Granulomatous Dermatitis in a Patient With Cholangiocarcinoma Treated With BRAF and MEK Inhibitors

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PRACTICE **POINTS**

- Granulomatous dermatitis (GD) is a potential rare side effect of the use of BRAF and MEK inhibitors for the treatment of BRAF V600 mutation–positive cancers, including metastatic cholangiocarcinoma.
- Granulomatous dermatitis can resolve despite continuation of BRAF and MEK inhibitor therapies.
- Histologically, GD can appear similar to disease recurrence. It is imperative that clinicians and pathologists recognize the cutaneous manifestations of BRAF and MEK inhibitors.

To the Editor:

Granulomatous dermatitis (GD) has been described as a rare side effect of MEK and BRAF inhibitor use in the treatment of BRAF V600E mutation–positive metastatic melanoma. As the utilization of BRAF and MEK inhibitors increases for the treatment of a variety of cancers, it is essential that clinicians and pathologists recognize GD as a potential cutaneous manifestation. We present the case of a 52-year-old woman who developed GD while being treated with vemurafenib and cobimetinib for BRAF V600E mutation–positive metastatic cholangiocarcinoma.

A 52-year-old White woman presented with faint patches of nonpalpable violaceous mottling that extended distally to proximally from the ankles to the thighs on the medial aspects of both legs. She was diagnosed with cholangiocarcinoma 10 months prior, with metastases to the lung, liver, and sternum. She underwent treatment with gemcitabine and cisplatin therapy. Computed tomography after several treatment cycles revealed progressive disease with multiple pulmonary nodules as well as metastatic intrathoracic and abdominal adenopathy. Treatment with gemcitabine and cisplatin failed to produce a favorable response and was discontinued after 6 treatment cycles.

Genomic testing performed at the time of diagnosis revealed a positive mutation for BRAF V600E. The patient subsequently enrolled in a clinical trial and started treatment with the BRAF inhibitor vemurafenib and the MEK inhibitor cobimetinib. She developed sun sensitivity and multiple sunburns after starting these therapies. The patient tolerated the next few cycles of therapy well with only moderate concerns of dry sensitive skin.

During the sixth cycle of therapy, she presented to dermatology after developing a rash. Over the next 2 weeks, similar lesions appeared on the arms. The patient denied the use of any new lotions, soaps, or other medications. Punch biopsies of the right forearm and right medial thigh revealed nonnecrotizing granulomas in the superficial dermis that extended into the subcutaneous adipose tissue (Figure 1). Surrounding chronic inflammation was scant, and the presence of rare eosinophils

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The authors report no conflict of interest.

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doi:10.12788/cutis.0859

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was noted (Figure 2). The histiocytes were highlighted by a CD68 immunohistochemical stain. An auramine-O special stain test was negative for acid-fast bacilli, and a Grocott methenamine-silver special stain test for fungal organisms was negative. These findings were consistent with GD. Computed tomography of the chest performed 2 months prior and 1 month after biopsy of the skin lesions revealed no axillary, mediastinal, or hilar lymphadenopathy. The calcium level at the time of skin biopsy was within reference range.

A topical steroid was prescribed; however, it was not utilized by the patient. Within 2 months of onset, the GD lesions resolved with no treatment. The GD lesions did not affect the patient's enrollment in the clinical trial, and no dose reductions were made. Due to progressive disease with metastases to the brain, the patient eventually discontinued the clinical trial.

BRAF inhibitors are US Food and Drug Administration approved for the treatment of metastatic melanoma to deactivate the serine-threonine kinase BRAF gene mutation, which leads to decreased generation and survival of melanoma cells.[1,2] Vemurafenib, dabrafenib, and encorafenib are the only BRAF inhibitors approved in the United States.[3] The most common side effects of vemurafenib include arthralgia, fatigue, rash, and photosensitivity.[1,4] There are 4 MEK inhibitors currently available in the United States: cobimetinib, trametinib, selumetinib and binimetinib. The addition of a MEK inhibitor to BRAF inhibitor therapy has shown increased patient response rates and prolonged survival in 3 phase 3 studies.[5-10]

