OBSERVATION

Pregabalin for the Treatment of Painful Hand-Foot Skin Reaction Associated With Dabrafenib

Cutaneous adverse effects are one of the most frequent adverse events (AEs) associated with the use of BRAF inhibitors, reported in 92% to 95% of patients.1 Such dermatologic reactions include maculopapular eruptions, photosensitivity, verrucous keratoses, keratosis pilaris–like eruptions, keratoacanthomas, and melanocytic proliferations.2 Hand-foot skin reaction (HFSR) occurs in 19% to 60% of patients taking BRAF inhibitors1,3 and presents as tender, erythematous patches on the palms and soles.3 Painful hyperkeratotic plaques develop over pressure points. Although 88% of patients have grade 1 symptoms,4 pain can be severe.

The pathogenesis is unknown, but the reaction is dose dependent and may be due to direct toxic effects of the drug. It has also been postulated that blockage of receptors for vascular endothelial growth factor and platelet-derived growth factor leads to reduced ability to repair vasculature that is subclinically traumatized in the skin. Previously described therapies include emollient creams, keratolytic creams, topical corticosteroids, pyridoxine, COX-2 inhibitors, phototherapy, and decreased chemotherapy dose.

Report of a Case | A man in his 50s with BRAF V600E–mutated metastatic melanoma treated with twice-daily dabrafenib, 150 mg, developed grade 2 HFSR on his feet after 1 week of treatment, which progressed to grade 3 within a month (grading based on Common Terminology Criteria for Adverse Events, v4.03; http://evs.nci.nih.gov/ftp1/CTCAE/About.html). This was his first treatment for metastatic disease. On the palms and soles bilaterally, he had thick, yellow, hyperkeratotic plaques with erythematous borders most pronounced on the weight-bearing areas, including the metacarpophalangeal joints of the hands, heels, and balls of the feet (Figure). These plaques caused significant pain, interfering with performance of activities of daily living.

Minimal improvement was seen after treatment with topical tazarotene, 0.05%, ointment, lidocaine, 5%, ointment, urea, 40%, ointment, and clobetasol, 0.05%, ointment under occlusion. For pain relief, he required use of long-acting oxycodone, 10 mg, every 12 hours, and oxycodone, 5 mg, every 4 hours, which provided mild pain control. He experienced significant improvement after halting treatment with dabrafenib for 2 weeks and subsequently resuming a reduced-dose dabrafenib regimen at 150 mg/d, but he still required narcotics for pain control.

After 2 weeks of low-dose dabrafenib, he started therapy with pregabalin, 50 mg, 3 times daily. Within a week and without any other change in his lifestyle or activity level, the pain in his feet dramatically decreased to the point where he no longer required narcotics and was able to participate in his previous activities. After 45 weeks, he continued to take pregabalin with continuous pain relief in his feet despite unchanged persistent thickened plaques on the soles, for which the topical therapies provided little therapeutic benefit. Of note, the patient had a lifelong history of bipolar disorder and had been taking bupropion, fluoxetine, lamotrigine, and quetiapine throughout this period.

Discussion | Pregabalin is an anticonvulsant widely used as first-line therapy for neuropathic pain secondary to a variety of

Figure. Hand-Foot Skin Reaction to Dabrafenib

Thick, yellow, hyperkeratotic plaques with erythematous borders most pronounced on the weight-bearing areas.
Diseases including diabetes, post-herpetic neuralgia, fibromyalgia, and spinal cord injuries. Pregabalin, like gabapentin, binds to voltage-gated calcium channels and decreases synaptic activity; pregabalin exerts its therapeutic effect at lower doses than does gabapentin, and thus patients experience fewer adverse effects with pregabalin. It has been found to be safe, the most common adverse effects being somnolence and dizziness, which frequently resolve within weeks.5

For the present patient, pregabalin provided more effective symptomatic control than narcotics did for pain related to recalcitrant HFSR. Although he had concurrent bipolar disorder, his psychotropic medication regimen remained stable throughout this period, suggesting that pregabalin helped specifically with his peripheral pain. Although peripheral neuropathy has been associated with acral erythrodysesthesia, agents used to treat neuropathic pain have not been reported for use in acral erythrodysesthesia or HFSR. This case report suggests that pregabalin may be useful as a symptomatic treatment for pain associated with HFSR induced by targeted therapies.

