

CE Credit - Case Report(s) & Topic Review

MEK Inhibitor-Associated Retinopathy Secondary to the Use of Trametinib

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ABSTRACT

Introduction: Mitogen-activated protein kinase (MEK) inhibitors have become an important component in the treatment of patients with BRAF-mutated cancers. Although generally well tolerated, these therapies have been associated with a range of ocular adverse effects. As the use of targeted oncologic therapies continues to increase, eye care providers should be familiar with these potential complications.

Case Report: A 74-year-old Caucasian female with stage IVB BRAF V600E-mutated anaplastic thyroid carcinoma presented with new-onset flashes and persistent floaters in the left eye after six weeks of treatment with trametinib and dabrafenib as part of a clinical trial, along with adjuvant radiation therapy. Dilated fundus exam and multimodal retinal imaging demonstrated bilateral peripheral retinal hemorrhages, greater in the right eye, subretinal fluid involving the right fovea, and an acute posterior vitreous detachment in the left eye without associated retinal tears or detachment. The patient was instructed to monitor for visual changes and return for follow-up in six weeks. At this follow-up visit, OCT demonstrated complete resolution of the subretinal fluid, and the peripheral retinal hemorrhages had nearly resolved, with only faint residual hemorrhages remaining in the right eye.

Conclusion: This case demonstrates the importance of considering treatment-related ocular findings in patients receiving targeted cancer therapies. Prompt recognition, multimodal retinal imaging, and communication between eye care providers and oncology teams are necessary for identifying medication-related toxicity and supporting preservation of vision and continuation of effective systemic therapy.

Keywords: BRAF mutation, MEK inhibitor, MEK inhibitor-associated retinopathy, Subretinal fluid, Trametinib

INTRODUCTION

The mitogen-activated protein kinase (MAPK) signaling pathway is an essential intracellular pathway involved in regulating cellular growth, proliferation, differentiation, and survival.¹⁻² Activating mutations in the BRAF gene lead to persistent MAPK pathway activation and contribute to the development of several malignancies, including melanoma, non-small cell lung cancer, and anaplastic thyroid carcinoma.¹⁻² The introduction of targeted therapies directed at this pathway has significantly improved outcomes for patients with BRAF-mutated cancers. Combination therapy with the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib have demonstrated improved disease control and survival, becoming a treatment strategy for advanced malignancies.¹⁻²

Despite their clinical benefits, MEK inhibitors are associated with a range of ocular adverse effects, which include MEK inhibitor-associated retinopathy (MEKAR). This case highlights the importance of comprehensive retinal evaluation and multimodal imaging in patients receiving targeted cancer therapies, as new retinal findings may represent medication-associated toxicity requiring collaboration between eye care providers and oncology teams.

CASE REPORT

A 74-year-old Caucasian female was referred for evaluation of new-onset flashes and floaters after initiation of targeted cancer therapy. Six weeks after starting combination trametinib and dabrafenib, she developed multiple flashes

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followed by a persistent, new floater in the left eye. The photopsia had resolved by the time of evaluation, although the floater remained unchanged. She denied ocular trauma or prior ocular surgery. Her most recent comprehensive eye exam was five months earlier, at which time she was monitored for age-related cataracts.

Her ocular medications included apraclonidine 0.5% twice daily in the right eye for a history of suspected Horner syndrome following prior neck dissection. Her medical history was significant for hypertension, hyperlipidemia, hypothyroidism, history of breast cancer, and stage IVB BRAF V600E-mutated anaplastic thyroid carcinoma. Her oncologic history included chemotherapy and radiation for breast cancer in 2003 and a left hemithyroidectomy in 1997, followed by completion radical thyroidectomy with bilateral neck dissections, including right central, right modified radical, and left selective neck dissections, as well as extensive dissection of the right carotid sheath with circumferential exposure of the carotid artery.

She was enrolled in a clinical trial receiving a combination of trametinib 2 mg and dabrafenib 200 mg administered through a PEG tube, along with six weeks of adjuvant radiation therapy for stage IVB BRAF V600E-mutated anaplastic thyroid carcinoma. Trametinib had been temporarily discontinued by her oncology team shortly before ophthalmic exam due to concern for possible medication-related ocular toxicity after the onset of flashes and floaters. Her antihypertensive medications had previously been discontinued following chemotherapy, radiation therapy, and significant weight loss. Additional systemic medications included clopidogrel, rosuvastatin, levothyroxine, oxybutynin, and esomeprazole. She also intermittently receives oral prednisone for chemotherapy-associated reactions. Her most recent course of oral prednisone was 10 mg daily for 5 days and was completed approximately 1 month prior to her ophthalmic exam.

