Delayed-onset vemurafenib-induced panniculitis

Stephen L. Vance, MD, MBA,[a] Hannah M. Singer, BS, BA,[b] David Silvers, MD,[c]
Sameera Husain, MD,[c] and Filamer Kabigting, MD[a]
New York, New York

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INTRODUCTION

Approved in 2011, vemurafenib is a selective serine/threonine kinase inhibitor directed against the V600E mutation in the *BRAF* gene. This drug is often used in dermatology as a targeted therapy for metastatic or unresectable melanomas, for which about 50% have this mutation.[1] Other tumors possessing the V600E mutation are targets for this therapy. The commonly reported adverse effects of vemurafenib include rash, squamoproliferative growths, photosensitivity, squamous cell carcinoma, milia, hand-foot skin reaction, and dry skin.[2] Panniculitis is a rare adverse effect associated with *BRAF* inhibitors. To the authors' knowledge, this is the first report of histopathologically confirmed delayed-onset vemurafenib-induced panniculitis in an adult, with the patient presenting 324 days after initiating therapy.

CASE REPORT

A 34-year-old Hispanic woman with a history of Langerhans cell histiocytosis of the hypothalamus, complicated by pan-hypopituitarism and central diabetes insipidus presented with a 1-week history of painful erythematous nodules. Initially, they appeared on the left distal upper extremity and subsequently spread to include all extremities. The patient also reported fevers, nausea, and vomiting coinciding with onset of the nodules.

The patient's oncologic history dated back to 2015 when she presented with galactorrhea, polyuria, polydipsia, and amenorrhea. Magnetic resonance imaging found hypothalamic-enhancing lesions leading to subsequent craniotomy for resection. Pathologic evaluation of the tumor found cells that expressed CD1a, S100, and langerin. Molecular analysis of the hypothalamic lesions showed the *BRAF* V600E mutation. Because of the select mutation, the patient was started on vemurafenib at a dose of 480 mg twice a day. During her initial course of therapy, she complained of erythematous rash on the face, palms, and soles that resolved in a self-limiting fashion. She had otherwise been well and adherent to her vemurafenib treatment for the 10 months preceding the onset of new, painful nodules.

On examination, the patient was found to have numerous, tender 2- to 3-cm subcutaneous nodules with overlying erythema, which on the proximal left upper extremity had become confluent in areas. The lesions were limited to the extremities and completely spared the trunk, head, and neck (Fig 1). She denied arthralgia but did complain of edema in the left hand. Clinically, the patient's appearance was consistent with that of a grade 3 panniculitis (National Cancer Institute Common Terminology Criteria for Adverse Events). Initially, these lesions were felt less likely to be associated with vemurafenib because of the longevity of her therapy (324 days at presentation). The initial differential diagnosis included erythema induratum, erythema nodosum, subcutaneous Sweet syndrome, and the other known causes of panniculitis. A biopsy from a left arm subcutaneous nodule was performed using a 3-mm punch tool, with 2 overlapping punches creating an ellipse and a third deep punch

From the Division of Dermatopathology,[c] Department of Dermatology,[a] and the College of Physicians and Surgeons,[b] Columbia University Medical Center.

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Correspondence to: Stephen L. Vance, MD, MBA, Department of Dermatology, Herbert Irving Pavilion, 12th Floor, 161 Fort Washington Avenue, New York, NY 10032. E-mail: sv2471@columbia.edu.

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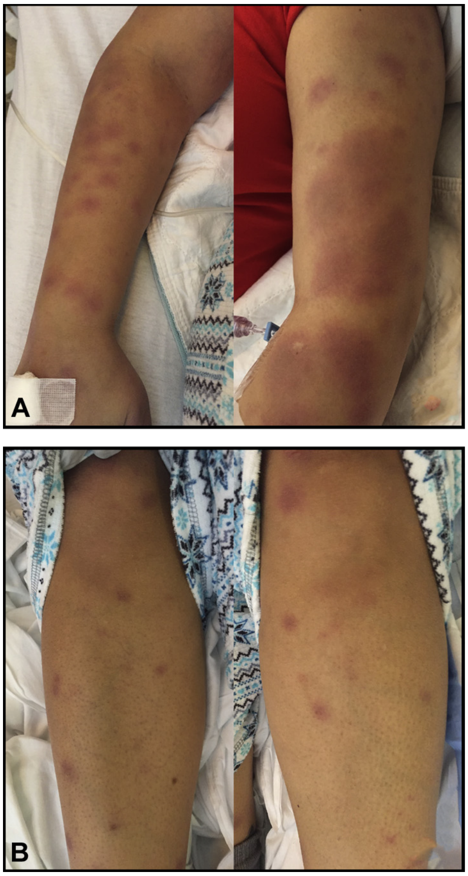

Fig 1. **A**, Erythematous tender subcutaneous nodules of the upper extremities with coalescence on the left upper arm. **B**, Discrete erythematous tender subcutaneous nodules of the bilateral lower legs.

