

## Severe Cutaneous and Neurologic Toxicity in Melanoma Patients during Vemurafenib Administration Following Anti-PD-1 Therapy

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### Abstract

Immune checkpoint inhibitors such as ipilimumab and targeted BRAF inhibitors have dramatically altered the landscape of melanoma therapeutics over the past few years. Agents targeting the programmed cell death-1/ligand (PD-1/PD-L1) axis are now being developed and seem to be highly active clinically with favorable toxicity profiles. We report on two patients with BRAF V600E-mutant melanoma who were treated with anti-PD-1 agents as first-line therapy without significant toxicity, followed by vemurafenib at disease progression. Both patients developed severe hypersensitivity drug eruptions with multiorgan injury early in their BRAF inhibitor treatment course. One patient subsequently developed acute inflammatory demyelinating polyneuropathy, and the other developed anaphylaxis upon low-dose vemurafenib rechallenge. Further investigation of the immune response during combination or sequences of melanoma therapeutics is warranted. Furthermore, clinicians should maintain a high index of suspicion for these toxicities when vemurafenib is administered following an anti-PD-1 agent. *Cancer Immunol Res*; 1(6); 373–7. ©2013 AACR.

### Introduction

Metastatic melanoma is historically associated with limited treatment options and poor outcomes. In 2011, two agents were approved for the treatment of advanced melanoma. Vemurafenib, a selective BRAF inhibitor, improved overall survival compared with cytotoxic chemotherapy in patients with BRAF V600E-mutant melanoma (1, 2). Ipilimumab, an immune modulator, also demonstrated an overall survival advantage with a minority of patients experiencing durable remissions (3). Additional immune-based therapies are being developed, notably agents targeting the PD-1/PD-L1 axis (programmed cell death-1/ligand), which also unleash suppressed tumor-specific immune responses by blocking a key immune regulatory checkpoint. In early trials, objective response rates ranged from 30% to 50%, many of which seem durable (4, 5). These newer agents are well tolerated although immune-related adverse events including pneumonitis occur infrequently.

Approximately 50% of metastatic melanomas harbor BRAF V600E mutations (6, 7). First-line therapy options for these patients include BRAF inhibitors or immune-based therapies although the optimal sequence has not been defined. As these

treatments are now more widely used, defining efficacy and toxicity profiles for various sequences and even combinations of immune-based and targeted therapies has become essential (8–10). We report on two patients treated with anti-PD-1 agents on clinical trials, who at disease progression were rapidly switched to commercially available vemurafenib and subsequently developed severe systemic toxicities (including cutaneous, neurologic, and allergic) during vemurafenib therapy.

### Case Presentations

#### Case 1

A 62-year-old woman was diagnosed with American Joint Committee on Cancer (AJCC) stage IIIB melanoma on the abdomen in March 2012 (4.65 mm Breslow depth with ulceration; two axillary lymph nodes harbored micrometastases). Molecular testing revealed a BRAF V600E mutation. In July 2012, the patient developed in-transit melanoma on her breast and was briefly treated with imiquimod and "debulking" surgery. Further disease progression ensued and in November 2012 she began anti-PD-1 (nivolumab, NCT00730639) treatment. Complications consisted of a self-limited pruritic rash and hypothyroidism. Subsequent to her final dose, she developed pulmonary and hepatic metastases and enlarging subcutaneous lesions. See Table 1 for timing of therapies.

In January 2013, the patient started vemurafenib treatment. After 7 days, she developed a tender erythematous macular eruption on her back that spread to her chest, extremities, and face; methylprednisolone (40 mg/day) and diphenhydramine were prescribed. The rash worsened over the next week, predominantly on the palms, soles, and face; she developed fever to 101°F, tachycardia, and hypotension. Her trunk, cheeks,

