been reported in 40% to 70% of papillary thyroid carcinomas, 5% to 20% of colorectal carcinomas, 10% to 20% of cholangiosarcomas, and 1% to 5% of lung cancers.⁵ The most common *BRAF* mutation results in a substitution of glutamic acid for valine at position 600 of the amino acid sequence.¹ To date, treatment of metastatic melanomas harboring *BRAF* mutations with the selective BRAF inhibitors (class I RAF inhibitors)⁶ vemurafenib or dabrafenib (GSK2118436) have resulted in response rates of 50% to 80% across clinical trials.⁷⁻¹⁰

In the present study, we describe 2 patients who developed a painful lobular panniculitis with arthralgia during therapy with 2 different selective *BRAF* inhibitors.

REPORT OF CASES

CASE 1

A 44-year-old woman initially presented in March 2006 with left axillary lymph node metastases consistent with a melanoma (unknown primary tumor). All left axillary lymph nodes were surgically removed, and 13 of 23 excised lymph nodes showed malignant infiltration leading to adjuvant treatment with high-dose interferon from May 2005 to May 2007. Three years later, a further metastatic lymph node was excised from the left periclavicular region, and intraoperative irradiation was performed. By re-examination in August 2010, the tumor had progressed to stage IV, and metastases were detected in lymph nodes of the cervical and supraclavicular regions, the lung, mesenteries, and bone. A molecular analysis of the periclavicular lymph node metastasis showed a *BRAF*^{V600E} mutation, making the patient eligible for a targeted therapy with an oral class I RAF inhibitor. The patient received 960 mg of a class I RAF inhibitor twice daily within a phase 3 randomized clinical trial.

The patient rapidly developed painful subcutaneous monomorphic 1- to 2-cm

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nodules 16 days after treatment initiation (**Figure 1**). The nodules were predominantly located on the upper

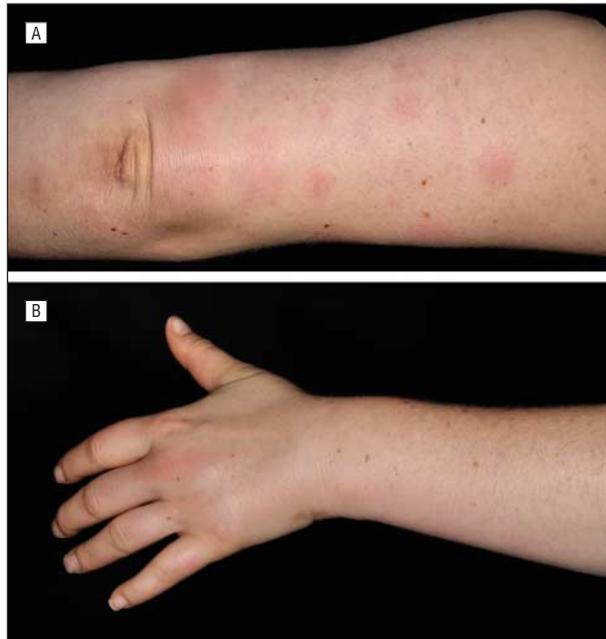


Figure 1. Dermatological adverse effects in patient 1. A, Erythematous to livid subcutaneous nodules on the upper arm. B, Symmetrical swelling of the small hand joints with accompanying arthralgia.

and lower extremities and the gluteal area (Figure 1A). In addition, the patient reported symmetrical swelling of several joints with accompanying arthralgia limiting her daily activities (Figure 1B). Small joints, especially of the hands, as well as the elbows and knees were affected. C-reactive protein level was elevated in the serum at 150 mg/L (upper institutional norm [UIN] <5 mg/L) (to convert to nanomoles per liter, multiply by 9.524). Anti-nuclear antibody titer was also mildly elevated (1:160; UIN <1:80). Titers for antibodies against histones or DNA and antineutrophilic cytoplasmic antibodies were within the normal range, as were concentrations of complement components 3 and 4, anticyclic citrullinated peptide, and rheumatoid factor. A biopsy of one of the painful nodules showed a mild, predominantly lobular neutrophilic panniculitis with vasculitis of small vessels (**Figure 2**). Findings from melan-A staining of adipose tissue were negative. Positron emission tomography/computed tomography (PET-CT) was performed 20 days after treatment initiation and revealed tumor regression and nearly complete loss of ^{18}F -2-fluoro-2-deoxy-D-glucose avidity in all tumor lesions compared with PET-CT performed at baseline.