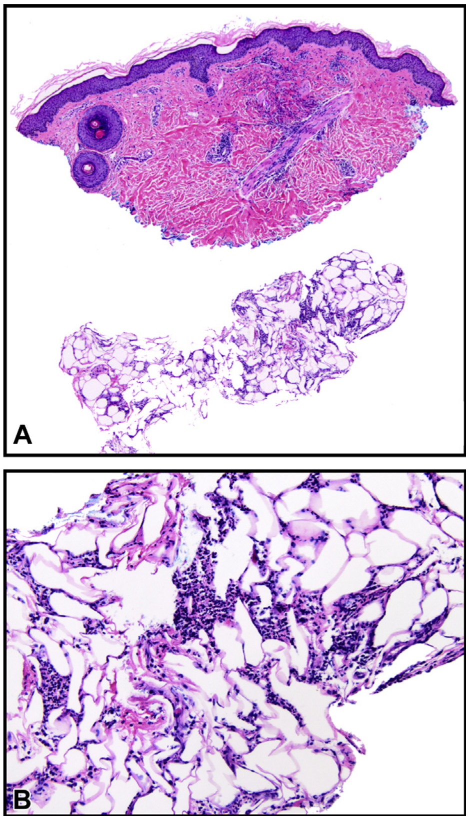

Fig 2. **A**, Biopsy findings show a lobular neutrophilic panniculitis with an overlying lymphocytic infiltrate in the dermis. **B**, At higher power, a florid neutrophilic panniculitis is evident. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×4; **B**, ×20.)

into the subcutis. Histopathology finding showed a lobular neutrophilic panniculitis with an overlying perivascular lymphocytic infiltrate in the dermis (Fig 2). Laboratory evaluation was significant for elevated C-reactive protein level (92.7 mg/L) and erythrocyte sedimentation rate (130 mm/h). An infectious workup of tissue culture, fungal culture, acid-fast bacilli culture, QuantiFERON TB Gold (QIAGEN, Germantown, MD), antistreptolysin O, and hepatitis A, B, and C proved unremarkable. Further evaluation found normal lipase (87 U/L), amylase (48 U/L), and α-1-antitrypsin (284 mg/dL) and no anti-nuclear antibodies. She was afebrile and had normal white blood cell counts, electrolytes, and renal function and stable supplemented thyroid function. Procalcitonin, C3, C4, and anti-neutrophil cytoplasmic antibodies were not obtained to further evaluate for erythema nodosum, as histopathology did not show a septal panniculitis suggestive of that entity.

At admission, the patient discontinued vemurafenib therapy, and her lesions slowly faded, completely flattening with residual faint erythema and hyperpigmentation by hospital day 3. Based on the negative laboratory findings, resolution after discontinuation of therapy, and histopathology findings consistent with a neutrophilic panniculits, the determined diagnosis was delayed-onset vemurafenib-induced panniculitis. She resumed therapy 1 week after discharge at a decreased dose of 240 mg twice a day with no recurrence.

DISCUSSION

Cutaneous side effects are common with *BRAF*-targeted therapies; however, panniculitis is an unusual reaction. Acute vemurafenib induced panniculitis has been biopsy confirmed and reported in 22 melanoma patients whose presentations ranged from 3 days to 111 days (mean, 30.6 days; median, 15 days).[3-8] A single reported pediatric patient treated for a brainstem glioma with vemurafenib had delayed-onset neutrophilic panniculitis after 10 months of therapy.[9] Typically, the lesions appear on the arm and legs.[3-5,7-10] Varied histopathology has been described; however, lobular neutrophilic panniculits is the most often reported.[3-5,7,9,10] Other reports include both lymphocytic and mixed infiltrates.[3-5,8] After presentation, patients have been treated with nonsteroidal anti-inflammatory drugs, acetaminophen, topical steroids, and short courses of systemic steroids.[4,10] The clinical course has been described as persistent, relapsing remitting, and resolving.[4]

This patient's long duration of therapy of 324 days initially favored etiologies other than vemurafenib-induced panniculitis. The lobular neutrophilic infiltrate and negative infectious workup eliminated erythema nodosum and infectious panniculitis. Lack of granulomas or vascular change in the subcutis ruled out erythema induratum. The normal α-1-antitrypsin level precluded α-1-antitrypsin deficiency—associated panniculitis. Pancreatic panniculitis was eliminated based on normal amylase and lipase levels. The patient's laboratory and clinical course did not favor the diagnosis of subcutaneous Sweet syndrome. Finally, for this drug reaction, one must consider vemurafenib's complicated pharmacokinetics. Our patient had no recent changes in medications, alterations in gallbladder or bile salt metabolism, ability to eliminate the drug, or simultaneous illness or iatrogenic events.

This case clearly demonstrates that with extended vemurafenib therapy, patients may rarely develop a delayed-onset panniculitis that develops many months beyond the typical presentation in the weeks after initiation of therapy. For patients undergoing treatment with vemurafenib and presenting with delayed-onset subcutaneous nodules, providers should consider a *BRAF*-induced panniculitis if infectious or autoimmune causes are eliminated.[11] Furthermore, of the previously reported cases, all patients were undergoing vemurafenib treatment for melanoma except the one other reported delayed-onset presentation in a 15-year-old patient with brainstem glioma.

We report a case of delayed-onset vemurafenib-induced panniculitis. Because *BRAF*-associated panniculitis is uncommon and typically occurs in the weeks after the initiation of therapy, the rare delayed-onset presentation may initially be a challenging diagnosis. Management of this process is determined by the severity of the patient's clinical presentation.

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