Altered mitogen-activated protein kinase signaling, with MEK as a component, contributes to tumor proliferation in a variety of solid cancers and has been shown to be responsive to the MEK inhibitor class of chemotherapeutic agents.\(^1\) Unique ocular toxic events have been observed in patients undergoing these treatments. A recently published case report\(^2\) highlighted bilateral subfoveal neurosensory retinal detachments in a patient with metastatic cutaneous melanoma receiving a MEK inhibitor. The early recognition, appropriate management, and improved understanding of these toxicities is of high importance now that the first MEK inhibitor, trametinib dimethyl sulfoxide (Mekinist; GlaxoSmithKline), has been approved by the US Food and Drug Administration for treatment in patients with BRAF V600 mutant metastatic melanoma.

Trametinib demonstrated improved survival compared with chemotherapy.\(^3\)

We describe 3 patients with metastatic cancer who were enrolled in MEK inhibitor clinical trials and developed MEK-associated subfoveal neurosensory retinal detachment. To our knowledge, this is the first case series reported in the ophthalmic literature.

The clinical records of all patients with metastatic cancer enrolled in clinical trials requiring protocol ophthalmologic evaluation at our center were reviewed. Patients were excluded if they were receiving a non-MEK inhibitor, such as a BRAF inhibitor. Results of visual acuity and ophthalmic diagnostic tests, as well as clinical course and management, were determined. Three patients who received oral MEK inhibitors developed bilateral subfoveal neurosensory retinal detachment. Patient 1 had metastatic uveal melanoma; the findings resolved without intervention, and subsequent mild uveitis was responsive to topical corticosteroids. Patient 2 had metastatic cholangiocarcinoma, and his findings resolved after 2 weeks of observation. Patient 3 had metastatic rectal cancer, with bilateral uveitis and bilateral subfoveal retinal detachment. Her findings resolved with observation and topical corticosteroids for uveitis. No patient developed permanent ocular sequelae, and none withdrew from the clinical trial of MEK inhibitor therapy.

In this series, we report the detailed clinical findings of bilateral subfoveal neurosensory retinal detachment associated with MEK inhibitor use for treatment of metastatic cancer. A clinical finding of uveitis may prompt the ophthalmologist to consider subfoveal neurosensory retinal detachment.
Retinal Detachment With MEK Inhibitor Use

Report of Cases

Case 1
A woman in her 60s had undergone enucleation surgery to treat a large uveal melanoma in the right eye. Two years later, she developed hepatic metastasis. She enrolled in a clinical trial with the MEK inhibitor XL518 and received 125 mg/d orally. Within 4 to 5 days, she noticed slightly blurred vision. On clinical examination, the woman’s Snellen visual acuity was 20/20, her anterior segment was normal, and her posterior segment revealed a blunted foveal light reflex. Findings from diagnostic testing with fluorescein angiography were normal. Testing with optical coherence tomography revealed subfoveal neurosensory retinal detachment (Figure 1A). Her drug dosage was lowered to 100 mg/d and her symptoms and clinical findings resolved in 1 week (Figure 1B). Her vision remained 20/20, but mild anterior uveitis was observed. The uveitis resolved with administration of topical corticosteroids, and the woman remained in the clinical trial.

Case 2
A man in his 60s with metastatic cholangiocarcinoma was enrolled in a clinical trial with the MEK inhibitor MEK162 at a dosage of 60 mg orally twice daily. At his second protocol ophthalmic evaluation 1 month after initiation of the study drug, the patient presented with no specific visual symptoms and had Snellen visual acuity of 20/20 in both eyes. On clinical examination, the anterior segment of both eyes was normal. Posterior segment examination of the macula revealed blunting of the foveal light reflex in both eyes. Findings from fluorescein angiography were normal (Figure 2A). Optical coherence tomography revealed bilateral subfoveal neurosensory retinal detachments (Figure 2B). His findings resolved within 2 weeks without intervention or alteration of the study drug dosage (Figure 2C).