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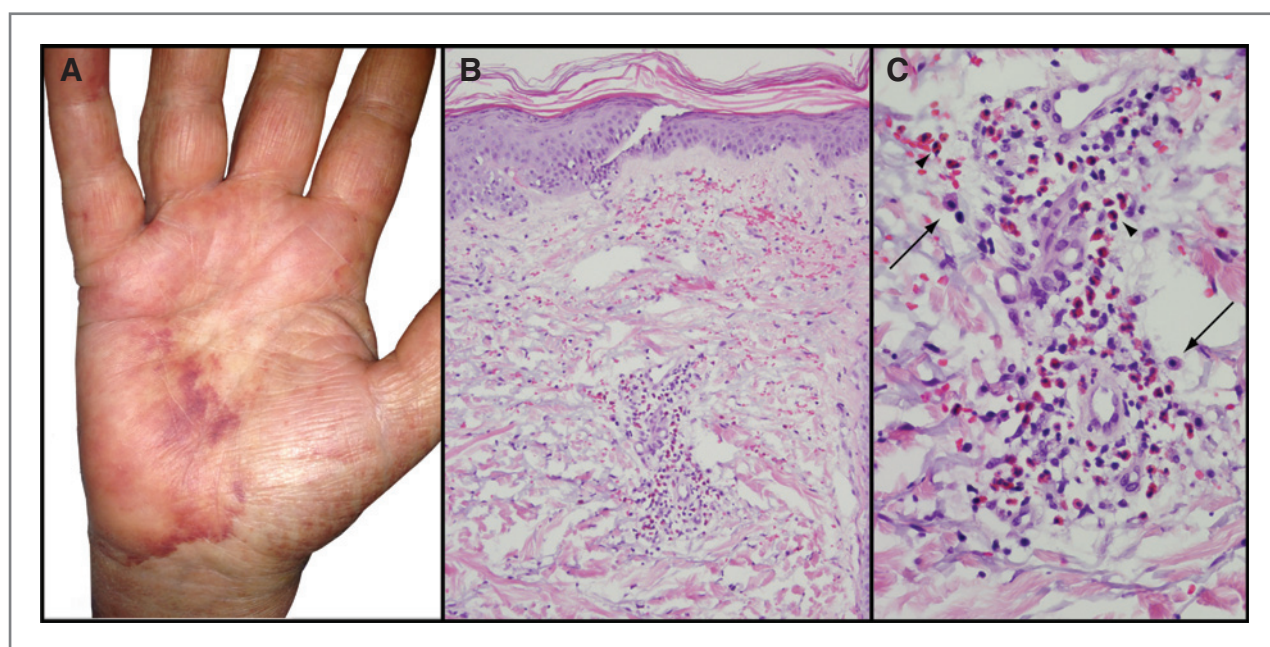
**Table 1.** Therapy timeline and laboratory values

	Patient 1		Patient 2	
Anti-PD-1 therapy	Nivolumab, 3 mg/kg		MK-3475, 2 mg/kg	
Anti-PD-1 treatment dates	November 5, 2012–December 17, 2012		October 12, 2012–December 14, 2012	
Vemurafenib (vem) start date	January 8, 2013		January 22, 2013	
Hospitalization dates	January 21, 2013–January 29, 2013		February 3, 2013–February 7, 2013	
Laboratory values (reference)	Pre-vem	Admission	Pre-vem	Admission
Hemoglobin (11.8–16.0 g/dL)	12.2	9.5 (after IV fluids)	12.6	10.8 (after IV fluids)
Platelets (135,000–371,000/mm <sup>3</sup> )	412	43 (after IV fluids)	240	93 (after IV fluids)
Creatinine (0.7–1.5 g/dL)	0.7	3.70	0.5	2.09
Aspartate aminotransferase (4–40 U/L)	20	200	27	56
Date of subsequent admission	February 4, 2013		March 5, 2013	

and extremities had warm, erythematous, blanching macules coalescing to patches without epidermal involvement. On her palms and feet were tender, violaceous, nonblanching patches with pedal and acral edema (Fig. 1A). She had hemorrhagic crusting on the lips and mild conjunctival injection, but no mucosal involvement, skin fragility, or bullae. Laboratory testing showed anemia, thrombocytopenia, and acute kidney and liver injury (Table 1); no eosinophilia or evidence of hemolysis was present. Skin biopsy showed a dense superficial perivascular lymphocytic infiltrate with numerous eosinophils, occasional mast cells, and no evidence of epidermal necrosis, consistent with a dermal hypersensitivity reaction (Fig. 1B and C). Because of somnolence and fever, cerebrospinal fluid (CSF) analysis was obtained and revealed elevated protein, normal glucose, and 39 nucleated cells (89% lympho-

cytes). CSF cytology, cultures, and viral and rickettsial serologies were negative. Prednisone, 60 mg daily, and broad-spectrum antibiotics were administered. The patient was felt to have a severe hypersensitivity reaction with multiorgan involvement from vemurafenib. Her symptoms and laboratory abnormalities rapidly improved on prednisone, and she was discharged with a prolonged steroid taper; vemurafenib was not restarted.

