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Separation of outer retinal layers secondary to selumetinib

Robert A. Avery, DO, MSCE,[a,b] Carmelina Trimboli-Heidler, CDOS,[a] and Lindsay B. Kilburn, MD[c,d]

New therapeutic agents targeting the mitogen-activated protein (MAP) kinase pathway, including MEK inhibitors, are currently being evaluated in phase 1 and 2 clinical trials for pediatric brain tumors. Ophthalmologic side effects from MEK inhibitors have previously only been reported in adults and included retinal vein occlusion, central retinal artery occlusion, and separation of the neurosensory retina. We report 2 patients with optic pathway gliomas who developed outer retinal layer separation visualized by optical coherence tomography while taking the MEK inhibitor selumetinib. After discontinuation of selumetinib, the outer retinal layer separation resolved without visual sequelae. One patient has been retreated with selumetinib and experienced recurrence of these findings.

Author affiliations: [a]The Gilbert Family Neurofibromatosis Institute, [b]Center for Neuroscience and Behavior, [c]Division of Oncology, Center for Cancer and Blood Disorders, and [d]The Brain Tumor Institute, Children's National Health System, Washington, DC

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Correspondence: Robert A. Avery, DO, MSCE, Division of Ophthalmology, Children's Hospital of Philadelphia, 34th and Civic Center Blvd, Philadelphia, PA 19104 (email: averyr@email.chop.edu).

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Mitogen-activated protein (MAP) kinase pathway inhibitors, including inhibitors of MEK, are a relatively new biologic therapy that have shown promising activity in treating tumors that demonstrate abnormalities in the *BRAF* gene. Early phase 1 and phase 2 clinical trials of MEK inhibitors in adults with advanced stages of cancer reported nondescript visual symptoms as well as retinal vein occlusion and optic neuropathy while taking MEK inhibitors.[1] Recent case series have described uveitis and subfoveal neurosensory retinal detachment within days to 1 month of taking a MEK inhibitor in adults with metastatic cancer.[2]

Low-grade gliomas of the visual pathway, commonly referred to as optic pathway gliomas, frequently demonstrate abnormalities in the *BRAF* gene, making them excellent candidates to be treated with the newly developed MEK inhibitor drugs.[3] Compared to intravenously administered chemotherapy, MEK inhibitors are particularly appealing for children, because they are taken orally, and preliminary studies suggest that they are generally tolerated and potentially effective therapies for children with low-grade gliomas. However, the toxicities of these agents continue to be defined. We report outer retinal changes in 2 patients undergoing treatment in a clinical trial with the MEK inhibitor selumetinib for their optic pathway gliomas.

Case 1

A 13-year-old girl diagnosed with a juvenile pilocytic astrocytoma of the optic chiasm infiltrating the hypothalamus and left optic nerve was being cared for at Children's National Health System. She was originally treated with weekly vinblastine for 6 months, but her therapy was discontinued due to progressive tumor growth and slow, progressive changes in her visual field. She was subsequently enrolled on a clinical trial evaluating the oral MEK inhibitor selumetinib. Before starting selumetinib, she underwent a baseline ophthalmology examination that included Humphrey visual field testing and spectral domain optical coherence tomography (OCT; Spectralis, Heidelberg Engineering, Germany) imaging of the optic nerve and macula (Figure 1A). Her examination and imaging were unremarkable except for a stable right infratemporal visual field defect (Figure 1A). Six months after starting selumetinib, she presented to clinic complaining of 2 days of near continuous visual phenomenon described as "large rain drops" that would obscure her central vision in both eyes. The size and intensity of the visual phenomenon would fluctuate throughout the day. On examination, her