The patient received oral prednisolone (1 mg/kg body weight with an absolute dose of 60 mg daily) for 4 days to treat both panniculitis and arthralgia. She received indomethacin (50 mg, 3 times daily) and dipy-

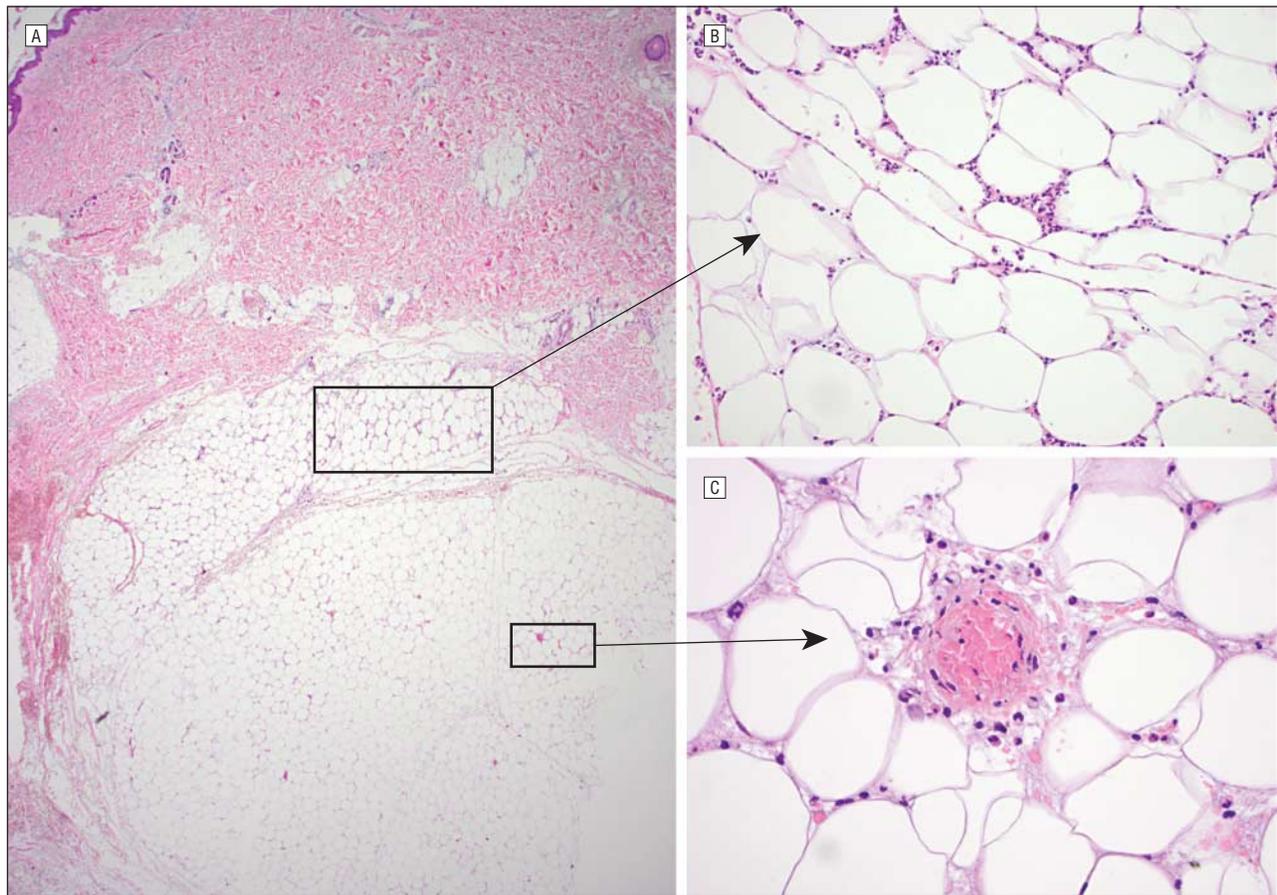


Figure 2. Nodule biopsy specimen stained with hematoxylin-eosin from patient 1. Mild, predominantly lobular neutrophilic panniculitis (A, original magnification $\times 20$; B, original magnification $\times 200$). C, Vasculitis of small vessels: the vessel wall shows fibrinoid necrosis, perivascular infiltrate consists of neutrophils (original magnification $\times 400$).

rone (750 mg, 4 times daily) for pain relief. Treatment with the class I RAF inhibitor was stopped owing to the painful panniculitis and arthralgia, qualifying as grade 3 common toxicity criteria of adverse events (CTCAE; version 4.0 of National Cancer Institute). Arthralgia and joint swelling had improved to grade 1 CTCAE after 11 days, and the subcutaneous nodules had completely regressed. Because the patient had responded impressively to class I RAF inhibitor treatment, treatment was restarted at a 25% dose reduction level (720 mg). Restarting treatment resulted in recurrence of joint pain after 5 days, but not of the subcutaneous nodules. Consequently, analgesic/anti-inflammatory treatment was adjusted to 160-mg tilidine hydrochloride and 8-mg naloxone hydrochloride twice daily, and 30-mg etoricoxib and 20-mg prednisolone daily. Arthralgia was gradually reduced with treatment. Treatments with prednisolone and analgesics were slowly reduced and then stopped on days 28 and 42, respectively, without further recurrence of arthralgia or skin changes.

CASE 2