During the next week, the patient developed progressive and severe bilateral lower-extremity weakness. On examination, she had decreased lower extremity strength (2-3/5 strength with hip and knee flexion bilaterally), absent patellar and ankle reflexes, and decreased vibratory sensation; arm strength was preserved. MRI of the thoracic and lumbar spine did not show spinal cord compression or enhancement. CSF evaluation



**Figure 1.** Left hand biopsy sections show dense superficial perivascular lymphocytic infiltrate with numerous eosinophils (A and B), occasional mast cells (C, arrows), and no evidence of epidermal necrosis B, H&E,  $\times 20$  original object magnification. C, H&E,  $\times 100$  original object magnification.

redemonstrated elevated protein and lymphocytic pleocytosis. Electromyography showed partial conduction block consistent with acute focal nerve injury and possible demyelination in multiple nerves. She was presumed to have acute inflammatory demyelinating polyneuropathy (AIDP) due to vemurafenib. She completed a 5-day course of intravenous immunoglobulin, and continued a prolonged prednisone taper. Her strength slowly improved although her melanoma continued to worsen with subsequent initiation of temozolomide.

## Case 2

A 41-year-old woman was diagnosed with AJCC stage IIIA melanoma in her left index finger in April 2011 (Breslow depth 3.1 mm, nonulcerated, one axillary lymph node involved). In December 2011, she developed in-transit lesions on her upper arm and was treated with imiquimod; molecular profiling revealed a BRAF V600E mutation. She then developed axillary lymphadenopathy and underwent resection, which was followed by further regional progression. She subsequently began anti-PD-1 (MK-3475, NCT01295827) and tolerated four cycles of therapy without side effects but developed new splenic and hepatic metastases.

The patient started on vemurafenib in January 2013. Nine days later, she developed a diffuse, pruritic eruption, composed of blanching erythematous macules and papules on the trunk and extremities, and was started on prednisone, 60 mg daily. Despite steroid administration, her rash became more confluent on the trunk with development of dark brown papules, plaques, and few pustules (Fig. 2A). She developed fever to 104.9°F, tachycardia, and hypotension; acute kidney injury, lactic acidosis, and mild transaminitis were noted (Table 1). Broad-spectrum antibiotics and aggressive i.v. fluid resuscitation were administered; vemurafenib was discontinued. Skin biopsy of the upper back showed superficial perivascular dermatitis with occasional eosinophils consistent with a dermal hypersensitivity reaction (Fig. 2B and C). Her prednisone was increased to 80 mg daily. Blood and urine cultures

remained negative; her symptoms and metabolic abnormalities improved dramatically over several days.

During the next month, her rash completely resolved although her cutaneous melanoma lesions enlarged. She restarted a low dose of vemurafenib (240 mg) while continuing prednisone, 20 mg, concurrently. Less than 6 hours after her first dose, she acutely developed a diffuse erythematous rash, severe shortness of breath, stridor, and vomiting. She was treated with epinephrine, corticosteroids, and antihistamines with rapid symptom resolution. Vemurafenib therapy was abandoned, and the patient is currently enrolled in a clinical trial evaluating a MEK inhibitor and a PI3K/AKT inhibitor.

## Discussion

Both of these patients experienced severe cutaneous and systemic toxicities while being treated with vemurafenib preceded by a course of anti-PD-1 antibodies. Their initial presentations were consistent with a severe drug hypersensitivity reaction with widespread morbilliform eruption, fever, hypotension, and multiorgan dysfunction. Initial differential diagnosis included DRESS (drug rash with eosinophilia and systemic symptoms), but diagnostic criteria, including peripheral eosinophilia, were not met (11). Severe neurologic and systemic toxicities subsequently ensued with presumed AIDP in one patient and anaphylaxis upon vemurafenib rechallenge in the other.

Vemurafenib has a well-defined toxicity profile of arthralgias, fatigue, and cutaneous manifestations, including hand-foot syndrome, photosensitivity, hyperkeratotic rash, and cutaneous squamous cell carcinomas (cuSCC; refs. 1, 12, 13). In addition, up to 50% of patients treated with vemurafenib on clinical trials are described to develop rashes that are not classified more specifically, some of which may represent hypersensitivity reactions (1, 2). These cutaneous effects are usually treatable with antihistamines, topical corticosteroids, or excision of cuSCCs; dose modification or systemic steroids are required occasionally (14). Rare side effects reported

