

# Nonmalignant Cutaneous Findings Associated With Vemurafenib

Fiona Sukhnandan, PA-C; Mark Robert Kahn, MD; Pradip Bhattacharjee, MD

## PRACTICE POINTS

- Prior to starting a BRAF inhibitor, clinicians should perform a baseline total-body skin examination and follow-up every 2 months.
- Take photographs of the patient's entire body on initial total-body skin examination.
- Encourage sun protection for exposed areas on the body in all seasons.

To the Editor:

A 53-year-old woman was referred by her oncologist to our dermatology office with lesions on the face and body that presented 8 days after starting vemurafenib 960 mg twice daily for metastatic melanoma. The patient denied any symptoms from the lesions but was concerned they would spread to cover her entire face and body.

The patient's medical history included a diagnosis of metastatic melanoma 6 years prior to presentation. She stated that the primary cutaneous melanoma site was unknown. The patient had endured numerous surgeries to excise lymph node tumors, with some lesions up to 3 cm. The patient recently started vemurafenib, a treatment for BRAF V600E mutation-positive metastatic melanoma. The patient's personal history was notable for hepatitis A, B, and C, and her family history revealed her mother had metastatic lung cancer.

Physical examination revealed numerous 2- to 3-mm, round-oval, flesh-colored to light-brown papules on the cheeks, chest, abdomen (Figure 1), back, and both arms and legs. Some papules were inflamed and some had a stuck-on appearance. Lesions on the chest between the breasts and inframammary region were slightly inflamed. Two skin biopsies were performed. Biopsy of the lesion on

the right lateral back revealed solar lentigo, early macular seborrheic keratosis, and a focus of inflamed mild solar keratosis. The dermis showed a mild superficial perivascular and interstitial inflammatory infiltrate composed mostly of lymphocytes, histiocytes, and eosinophils. There were occasional melanophages present (Figure 2). Biopsy of the lesion between the breasts revealed inflamed verrucous seborrheic keratosis (Figure 3).

We treated the lesion on the right lateral back with cycles of cryotherapy and explained to the patient that the lesion between the breasts was benign. We also reiterated to the patient the importance of wearing sun-protective clothing and UVA/UVB sunblock with a sun protection factor of 30 or higher.

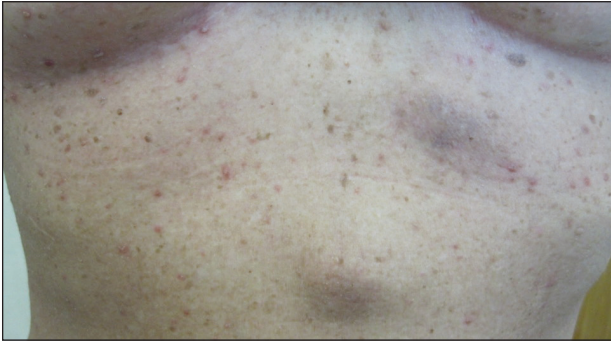
Our patient was diagnosed with pneumonia and subsequently had to discontinue vemurafenib. During the period of nontreatment, the keratotic lesions cleared with postinflammatory hyperpigmentation and no epidermal changes, which showed a possible inference of a direct relationship between the vemurafenib and the appearance of the nonmalignant cutaneous lesions. Although this report only represents 1 patient, other patients possibly can benefit from a modified dose of vemurafenib, which either would resolve or lessen the quantity of these lesions.

Vemurafenib is the first US Food and Drug Administration–approved treatment for nonresectable metastatic melanoma with the BRAF V600E mutation as detected by a US Food and Drug Administration–approved test.<sup>1,2</sup> Mutated BRAF is present in approximately 60% of cutaneous melanomas.<sup>3</sup> Vemurafenib targets the oncogenic BRAF V600E making the protein inactive, thus inhibiting cell proliferation and leading to apoptosis and shrinkage of the metastatic tumors.<sup>3-5</sup> Vemurafenib has a response rate of more than 50% and is associated with rapid improvement in quality of life.<sup>3</sup>

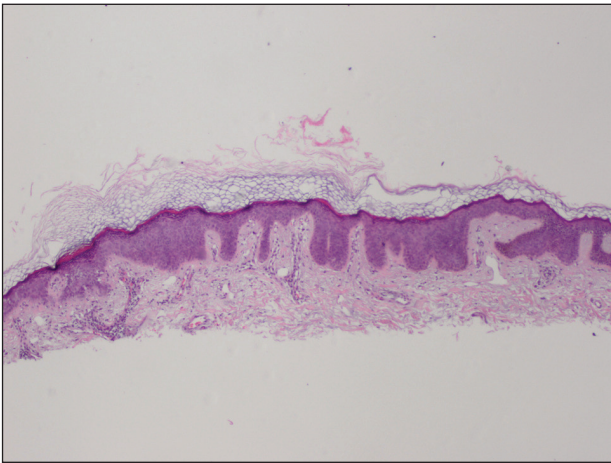
From Atlantic Dermatologic Associates, Lynbrook, New York.