Corrected visual acuity was 20/30 in both eyes, improving with pinhole testing to 20/20-1 in the right eye and 20/25-2 in the left eye. Pupils and extraocular motility were normal in both eyes. Intraocular pressure was 10 mmHg in the right eye and 19 mmHg in the left eye with iCare. Confrontation visual fields were full. Anterior segment exam was notable only for bilateral upper eyelid dermatochalasis and grade 1+ nuclear sclerotic cataracts. Dilated fundus exam demonstrated vitreous syneresis in the right eye and an acute posterior vitreous detachment with a Weiss ring in the left eye. Subretinal fluid involving the fovea of the right eye was identified and confirmed with optical coherence tomography (OCT) (Figure 1). The optic nerves appeared healthy with a cup-to-disc ratio of 0.55 in both eyes. Retinal vasculature was normal without evidence of neovascularization. Peripheral dot-blot hemorrhages were present in both eyes, but worse in the right eye (Figure 2-3). The retina remained flat and attached 360 degrees without retinal breaks or detachment.

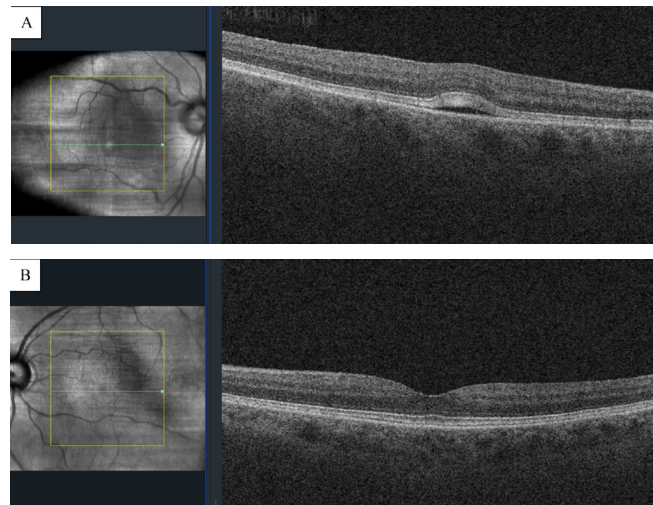


Figure 1: Optical coherence tomography of the right eye (A) captures subretinal fluid without evidence of a choroidal neovascular membrane or disruption to photoreceptors. Optical coherence tomography of the left eye (B) was unremarkable, with no evidence of maculopathy.



Figure 2: Color fundus photograph of the right eye (A) captures peripheral hemorrhages along the temporal arcades (yellow circle) and subretinal fluid involving the fovea (yellow arrow). Fundus autofluorescence of the right eye (B) captures foveal hyperautofluorescence without gravitational tracts. (yellow arrow).

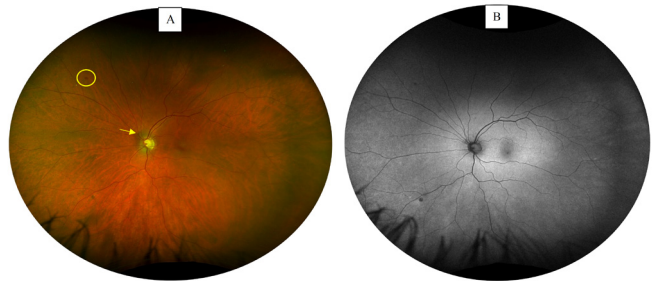


Figure 3: Color fundus photograph of the left eye (A) captures a single hemorrhage along the superior-nasal arcade (yellow circle) and posterior vitreous detachment nasal to optic nerve head (yellow arrow). Fundus autofluorescence of the left eye (B) demonstrates no abnormal foveal autofluorescence.

The differential diagnosis for the macular changes included central serous chorioretinopathy, exudative age-related macular degeneration, and MEK inhibitor-associated retinopathy. Central serous chorioretinopathy was considered given the patient's five-day course of oral prednisone approximately one month before the initial exam but was less likely due to the short duration

of steroid use, absence of gravitational tracts on fundus autofluorescence, and lack of photoreceptor disruption. Exudative age-related macular degeneration was also considered based on the patient's demographics but was less likely given the absence of drusen, significant macular pigmentary changes, or choroidal neovascularization on OCT. MEK inhibitor-associated retinopathy was considered the most likely diagnosis based on the recent initiation of trametinib and the presence of unilateral subretinal fluid without macular pigmentary changes or photoreceptor disruption on OCT.