A 59-year-old woman was diagnosed as having a 1.01-mm plantar melanoma in July 2004. In March 2010, inguinal lymph node metastases were detected, and a complete ilio-inguinal lymph node dissection showed melanoma metastases in 4 of 16 resected lymph nodes. The patient received recombinant MAGE-A3 + AS-15 antigen-specific cancer immunotherapy vs placebo within an adjuvant phase 3 trial (NCT00796445). After 4 months, the disease had progressed to stage IV with pulmonary, hepatic, bone, and further lymph node metastases, and treatment was stopped. Because her tumor exhibited a *BRAF*^{V600E} mutation, the patient was enrolled into a phase 2, single-arm study with another potent class I RAF inhibitor. The patient received class I RAF inhibitor, 150 mg twice daily.

The patient developed painful livid subcutaneous nodules predominantly on the upper and lower extremities 7 weeks after treatment initiation (**Figure 3**). In addition, mild arthralgia of the hands and ankles but no joint swelling was reported. C-reactive protein level was mildly elevated in the serum (46 mg/L). Biopsy of one of the nodules revealed a septolobular panniculitis (**Figure 4**) infiltrated with neutrophils and minor groups of other inflammatory cells and included isolated noncaseating granulomas. Findings from melan-A staining of the nodule biopsy were negative, indicating an absence of cancer cells. Computed tomographic imaging of the chest and abdomen performed 2 weeks after the first occurrence of skin changes revealed a partial response of the tumor lesions to BRAF inhibitor therapy.

Since the first patient responded well to analgesic/anti-inflammatory treatment for the panniculitis with arthralgia, treatment with 30-mg etoricoxib daily was started directly. It was decided that class I RAF inhibitor treatment should be continued at full dosage, since the patient responded well to etoricoxib and was not limited in her daily activities by the panniculitis or the arthralgia, which only reached grade 1 CTCAE. The patient had fully recovered after 4 weeks and experienced no recur-



Figure 3. Dermatological adverse effects in patient 2. Livid, erythematous subcutaneous nodules on the left thigh.

rence of arthralgia or the subcutaneous nodules during continued BRAF inhibitor treatment.