Response rates remain low in the treatment of advanced cholangiocarcinoma with standard chemotherapy. Recent research has explored if targeted therapies at the molecular level would be of benefit.[11] Our patient was enrolled in the American Society of Clinical Oncology Targeted Agent and Profiling Utilization Registry (TAPUR) trial, a phase 2, prospective, nonrandomized trial that matches eligible participants to US Food and Drug Administration–approved study medications based on specific data from their molecular testing results.[12] Some of the most common mutations in intrahepatic cholangiocarcinoma include *HER2*, *KRAS*, *MET*, and *BRAF*.[13-17] Our patient's molecular test results were positive for a BRAF V600E–positive mutation, and she subsequently started therapy with vemurafenib and cobimetinib. The use of personalized genomic treatment approaches for BRAF V600E mutation–positive cholangiocarcinoma has produced a dramatic patient response to BRAF and MEK inhibitor combination therapies.[11,18-20]

Drug-induced GD most likely is caused by vascular insults that lead to deposition of immune complexes in vessels causing inflammation and a consequent granulomatous infiltrate.[21,22] Although cordlike lesions in the subcutaneous tissue on the trunk commonly are reported, the presentation of GD can vary considerably. Other presentations include areas of violaceous or erythematous

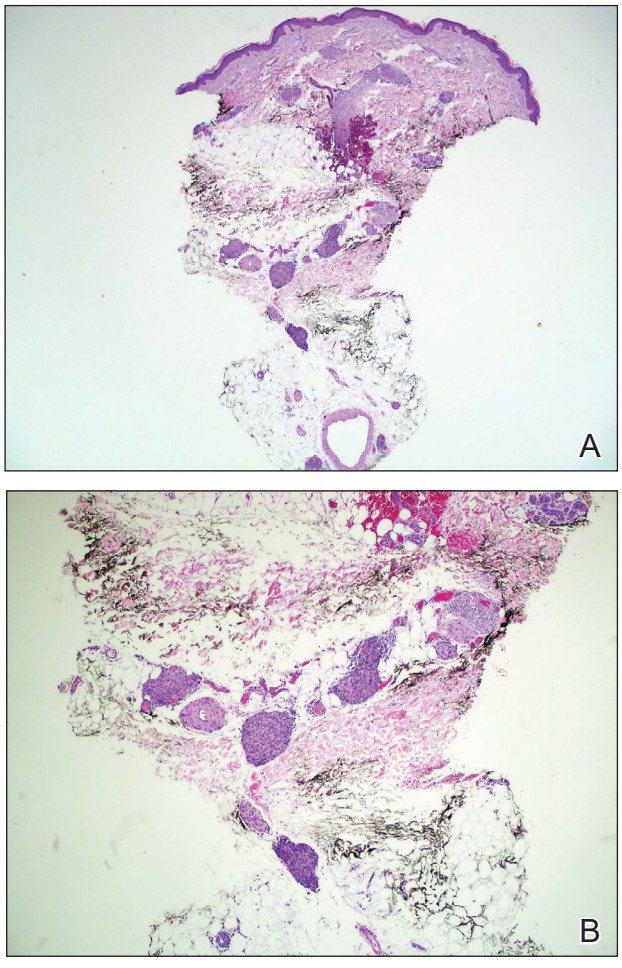

FIGURE 1. A, A punch biopsy of skin from the patient's right thigh revealed nonnecrotizing granulomas in the superficial dermis and subcutaneous adipose tissue (H&E, original magnification ×20). B, Granulomas extended into the subcutaneous adipose tissue (H&E, original magnification ×40).

