Transient Eruption of Verrucous Keratoses During Encorafenib Therapy: Adverse Event or Paraneoplastic Phenomenon?

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PRACTICE **POINTS**

- Verrucous keratoses are common cutaneous adverse events (AEs) associated with BRAF inhibitor therapy.
- Verrucous papules may be a paraneoplastic phenomenon and can be differentiated from a treatment-related AE based on the timing and progression in relation to tumor burden.
- Although treatment of particularly bothersome lesions with cryotherapy may be warranted, verrucous papules secondary to BRAF inhibitor therapy may resolve spontaneously.

To the Editor:

Mutations of the *BRAF* protein kinase gene are implicated in a variety of malignancies.[1] *BRAF* mutations in malignancies cause the mitogen-activated protein kinase (MAPK) pathway to become constitutively active, which results in unchecked cellular proliferation,[2,3] making the *BRAF* mutation an attractive target for inhibition with pharmacologic agents to potentially halt cancer growth.[4] Vemurafenib—the first selective BRAF inhibitor used in clinical practice—initially was approved by the US Food and Drug Administration in 2011. The approval of dabrafenib followed in 2013 and most recently encorafenib in 2018.[5]

Although targeted treatment of *BRAF*-mutated malignancies with BRAF inhibitors has become common, it often is associated with cutaneous adverse events (AEs), such as rash, pruritus, photosensitivity, actinic keratosis, and verrucous keratosis. Some reports demonstrate these events in up to 95% of patients undergoing BRAF inhibitor treatment.[6] In several cases the eruption of verrucous keratoses is among the most common cutaneous AEs seen among patients receiving BRAF inhibitor treatment.[5-7]

In general, lesions can appear days to months after therapy is initiated and may resolve after switching to dual therapy with a MEK inhibitor or with complete cessation of BRAF inhibitor therapy.[5,7,8] One case of spontaneous resolution of vemurafenib-associated panniculitis during ongoing BRAF inhibitor therapy has been reported[9]; however, spontaneous resolution of cutaneous AEs is uncommon. Herein, we describe verrucous keratoses in a patient undergoing treatment with encorafenib that resolved spontaneously despite ongoing BRAF inhibitor therapy.

A 61-year-old woman presented to the emergency department with pain in the right lower quadrant. Computed tomography (CT) of the abdomen and pelvis revealed a large ovarian mass. Subsequent bloodwork revealed elevated carcinoembryonic antigen levels. The patient underwent a hysterectomy, bilateral salpingo-oophorectomy, omentectomy, right hemicolectomy with ileotransverse side-to-side anastomosis, right pelvic lymph node reduction, and complete cytoreduction. Histopathology revealed an adenocarcinoma of the cecum with tumor invasion into the visceral peritoneum and

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metastases to the left ovary, fallopian tube, and omentum. A *BRAF* V600E mutation was detected.

Two months after the initial presentation, the patient started her first cycle of chemotherapy with a combination of folinic acid, fluorouracil, and oxaliplatin. She completed 11 cycles of this regimen, then was switched to capecitabine and oxaliplatin for an additional 2 cycles due to insurance concerns. At the end of treatment, there was no evidence of disease on CT, thus the patient was followed with observation. However, she presented 10 months later to the emergency department with abdominal pain, and CT revealed new lesions in the liver that were concerning for potential metastases. She started oral encorafenib 300 mg/d and intravenous cetuximab 500 mg weekly; after 1 week, encorafenib was reduced to 150 mg/d due to nausea and loss of appetite. Within 2 weeks of starting treatment, the patient reported the relatively abrupt appearance of more than 50 small papules across the shoulders and back (Figure 1A). She was referred to dermatology, and shave biopsies of 2 lesions—one from the left anterior thigh, the other from the right posterior shoulder—revealed verrucous keratosis pathology (Figure 2). At this time, encorafenib was increased again to 300 mg/d as the patient had been tolerating the reduced dose. She continued to report the appearance of new lesions for the next 3 months, after which the lesions were stable for approximately 2 months. By 2.5 months after initiation of therapy, the patient had undergone CT demonstrating resolution of the liver lesions. At 5 months of therapy, the patient reported a stable to slightly reduced number of skin lesions but had begun to experience worsening joint pain, and the dosage of encorafenib was reduced to 225 mg/d. At 7 months of therapy, the dosage was further reduced to 150 mg/d due to persistent arthralgia. A follow-up examination at 10 months of therapy showed improvement in the number and size of the verrucous keratoses, and near resolution was seen by 14 months after the initial onset of the lesions (Figure 1B). At 20 months after initial onset, only 1 remaining verrucous keratosis was identified on physical examination and biopsy. The patient had continued a regimen of encorafenib 150 mg/d and weekly intravenous 500 mg cetuximab up to this point. Over the entire time period that the patient was seen, up to 12 lesions located in high-friction areas had become irritated and were treated with cryotherapy, but this contributed only minorly to the patient's overall presentation.