COMMENT

Frequent adverse effects of the class I RAF inhibitors vemurafenib and dabrafenib are arthralgia, fatigue, skin toxic effects, such as cutaneous eruptions, pruritus, alopecia, palmoplantar erythrodysesthesia, and other skin conditions, including cutaneous squamous cell carcinomas, hyperkeratosis, and keratoacanthomas.⁷⁻¹⁰ Photosensitive skin reactions are only reported during systemic therapy with vemurafenib and can be prevented by using sunblock.^{7,8,10} The development of lobular panniculitis as described herein in 2 patients who received 2 different selective oral BRAF inhibitors appears to be a novel cutaneous adverse effect of this class of agents.

To our knowledge, Infante et al¹¹ were the first to report on a patient with recurrent grade 2 CTCAE neutrophilic panniculitis while undergoing treatment with the oral MEK1/2 inhibitor trametinib (GSK1120212) and the oral BRAF inhibitor dabrafenib (GSK2118436) within the ongoing phase 1/2 trial (NCT01072175). Similar to our 2 patients, the patient developed painful, red nodular lesions on the extremities accompanied by a fever and chills. A deep skin punch biopsy showed fibrinoid necrosis with destroyed vessels and a predominant neutrophilic inflammatory response in the subcutaneous tissue.¹¹ We could not identify any other reports on patients with panniculitis or vasculitis during oral therapy with selective BRAF or MEK inhibitors. Inflammatory skin metastases of melanoma that present as panniculitis have been described but

