Unusual Adverse Events in a Patient With *BRAF*-Mutated Non–Small Cell Lung Cancer Treated With BRAF/MEK Inhibition

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ABSTRACT

BRAF/MEK inhibition remains standard of care for treatment of *BRAF*-mutated non–small cell lung cancer (NSCLC). Although common adverse events (AEs) have been reported through clinical trials and ongoing clinical practice, only a handful of reports have detailed unusual adverse events associated with these medications. This report presents a patient with *BRAF*-mutated NSCLC treated with dabrafenib and trametinib who experienced 2 unusual AEs—Sweet syndrome and MEK-associated retinopathy—that responded to steroid treatment. The patient was able to continue BRAF/MEK inhibition through a coordinated multidisciplinary approach. This case highlights the importance for all clinicians to recognize unusual AEs associated with BRAF/MEK inhibition, particularly in the setting of expanded use for all *BRAF* V600E–mutated solid tumors.

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Case Report

A 52-year-old female never-smoker with metastatic lung adenocarcinoma and malignant pleural effusion harboring a *BRAF* V600E mutation (via overlapping multiplex PCR amplification on Illumina MiSeq platform) presented with a painful eruption over the bilateral lower extremities. First-line treatment with a BRAF inhibitor, dabrafenib at 150 mg twice daily, and an MEK inhibitor, trametinib at 2 mg daily, had been initiated 3 months prior. She had no pertinent dermatologic history at the time of evaluation. Physical examination revealed an erythematous and edematous plaque on the left thigh with associated lesional edema (Figure 1A). Scattered erythematous macules were noted on the bilateral lower extremities and the left upper extremity. The lesions were intermittent and occasionally accompanied by low-grade fevers. A skin biopsy of the thigh revealed mild perivascular and subcutaneous infiltrate of lymphocytes and few neutrophils consistent with neutrophilic dermatosis (Figure 1B, C). She was started on 60 mg of oral prednisone for 3 days for management, which resulted in complete resolution of her rash. She remained on dose-reduced BRAF/MEK inhibitors given the significant clinical response of her lung cancer with resolution of her right upper lobe opacity and improved pleural effusion and mediastinal lymphadenopathy.

Approximately 3 months later, the patient noted progressive visual changes, including seeing yellow and purple colors in the left eye, visual distortions, and conjunctival hyperemia. Ocular history was notable for myopia. She was referred to ophthalmology, where she was noted on slit light examination to have 2+ episcleral hyperemia. Anterior chambers showed 2+ cell and flare in the right eye and fibrous deposits on the lens and iris in the left eye. Indirect ophthalmoscopy was notable for vitreous cells and swollen discs of both eyes, as well as serous retinal detachment involving the macula and peripheral retina (Figure 2A). Visual acuity (corrected) was noted to be 20/80 in the right eye and 20/150 in the left eye. BRAF/MEK inhibition was discontinued immediately given concern for serous retinopathy/uveitis, and

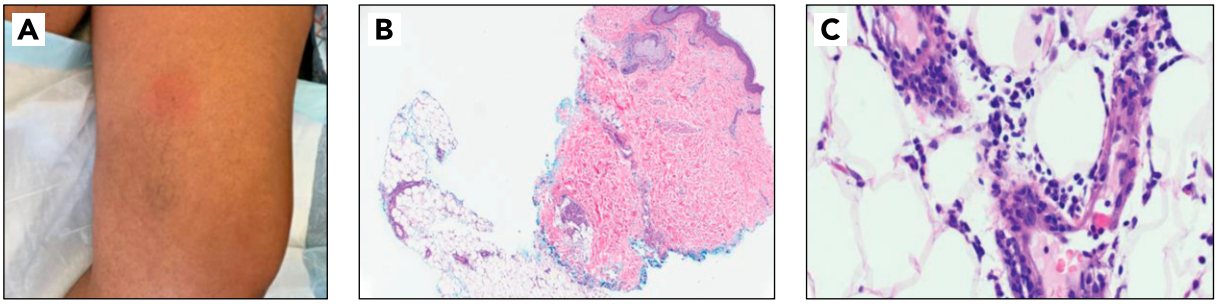

Figure 1. (A) Early erythematous thin plaque on the left thigh that resolved without intervention. **(B)** Histopathology of the skin biopsy on low power magnification (hematoxylin-eosin, original magnification ×40) exhibits a mild infiltrate in the dermis and subcutaneous adipose tissue. **(C)** High-power magnification of the subcutis (hematoxylin-eosin, original magnification ×600) shows that the infiltrate is composed of lymphocytes and neutrophils.

the patient was started on topical corticosteroid drops with no improvement and even progression of symptoms. On repeat examination, visual acuity (corrected) had worsened to 20/200 in the right eye and 20/800 in the left eye. She was subsequently escalated to 1 g of intravenous solumedrol for 3 days followed by prednisone at 1 mg/kg daily thereafter. After significant improvement of her ocular symptoms, she was reinitiated on BRAF/MEK inhibition (dabrafenib, 75 mg twice daily, and trametinib, 1 mg daily), with simultaneous steroid taper based on biweekly ophthalmic evaluations (Figure 2B).