Case 3
A woman in her 50s with metastatic rectal cancer enrolled in a MEK inhibitor clinical trial that examined the combination of MEK inhibition and a PI3 kinase inhibitor. The day after her first dose, she noticed blurred vision and described central “tan circles” in both eyes. She underwent ophthalmic evaluation several days later and reported that most of her visual symptoms had improved. Her Snellen visual acuity was 20/30 in the right eye and 20/20 in the left eye. Clinical examination revealed moderate anterior uveitis in the right eye and mild anterior uveitis in the left eye. Posterior segment examination revealed blunted foveal reflexes in both eyes. Results of fluorescein angiography were normal (Figure 3A). Optical coherence tomography revealed bilateral subfoveal neurosensory retinal detachments (Figure 3B). She was given topical corticosteroids for the uveitis. In 1 week, both the uveitis and subfoveal neurosensory retinal detachments had resolved (Figure 3C). The woman remained in the clinical trial.

Discussion

We report 3 cases of patients who developed subfoveal neurosensory retinal detachment following treatment with MEK inhibitors while enrolled in clinical trials for metastatic cancer. In each case, the toxic adverse effect occurred within days after initiation of drug therapy, presented with minimal or mild visual symptoms, was self-limited, and, in 2 of the 3 cases, was associated with anterior uveitis.

To our knowledge, there have been no previously published series in the ophthalmology literature describing the unique ocular toxic phenomenon of bilateral subfoveal neurosensory retinal detachment or uveitis associated with MEK inhibitor use. Clinical trial reports refer to this entity as central serous chorioretinopathy (CSCR)-like. However, the 3 cases described in this report are in fact distinct from actual CSCR (also known as central serous retinopathy). Central serous chorioretinopathy has been classically described as a disease of young males with type A personality who present with unilateral central visual distortion due to a neurosensory and/or retinal pigment epithelial detachment (RPED) of the macula that is associated with retinal pigment epithelial disturbance that may be clinically evident as pigmented mottling. The most common association is use of any formulation of corticosteroids. The condition may resolve spontaneously after a few months, and cases with chronic subretinal fluid may benefit...
from laser therapy. Fluorescein angiographic findings frequently demonstrate retinal pigment epithelial alterations in CSCR, and optical coherence tomography may demonstrate both neurosensory submacular retinal detachment and RPEDs. Although subfoveal neurosensory detachments may be seen in both conditions, we have not observed RPED with MEK inhibitor–associated toxic effects.

Furthermore, retinal conditions unique to patients with metastatic cancer must be recognized and distinguished from MEK inhibitor–specific toxic effects. One such entity is paraneoplastic vitelliform retinopathy, a condition that involves multiple RPEDs of the macula and frequently involves the fovea (Supplement [eFigure 1]). A second is bilateral diffuse uveal melanocytic proliferation involving multiple pigmented choroidal tumors (Supplement [eFigure 2]).

The mechanism of subfoveal neurosensory retinal detachment or uveitis with MEK inhibition is not clearly understood. The observation that the retinal vasculature is normal on fluorescein angiography suggests that the leakage of fluid may be attributed to mild or transient dysfunction at the level of the retinal pigment epithelium. The main function of the retinal pigment epithelium is to regulate fluid transport between the neurosensory retina. There is evidence that the mitogen-activated protein kinase pathway regulates tight junctions between retinal pigment epithelial cells so that MEK inhibition may interfere with fluid transport, resulting in the accumulation of fluid beneath the fovea. By extension, interference of the tight junctions in the nonpigmented ciliary body epithelium may contribute to uveitis.

Figure 2. Case 2: Examination of Both Eyes

Color fundus photographs (A) and midphase fluorescein angiogram (B) centered on the macula of the right and left eyes demonstrating no detectable clinical abnormality. Optical coherence tomographic image showing subfoveal neurosensory retinal detachment in both eyes (C).
Conclusions

We describe 3 cases of subfoveal neurosensory retinal detachment associated with MEK inhibitor use for metastatic cancer. Two of the patients developed uveitis. Although our series is small, continued close observation of patients receiving MEK inhibitor therapy is warranted to better understand and characterize these findings as they occur in patients with metastatic cancer.

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