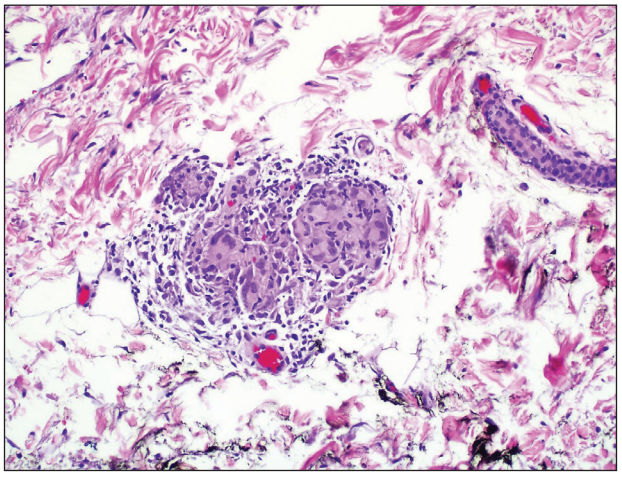

FIGURE 2. Nonnecrotizing granuloma with scant surrounding lymphocytes was present (H&E, original magnification ×200).

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patches or plaques on the limbs, intertriginous areas, and upper trunk. Diffuse macular erythema or small flesh-colored papules also can be observed.[23]

Granulomatous dermatitis secondary to drug reactions can have varying morphologies. The infiltrate often can have an interstitial appearance with the presence of lymphocytes, plasma cells, histiocytes, eosinophils, and multinucleated giant cells.[24] These findings can be confused with interstitial granuloma annulare. Other cases, such as in our patient, can have discrete granulomata formation with a sarcoidlike appearance. These naked granulomas lack surrounding inflammation and suggest a differential diagnosis of sarcoidosis and infection. Use of immune checkpoint inhibitors (CIs) and kinase inhibitors has been proven to cause sarcoidosislike reactions.[25] The development of granulomatous/sarcoidlike lesions associated with the use of BRAF and MEK inhibitors may clinically and radiographically mimic disease recurrence. An awareness of this type of reaction by clinicians and pathologists is important to ensure appropriate management in patients who develop GD.[26]

Checkpoint inhibitor–induced GD that remains asymptomatic does not necessarily warrant treatment; however, corticosteroid use and elimination of CI therapies have resolved GD in prior cases. Responsiveness of the cancer to CI therapy and severity of GD symptoms should be considered before discontinuation of a CI trial.[25]

One case report described complete resolution of a GD eruption without interruption of the scheduled BRAF and MEK inhibitor therapies for the treatment of metastatic melanoma. There was no reported use of a steroidal cream or other topical medication to aid in controlling the eruption.[27] The exact mechanism of how GD resolves while continuing therapy is unknown; however, it has been suggested that a GD eruption may be the consequence of a BRAF and MEK inhibitor–mediated immune response against a subclinical area of metastatic melanoma.[28] If the immune response successfully eliminates the subclinical tumor, one could postulate that the inflammatory response and granulomatous eruption would resolve. Future studies are necessary to further elucidate the exact mechanisms involved.

There have been several case reports of GD with vemurafenib treatment,[29,30] 1 report of GD and erythema induratum with vemurafenib and cobimetinib treatment,[31] 2 reports of GD with dabrafenib treatment,[27,30] and a few reports of GD with the BRAF inhibitor dabrafenib combined with the MEK inhibitor trametinib,[28,32,33] all for the treatment of metastatic melanoma. Additionally, a report described a 3-year-old boy who developed GD secondary to vemurafenib for the treatment of Langerhans cell histiocytosis.[34] We present a unique case of BRAF and MEK inhibitor therapy–induced GD in the treatment of metastatic cholangiocarcinoma with vemurafenib and cobimetinib.

BRAF and MEK inhibitor therapy is used in patients with metastatic melanomas with a positive BRAF V600E mutation. Due to advancements in next-generation DNA sequencing, these therapies also are being tested in clinical trials for use in the treatment of other cancers with the same checkpoint mutation, such as metastatic cholangiocarcinoma. Cutaneous reactions frequently are documented side effects that occur during treatment with BRAF and MEK inhibitors; GD is an uncommon finding. As the utilization of BRAF and MEK inhibitors increases for the treatment of a variety of other cancers, it is essential that clinicians and pathologists recognize GD as a potential cutaneous manifestation.

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