The authors report no conflict of interest.

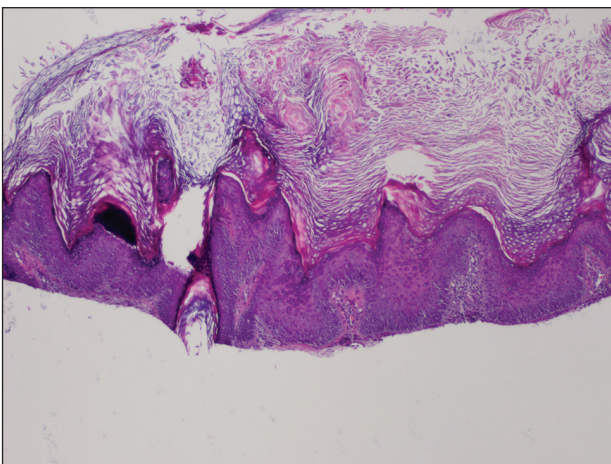
Correspondence: Fiona Sukhnandan, PA-C, 30 South Central Ave, Valley Stream, NY (derm\_pa@hotmail.com).



**FIGURE 1.** Numerous brown and inflamed papules on the upper abdomen and inframammary area, with 2 tumors on the left inframammary region and mid upper abdomen.



**FIGURE 2.** Shave biopsy from the right lateral back showed hyperkeratosis, acanthosis, papillomatosis, and a mild superficial perivascular and lymphohistiocytic inflammatory infiltrate, with mild postinflammatory pigmentary alteration (H&E, original magnification  $\times 4$ ).



**FIGURE 3.** Shave biopsy from between the breasts showed hyperplastic epidermis with acuminate papillations covered by orthokeratosis. An inflammatory infiltrate also was present (H&E, original magnification  $\times 20$ ).

Cutaneous side effects include increased incidence of squamous cell carcinoma and keratoacanthomas, appearing approximately 7 to 8 weeks after starting vemurafenib.<sup>4</sup> The incidence of these lesions increases in patients 65 years and older and in patients with prior skin cancer and chronic sun exposure. The paradoxical activation of the mitogen-activated protein kinase pathway by mutant BRAF-selective inhibitors provides an explanation of the induction of squamous cell carcinomas.<sup>4</sup> Prior to the initiation of vemurafenib, all patients should receive a total-body skin examination and every 2 months thereafter while on treatment. After discontinuation of the medicine, the patient should continue to receive total-body skin evaluations every 6 months indefinitely.

Patients should be aware of the potential for mild to severe photosensitivity reactions. They should be advised to limit their sun exposure time and to wear sun-protective clothing when outdoors. The use of broad-spectrum UVA/UVB sunscreen and lip protectant with a sun protection factor of 30 or higher also should be stressed.<sup>6,7</sup> Patients should be aware that UVA rays penetrate glass; therefore, UV-protective clothing should be worn throughout the day and during all seasons.<sup>7</sup>

In clinical trials of vemurafenib, Stevens-Johnson syndrome and toxic epidermal necrolysis was reported in 2 patients.<sup>8,9</sup> Clinical trials also reported patients developing new primary malignant melanoma lesions.<sup>10</sup> These findings further emphasize the need for patients to undergo total-body skin examinations during and after treatment.

Other possible dermatologic reactions include a generalized rash, erythema, alopecia, and pruritus.<sup>2,3</sup> The development of benign growths associated with patients on vemurafenib include follicular plugging seen in keratosis pilaris, palmar and plantar hyperkeratosis, seborrheic dermatitis-like rashes, verrucous keratosis, and acantholytic dyskeratosis.<sup>8,11,12</sup>

We report a case of nonmalignant growths occurring 8 days after starting vemurafenib. This case illustrates potential cutaneous adverse reactions that were benign yet still of great concern to our patient. Many of these nonmalignant cutaneous findings are associated with abnormal follicular keratinization thought to be secondary to abnormal signaling of the mitogen-activated protein kinase pathway that occurs with the use of BRAF inhibitors.<sup>8</sup> Although in this case malignant lesions were not discovered, the need for total-body skin examinations exists during all stages of treatment. Supportive care and reassurance should be given to patients along with local treatments including topical therapies (steroids, retinoids), cryotherapy, and biopsies or excisions when necessary.<sup>13,14</sup>

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