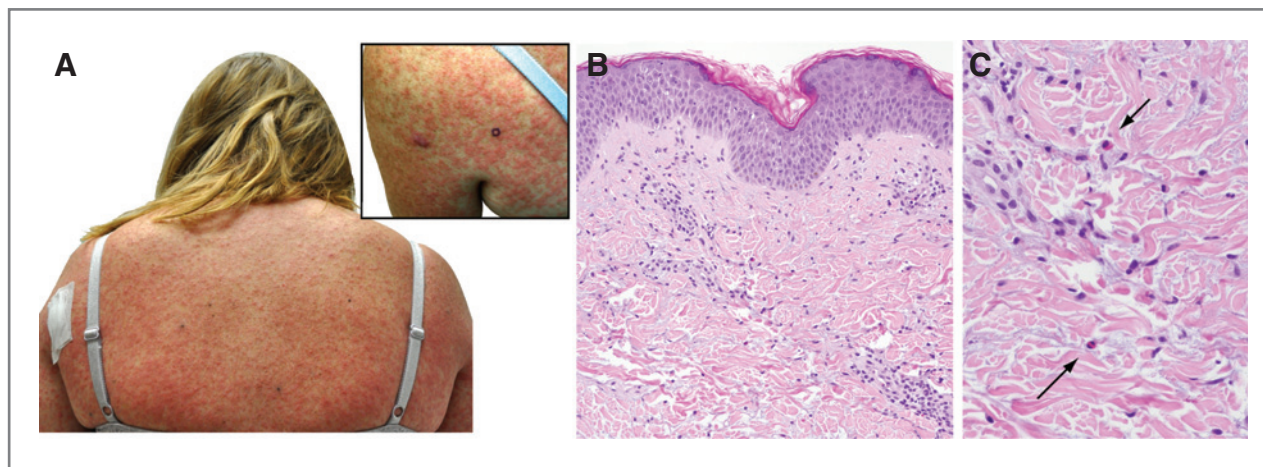


Figure 2. A (and inset), diffuse erythematous papules covering the back and upper extremities with histologic evidence of superficial perivascular dermatitis with occasional eosinophils B, H&E,  $\times 20$  original object magnification C, H&E,  $\times 100$  original object magnification.

include facial nerve palsy, hepatotoxicity, pancreatitis, and Stevens–Johnson syndrome, although life-threatening toxicities are uncommon (2, 15–17). To our knowledge, the toxicities observed in our patients have not been described with vemurafenib in the medical literature, leading to the concern that the preceding anti-PD-1 may have played a role.

Significant interest has been expressed in combining BRAF inhibitors with immune-based therapies, tempered by a concern that combination or sequential therapy may augment toxicities. BRAF inhibitors likely mediate their antimelanoma effects in part through immune-based mechanisms. In preclinical and clinical studies, vemurafenib caused marked tumor infiltration of CD8<sup>+</sup> CTLs as well as upregulation of the immune checkpoint PD-L1 (18, 19). Furthermore, the presence of functional host CTLs seems to play an essential role in effecting responses to BRAF inhibitor therapy (20). This observed effector T-cell activation may be explained by paradoxical activation of mitogen-activated protein kinase (MAPK) signaling in BRAF wild-type cells through enhanced CRAF dimerization (21).

In both of our patients, anti-PD-1 therapy had been well tolerated before vemurafenib. However, these agents may have "primed" the immune system, predisposing these patients to severe BRAF inhibitor toxicities. This phenomenon seemed to occur in a small series of patients with unusually high rates of cutaneous toxicity and hypersensitivity reactions when treated with vemurafenib preceded by ipilimumab, although no systemic toxicities were reported (22). In addition, the combination of ipilimumab and vemurafenib administered simultaneously led to an unacceptable frequency of severe hepatotoxicity (23). With generally more tumor-specific immune responses with anti-PD-1 therapy, it could be predicted that these agents would be better tolerated in combination therapy.

Earlier in their treatment courses, both patients received imiquimod for in-transit metastases. Imiquimod is a Toll-like receptor 7 agonist that induces a local inflammatory response through recruitment of CTLs and cytokine production (24). Although imiquimod is immune activating, more than 3 months in one case and 6 months in the other had elapsed since its cessation. Furthermore, generalized hypersensitivity reactions during therapy have not been described (25). The role of imiquimod is not clear in these cases. Notably, from our two institutions, this report represents two of three patients treated

with anti-PD-1 followed by vemurafenib. The additional patient received nivolumab without an objective response and then was treated with commercially available vemurafenib at an outside institution. Subsequent clinic notes describe that the patient developed a confluent generalized eruption but was able to continue therapy after dose interruption.

Anti-PD-1 agents are being evaluated in clinical trials currently. With frequent and durable responses observed and a favorable toxicity profile (rarely including immune-related pneumonitis), these novel agents have been attractive treatment options in clinical trials (4, 5). If patients with BRAF-mutant melanoma have disease progression on anti-PD-1 therapy, their treating clinicians should maintain a high index of suspicion for dangerous toxicities if vemurafenib is selected as a subsequent treatment option. Furthermore, trials to explore the combination or sequence of anti-PD-1 with BRAF-targeted treatment will need to be performed with great caution.

### Disclosure of Potential Conflicts of Interest

M.C. Kelley has a commercial research grant from GlaxoSmithKline through the National Comprehensive Cancer Network. R.W. Joseph is a consultant/advisory board member of Merck. No potential conflicts of interest were disclosed by the other authors.

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**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** D.N. Cohen  
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