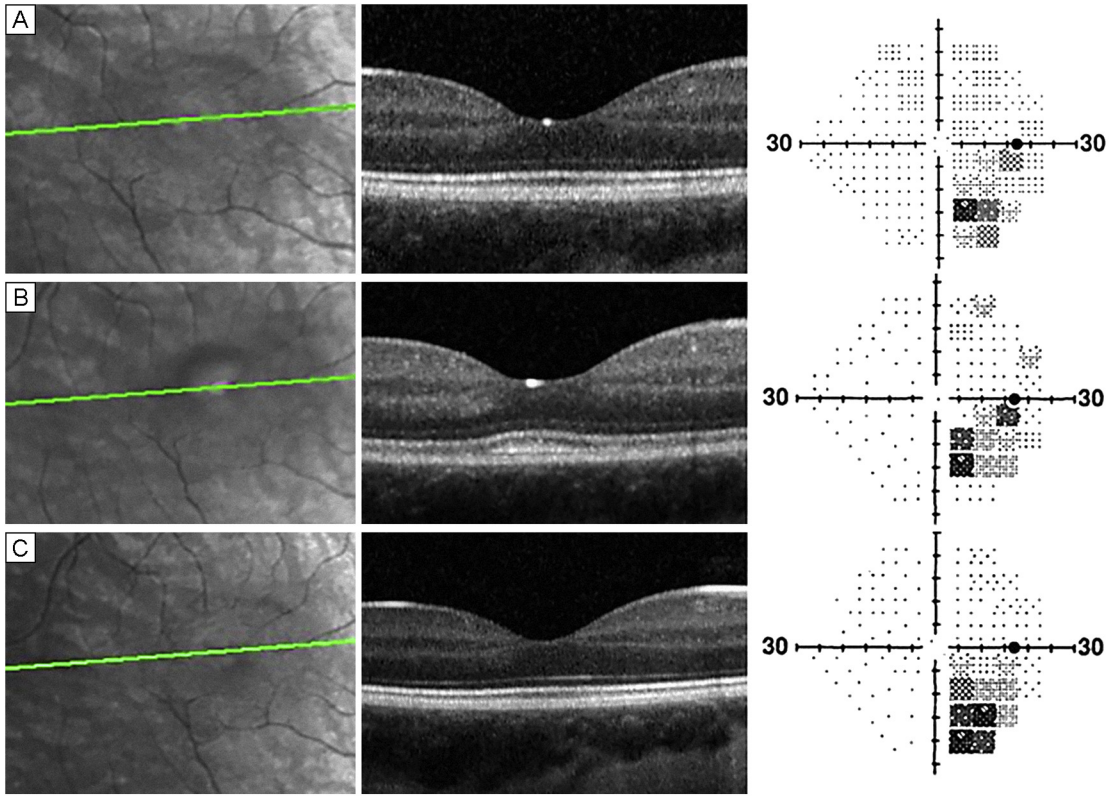

FIG 1. Infrared and OCT images and Humphrey visual fields of case 1. A, Before treatment with selumetinib. B, At the onset of visual symptoms, highlighting outer retinal layer separation and a highly reflective band. C, Twelve days after stopping selumetinib, showing resolution of OCT findings.

visual acuity was 20/20 in each eye and she identified 10/10 Ishihara color plates with each eye. Amsler grid testing was normal. Pupils were normal, with no relative afferent defect. Humphrey visual field demonstrated a stable right infratemporal defect (Figure 1B). Ocular ductions and alignment were normal. Slit-lamp examination of the anterior segment was normal, with no evidence of uveitis. Indirect and direct ophthalmoscopy demonstrated a normal-appearing optic nerve, but there was a questionable abnormal foveal reflex. OCT of the optic nerve revealed a stable circumpapillary retinal nerve fiber layer thickness. Macula OCT using both volume and raster scans visualized separation and a new highly reflective band between the retinal pigmented epithelium (RPE) and the ellipsoid segment (Figure 1B) equally in both eyes. Infrared OCT images showed questionable signal changes surrounding the fovea. Given these new visual complaints with associated retinal changes, her treatment with selumetinib was stopped. Within 2 days of stopping selumetinib, her visual symptoms resolved. Her examination was stable 12 days after stopping selumetinib, and the OCT findings had resolved (Figure 1C).

Case 2

A 6-year-old boy with a longstanding suprasellar/chiasmatic pilocytic astrocytoma began treatment with selumetinib after failing multiple prior chemotherapy regimens. The patient is autistic, nonverbal, and unable to cooperate with quantitative visual acuity testing. Prior to starting the clinical trial for selumetinib, his mild temporal pallor of both optic nerves was stable. During an OCT imaging session (Envisu Bioptigen, Morrisville, NC [now Leica Microsystems, Wetzlar, Germany]) for a research study prior to the start of selumetinib, images of both macula were qualitatively normal (Figure 2A). Seven months after starting selumetinib, his OCT demonstrated separation across the RPE and interdigitation zone (Figure 2B). Selumetinib dosing was held, and repeat OCT imaging was performed 7 days later, with complete resolution of the macular findings (Figure 2C). He was then restarted on selumetinib at the same dose. OCT imaging 6 weeks, 3 months, and 6 months (Figure 2D) later demonstrated continued resolution of the macular findings; however, 8 months after restarting selumetinib, the retinal separation returned (Figure 2E).

Discussion

MEK inhibitors are known to alter the outer blood–retina barrier.[4,5] It is unclear whether the previously reported retinal vein occlusions in adults with advanced cancer were due to MEK inhibitor induced alteration in the outer blood retinal barrier rather than the other known systemic risk factors (eg, hypertension, atherlosclerosis).[5] Over 10 different MEK inhibitors have been developed, all of which have different chemical structures, mechanism of action, and side effect profiles.[6,7]