Verrucous keratosis is a known cutaneous AE of BRAF inhibitor treatment with vemurafenib and dabrafenib, with fewer cases attributed to encorafenib.[5,6] Within the oncologic setting, the eruption of verrucous papules as

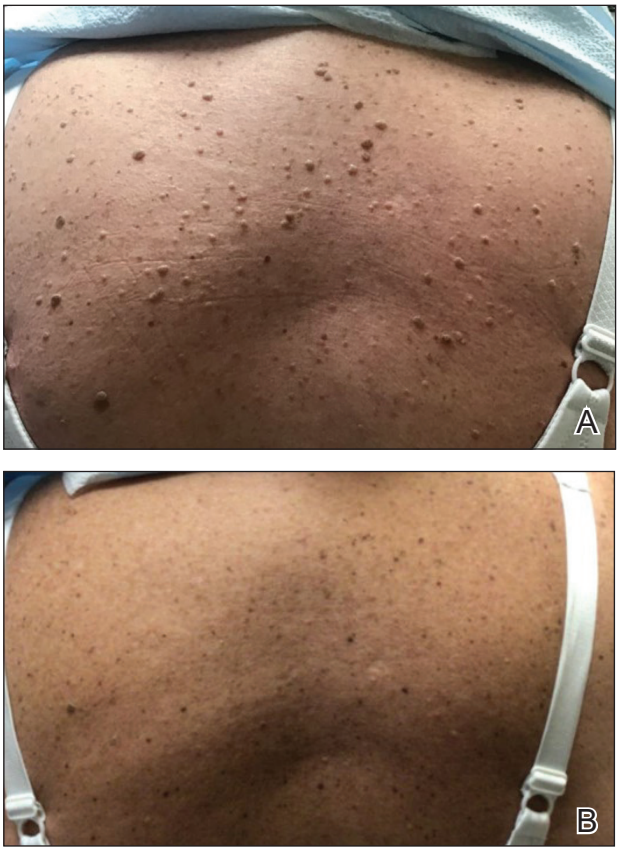

FIGURE 1. A, The patient presented with more than 50 verrucous keratoses across the back and shoulders within 2 weeks of initiating encorafenib for treatment of adenocarcinoma. B, Notable improvement was seen in the number and size of the lesions 14 months after the initial onset, despite ongoing encorafenib treatment.

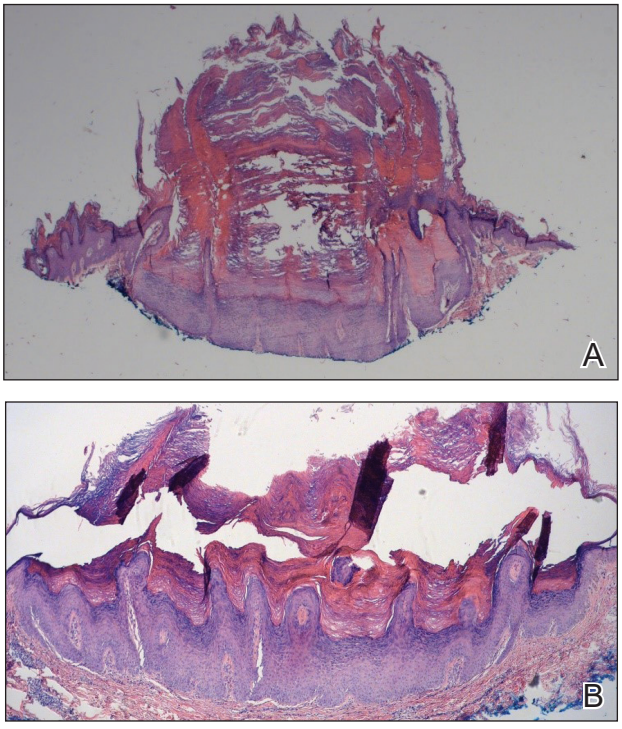

FIGURE 2. A and B, Histopathology revealed hyperkeratosis, acanthosis, and papillomatosis—all features of verrucous keratoses (H&E, original magnifications ×20 and ×40).

a paraneoplastic phenomenon is heavily debated in the literature and is known as the Leser-Trélat sign. This phenomenon is commonly associated with adenocarcinomas of the gastrointestinal tract, as seen in our patient.[10] Based on Curth's postulates—the criteria used to evaluate the relationship between an internal malignancy and a cutaneous disorder—this was unlikely in our patient. The criteria, which do not all need to be met to suggest a paraneoplastic phenomenon, include concurrent onset of the malignancy and the dermatosis, parallel course, association of a specific dermatosis with a specific malignancy, statistical significance of the association, and the presence of a genetic basis for the association.[11] Several features favored a drug-related cutaneous eruption vs a paraneoplastic phenomenon: (1) the malignancy was identified months before the cutaneous eruptions manifested; (2) the cutaneous lesions appeared once treatment had already been initiated; and (3) the cutaneous lesions persisted long after the malignancy was no longer identifiable on CT. Indeed, eruption of the papules temporally coincided closely with the initiation of BRAF inhibitor therapy, arguing for correlation.

As a suspected BRAF inhibitor–associated cutaneous AE, the eruption of verrucous keratoses in our patient is remarkable for its spontaneous resolution despite ongoing therapy. It is speculated that keratinocytic proliferation while on BRAF inhibitor therapy may be caused by a paradoxical increase in signaling through CRAF, another Raf isoform that plays a role in the induction of terminal differentiation of keratinocytes, with a subsequent increase in MAPK signaling.[12-14] Self-resolution of this cycle despite continuing BRAF inhibitor therapy suggests the possible involvement of balancing and/or alternative mechanistic pathways that may be related to the immune system. Although verrucous keratoses are considered benign proliferations and do not necessarily require any specific treatment or reduction in BRAF inhibitor dosage, they may be treated with cryotherapy, electrocautery, shave removal, or excision,[15] which often is done if the lesions become inflamed and cause pain. Additionally, some patients may feel distress from the appearance of the lesions and desire treatment for this reason. Understanding that verrucous keratoses can be a transient cutaneous AE rather than a persistent one may be useful to clinicians as they manage AEs during BRAF inhibitor therapy.

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