

# Vemurafenib-Induced Plantar Hyperkeratosis

Benjamin R. Bashline, DO; Paul M. Bedocs, DO

## PRACTICE POINTS

- BRAF inhibitors such as vemurafenib are associated with a high incidence of cutaneous side effects, including rash, hyperkeratosis, and cutaneous squamous cell carcinoma.
- Practitioners should be aware of these side effects and their management to avoid discontinuation or interruption of therapy.

To the Editor:

Vemurafenib, a selective BRAF inhibitor, is a chemotherapeutic agent used in the treatment of metastatic melanoma with BRAF mutations. It has been associated with various cutaneous side effects. We report a case of metastatic melanoma with acquired plantar hyperkeratosis secondary to vemurafenib therapy.

A 49-year-old man presented for evaluation of a pigmented plaque on the left pretibial region that had been enlarging over the last 2 months. The lesion had been diagnosed as folliculitis by his primary care physician 1 month prior to the current presentation and was being treated with oral antibiotics. The patient reported occasional bleeding from the lesion but denied other symptoms. Physical examination revealed a 1.4-cm pigmented plaque distributed over the left shin. Excisional biopsy was performed to rule out melanoma. Histopathology revealed well-circumscribed and symmetric proliferation of nested and single atypical melanocytes throughout all layers to the deep reticular dermis, confirming a clinical diagnosis of malignant melanoma. The lesion demonstrated angiolymphatic invasion, mitotic activity, and a Breslow depth of 2.5 mm. The patient underwent wide local excision with 3-cm margins and left inguinal sentinel lymph

node biopsy; 2 of 14 lymph nodes were positive for melanoma. Positron emission tomography–computed tomography was negative for further metastatic disease. The patient underwent isolated limb perfusion with ipilimumab, but treatment was discontinued due to regional progression of multiple cutaneous metastases that were positive for the BRAFV600E mutation.

The patient was then started on vemurafenib therapy. Within 2 weeks, the patient reported various cutaneous symptoms, including morbiliform drug eruption covering approximately 70% of the body surface area that resolved with topical steroids and oral antihistamines, as well as the appearance of melanocytic nevi on the posterior neck, back, and abdomen. After 5 months of vemurafenib therapy, the patient began to develop hyperkeratosis of the bilateral soles of the feet (Figure). A diagnosis of acquired plantar hyperkeratosis secondary to vemurafenib therapy was made. Treatment with keratolytics was initiated and vemurafenib was not discontinued. The patient died approximately 1 year after therapy was started.

Metastatic melanoma is challenging to treat and continues to have a high mortality rate; however, newer chemotherapeutic agents targeting specific mutations found in melanoma, including the BRAFV600E mutation, are promising.

The US Food and Drug Administration first approved vemurafenib, a selective BRAF inhibitor, in 2011 for treatment of metastatic melanoma. Activating BRAF mutations have been detected in up to 60% of cutaneous melanomas.<sup>1</sup> In the majority of these mutations, valine (V) is inserted at codon 600 instead of glutamic acid (E); therefore, the mutation is named V600E.<sup>2</sup> In a phase 3 trial of 675 metastatic melanoma patients with positive V600E who were randomized to receive either vemurafenib or dacarbazine, the overall survival rate in the vemurafenib group improved by 84% versus 64% in the dacarbazine group at 6 months.<sup>3</sup>

Dr. Bashline is from The Dermatology Group, West Orange, New Jersey. Dr. Bedocs is from the Heritage College of Osteopathic Medicine, Ohio University, Athens.

The authors report no conflict of interest.

Correspondence: Benjamin R. Bashline, DO (Benjamin.bashline@gmail.com).



Hyperkeratosis of left plantar foot in a patient undergoing vemurafenib therapy for metastatic melanoma (A–C).

Vemurafenib and other BRAF inhibitors have been associated with multiple cutaneous side effects, including rash, alopecia, squamous cell carcinoma, photosensitivity, evolution of existing nevi, and less commonly palmoplantar hyperkeratosis.<sup>2–5</sup> Constitutional symptoms including arthralgia, nausea, and fatigue also have been commonly reported.<sup>2–5</sup> In several large studies comprising 1138 patients, cutaneous side effects were seen in 92% to 95% of patients.<sup>3,5</sup> Adverse effects caused interruption or modification of therapy in 38% of patients.<sup>3</sup>

Palmoplantar keratoderma is a known side effect of vemurafenib therapy, but it is less commonly reported than other cutaneous adverse effects. It is believed that vemurafenib has the ability to paradoxically activate the mitogen-activated protein kinase pathway, leading to keratinocyte proliferation in cells without BRAF mutations.<sup>6–8</sup> In the phase 3 trial, approximately 23% to 30% of patients developed some form of hyperkeratosis.<sup>5</sup> Comparatively, 64% of patients developed a rash and 23% developed cutaneous squamous cell carcinoma. Incidence of palmoplantar hyperkeratosis was similar in the vemurafenib and dabrafenib groups (6% vs 8%).<sup>3,9</sup> Development of keratoderma also has been associated with other multikinase inhibitors (eg, sorafenib, sunitinib).<sup>10,11</sup>

In our case, the patient displayed multiple side effects while undergoing vemurafenib therapy. Within the first 2 weeks of therapy, he experienced a drug eruption that affected approximately 70% of the body surface area. The eruption resolved with topical steroids and oral antihistamines. The patient also noted the appearance of several new melanocytic nevi on the posterior neck as well as several evolving nevi on the back and abdomen. Five months into the treatment cycle, the

patient began to develop hyperkeratosis on the bilateral plantar feet. Treatment consisted of keratolytics. Vemurafenib therapy was not discontinued secondary to any adverse effects.

Vemurafenib and other BRAF inhibitors are efficacious in the treatment of metastatic melanoma with V600E mutations. The use of these therapies is likely to continue and increase in the future. BRAF inhibitors have been associated with a variety of side effects, including palmoplantar hyperkeratosis. Awareness of and appropriate response to adverse reactions is essential to proper patient care and continuation of potentially life-extending therapies.

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