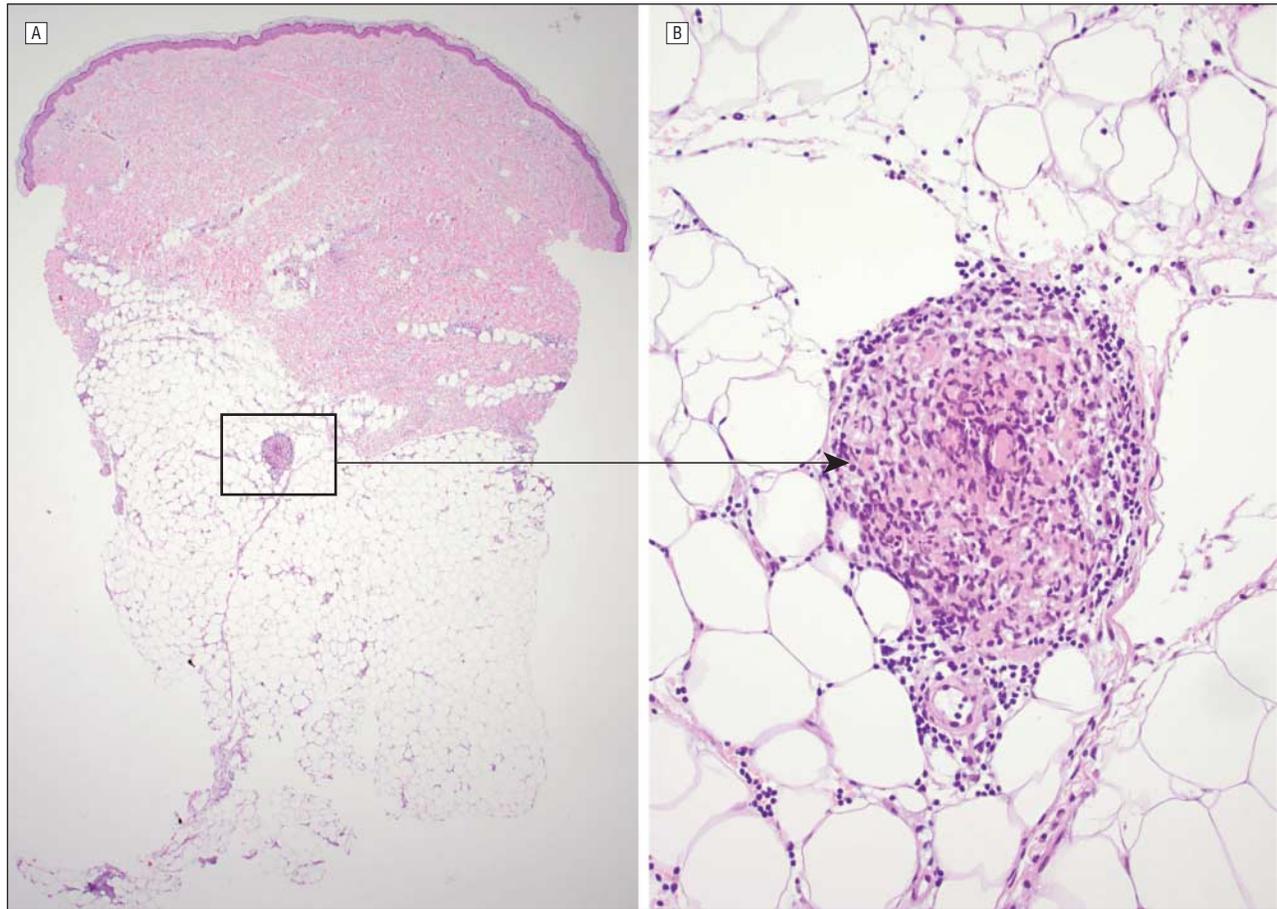


Figure 4. Biopsy of 1 nodule stained with hematoxylin-eosin from patient 2. A, Septolobular panniculitis with a solitary granuloma in the upper adipose tissue (original magnification $\times 20$). B, Noncaseating granuloma (original magnification $\times 200$).

are an exceedingly rare phenomenon. Cotton et al¹² described a patient with an erysipelas melanomatousum that presented as panniculitis, and Piérard¹³ described a patient ultimately diagnosed as having an occult metastatic melanoma, who presented with melanophagic dermatitis and panniculitis. In the 2 cases reported herein, the patients developed painful livid, erythematous subcutaneous nodules with arthralgia predominantly on the upper and lower extremities. Nodule biopsy specimens showed a mild, predominantly lobular neutrophilic panniculitis devoid of melanoma cells (melan-A negative). Superficial and deep dermal blood vessels and lymphatic spaces contained no melanophages or atypical cells, ruling out a recurrence of melanoma.

The mechanism by which BRAF inhibitors cause panniculitis is not yet known. In the case of the patients described herein, it appears to be part of a systemic, noninfectious inflammatory reaction, since patients exhibited signs of systemic inflammation with arthralgia and painful joint swelling that responded well to the nonsteroidal anti-inflammatory drug etoricoxib. Panniculitis developed during combination therapy with the MEK inhibitor trametinib and the selective BRAF inhibitor dabrafenib as well as during monotherapy with selective BRAF inhibitors but not during monotherapy with MEK inhibitors. Thus, panniculitis is more likely to be an adverse effect of the BRAF inhibi-

tors. Based on the cases reported herein, it appears that panniculitis does not belong to the skin toxic effects that are reduced by combined MEK and BRAF inhibitor therapy, such as treatment-related cutaneous eruption and hyperproliferative skin lesions induced by BRAF inhibitors.¹¹

Results of PET-CT tumor imaging performed after the first occurrence of the skin changes showed that the melanomas in both patients responded well to BRAF inhibitor therapy, in line with the excellent clinical response reported for selective BRAF inhibitors, to date.⁷⁻¹⁰ It remains to be determined whether the occurrence of panniculitis during BRAF inhibitor treatment correlates with better treatment response, as is the case for epidermal growth factor receptor inhibitors.¹⁴ During therapy with selective BRAF inhibitors, panniculitis with arthralgia represents an important adverse effect, which can require dose reduction. Treatment with nonsteroidal anti-inflammatory drugs, such as etoricoxib, should be initiated early to keep patients on treatment and to avoid drug discontinuation and tumor progression.

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