Evelyn Lilly, MD
Matthew Burke, MBA, RN, MSN, APRN-BC
Harriet Kluger, MD
Jennifer Choi, MD

Author Affiliations: Department of Dermatology, Yale University School of Medicine, New Haven, Connecticut (Lilly, Choi); Yale Comprehensive Cancer Center, New Haven, Connecticut (Burke, Kluger, Choi).

Corresponding Author: Jennifer Choi, MD, Department of Dermatology, Yale University School of Medicine, 333 Cedar St, Laboratory for Medicine and Pediatrics 5040, New Haven, CT 06510 (Jennifer.choi@yale.edu).


Conflict of Interest Disclosures: Dr Choi serves as speaker for Onyx Pharmaceuticals. Mr Burke serves as a speaker for Bristol-Myers-Squibb, Genentech, and Pfizer (a manufacturer of pregabalin). Mr Burke also serves on the advisory board of Pfizer and Merck. No other disclosures are reported.


Dermoscopic Appearance of Intraluminal Hematogenous and Lymphatic Patterns of Cutaneous Melanoma Metastases

Cutaneous melanoma metastases can be categorized into satellite (<2 cm from primary melanoma), in-transit (>2 cm from primary melanoma but not beyond the regional nodal basin), and distant metastases (>2 cm from primary melanoma and beyond the regional nodal basin). The presence of cutaneous melanoma metastases is a component of the American Joint Committee on Cancer 2010 TNM (tumor node metastasis) staging system and is a poor prognostic criterion.4 Dermoscopy is a skin imaging technique using a handheld device that permits visualization of colors, structures, and patterns in skin lesions not evident to the naked eye. We describe 2 patients with in-transit cutaneous melanoma metastases having unusual clinical and dermoscopic features and distinct microanatomic routes of melanoma dissemination.

Report of Cases | Case 1. Patient 1 was diagnosed as having a primary cutaneous melanoma of the left forehead (stage IIIb; Breslow thickness, 2.11 mm), which was treated with wide local excision. A year later, the patient received localized irradiation for satellite skin metastases. One year after that, skin examination revealed 6 blue macules on the mid frontal scalp more than 2 cm from the excision scar. Dermoscopy revealed nonblanching bluish lines in a branched pattern (Figure 1A). No palpable lymphadenopathy was detected and positron emission tomography–computed tomography (PET-CT) revealed no evidence of distant metastases. Histopathologic examination of a skin biopsy specimen confirmed in-transit metastatic melanoma with atypical melanocytes present in superficial dermal lymphatics (Figure 1B).

Case 2. Patient 2 had a history of multiple primary melanomas and presented for dermatology follow-up. The most recent melanoma, on the right chest (stage IIIA; Breslow thickness, 0.75 mm) had been diagnosed 5 years earlier and was treated with wide local excision. The axillary sentinel lymph node biopsy findings were positive, and the patient elected to undergo completion lymphadenectomy. Skin examination revealed 8 blue-gray macules on the right chest, all more than 2 cm from his excision scar. Dermoscopy revealed nonblanching, red-bluish, fuzzy, branching lines (Figure 2A). No palpable lymphadenopathy was detected, and PET-CT revealed no evidence of distant metastases. Histopathologic examination of a skin biopsy specimen confirmed in-transit metastatic melanoma with atypical melanocytes present in superficial dermal blood vessels (Figure 2B).

Discussion | Studies have identified the most common dermoscopic features of cutaneous melanoma metastases, including peripheral gray spots, “atypical” vessels, and a blue nesvislike pattern.2,3 To our knowledge, there are no reports of a blue or red-blue, linear, branched dermoscopic pattern associated with cutaneous melanoma metastases, although we acknowledge that authors may have previously categorized this pattern as atypical vessels.

The histopathologic findings in our cases suggest that the dermoscopic color differences correspond to unique microanatomic routes of melanoma dissemination, with blue and red-blue lines corresponding to lymphatic and hematogenous tumoral dissemination, respectively. A blue dermoscopic color has been correlated with the presence of melanin in the dermis.4 Intraluminal melanoma dissemination within lymphatic dermal vessels would therefore be expected to produce branched blue lines. A red color may be observed if significant red blood cells were admixed with intraluminal melanoma cells, such as within dermal blood vessels.