Discussion

Lung cancer remains one of the most common malignancies in the United States, with an estimated 119,100 new cases and 69,410 deaths in 2021, with NSCLC accounting for 80% to 85% of all cases.[1,2] *BRAF* mutations have been described in a number of malignancies, including melanoma and colon cancer, and account for approximately 2% to 4% of NSCLC.[3] Although a number of *BRAF* mutations have been identified, clinical efficacy of targeted therapies has largely been confined to the class I mutations at the V600 position.[4] For patients with a V600E mutation, the combination of dabrafenib + trametinib was approved by the FDA in 2017 based on the results of the BRF113928 study (ClinicalTrials.gov identifier: NCT01336634).[5,6] Common adverse events (AEs) affecting >30% of patients receiving this combination treatment include pyrexia, chills, fatigue, peripheral edema, nausea/vomiting, diarrhea, abdominal pain, headache, and rash.

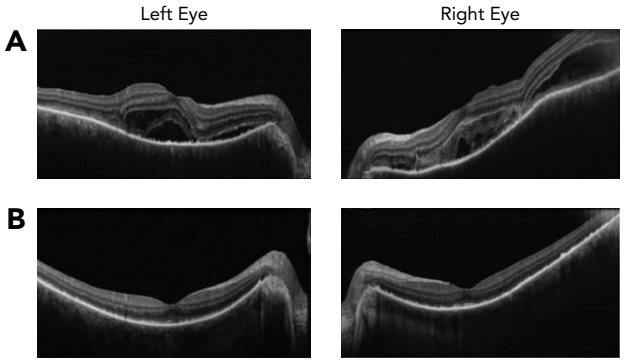

Figure 2. (A) Optical coherence tomography (OCT) B-scans of the left and right eyes at the time of diagnosis revealed dome-shaped fluid accumulation in the subretinal space with displacement of the outer and inner retinal layers. **(B)** OCT B-scans of the left and right eyes on-treatment with systemic corticosteroids showed near complete resolution.

Therapeutic agents targeting BRAF and MEK have been associated with numerous dermatologic AEs, including maculopapular rash, phototoxic reactions, palmoplantar hyperkeratosis, and acneiform eruption. Drug-induced neutrophilic dermatoses, such as Sweet syndrome (SS) and neutrophilic panniculitis, have also been reported in these patients. SS is a febrile neutrophilic dermatosis characterized by abrupt onset of tender erythematous nodules and associated with constitutional symptoms, including fever, malaise, arthralgias/myalgias, and leukocytosis. Drug-induced SS was first reported in 1986 in a patient receiving trimethoprim-sulfamethoxazole.[7] Since that report, numerous medications have been associated with drug-induced SS and formal criteria for diagnosis have been suggested.[8] Several recent case reports have associated BRAF inhibitors with drug-induced SS and histiocytoid SS, a rare variant of SS.[9–11] The case described herein adds to the increasing literature on BRAF inhibitor–related SS.

Complicating serous retinopathy and uveitis has also been well described since the initial clinical studies evaluated BRAF/MEK inhibition in the treatment of cutaneous melanoma, where it was reported as a subfoveal neurosensory retinal detachment similar to central serous chorioretinopathy (CSR).[12,13] Since its initial description, unique clinical and morphologic characteristics, including bilateral involvement, multifocal fluid foci, subretinal shifting fluid, subfoveal focus, normal choroidal thickness, and association with intraocular inflammation, have helped define MEK-associated retinopathy (MEKAR) as a separate entity from CSR.[14] In contrast to CSR, which may be triggered by steroid use, MEKAR is primarily treated with systemic steroids. Risk

factors for MEKAR include history of ocular disease and inflammatory disorders of the anterior eye, decreased estimated glomerular filtration rate, and advanced age.[15]

Conclusions

Overall, this case highlights some of the unusual AEs associated with BRAF/MEK inhibition and the importance of early recognition and multidisciplinary collaboration to guide management. The prompt diagnosis and initiation of treatment for BRAF/MEK-associated SS and MEKAR resulted in resolution of active dermatologic and ocular symptoms, although there remain ongoing sequelae of the patient's vision changes. However, given the limited therapeutic options for *BRAF* V600E lung adenocarcinoma and the desire to remain off chemotherapy, the patient and her team opted to restart and continue trametinib + dabrafenib for as long as possible. She is currently on dabrafenib, 150 mg twice daily, and trametinib, 1 mg daily, while she continues with oral prednisone and careful ophthalmologic monitoring. The team decision to recommend continuation of BRAF/MEK inhibition was based on the development of a collaborative monitoring and communication plan. It remains vitally important for clinicians to be aware of uncommon but clinically significant adverse reactions, especially because use of these agents expands into all solid tumors harboring *BRAF* V600E mutations after the recent FDA accelerated approval.[16]

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