The peripheral retinal hemorrhages were considered separately, with hypertensive and radiation retinopathy included in the differential. Hypertensive retinopathy was less likely given the absence of arteriolar narrowing, arteriovenous crossing changes, nerve fiber layer hemorrhages, or cotton-wool spots. Radiation retinopathy was considered given the patient's history of radiation therapy. However, the hemorrhages developed during treatment, whereas radiation-induced retinal vascular changes generally have a delayed onset following radiation exposure. Although peripheral retinal hemorrhages are not typical of MEK inhibitor-associated retinopathy, the development of both subretinal fluid and peripheral retinal hemorrhages after the initiation of trametinib raised concern for treatment-related ocular toxicity. The acute posterior vitreous detachment in the left eye was considered unrelated to targeted therapy and most likely associated with age-related vitreous changes.

The patient was provided with an Amsler grid for home monitoring and instructed to check vision at least two to three times daily. The patient was also educated on symptoms for retinal breaks or detachment, including increasing flashes, new or worsening floaters, or a curtain-like shadow over vision. After discussion with the oncology team, trametinib 2 mg was resumed given the absence of significant visual symptoms or vision-threatening retinal complications. A follow-up exam was scheduled in six weeks, including repeat dilated fundus exam, OCT, and widefield retinal imaging to monitor resolution of the subretinal fluid and retinal hemorrhages.

FOLLOW-UP VISIT #1

Six weeks after the initial exam, the patient returned for follow-up. She reported that symptoms remained largely unchanged, with continued presence of the left eye floater but no recurrence of flashes, metamorphopsia, or additional visual disturbances. She denied worsening vision or new ocular complaints. At this time, she remained on trametinib 2 mg and dabrafenib 200 mg and had completed radiation therapy.

Corrected visual acuity was 20/30-1 in the right eye and 20/50-2 in the left eye, improving with pinhole testing to 20/25-2 and 20/30, respectively. Pupils and extraocular

motility were normal in both eyes. Intraocular pressure was 11 mmHg in the right eye and 14 mmHg in the left eye with Tonopen. Anterior segment exam was unchanged. Dilated fundus exam demonstrated stable vitreous syneresis in the right eye and posterior vitreous detachment in the left eye. The previously noted foveal subretinal fluid in the right eye had resolved on OCT imaging (Figure 4). Peripheral retinal hemorrhages had also improved, with complete resolution in the left eye and residual pinpoint temporal hemorrhages near the ora serrata in the right eye (Figures 5-6). The retina remained flat and attached 360 degrees without retinal breaks or detachment.

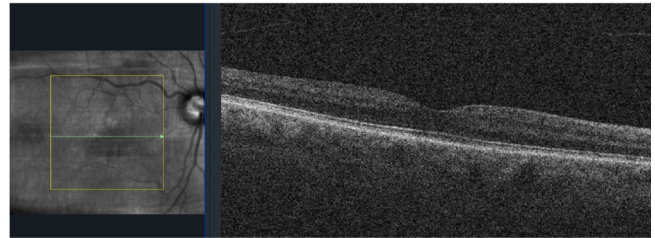


Figure 4: Optical coherence tomography of the right eye demonstrating resolution of the subretinal fluid without evidence of a choroidal neovascular membrane or photoreceptor disruption.

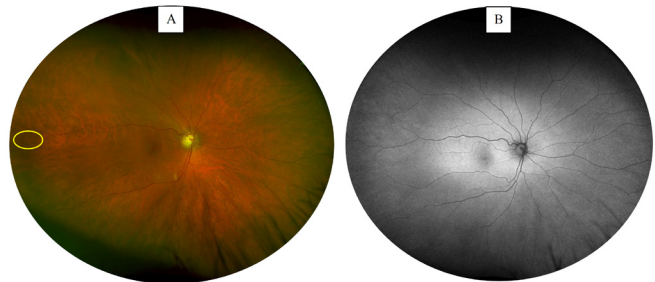


Figure 5: Color fundus photograph of the right eye (A) demonstrating pinpoint residual hemorrhages along the temporal arcades (yellow circle), which are subtle and difficult to appreciate on photography. Fundus autofluorescence of the right eye (B) demonstrates no abnormal foveal autofluorescence.

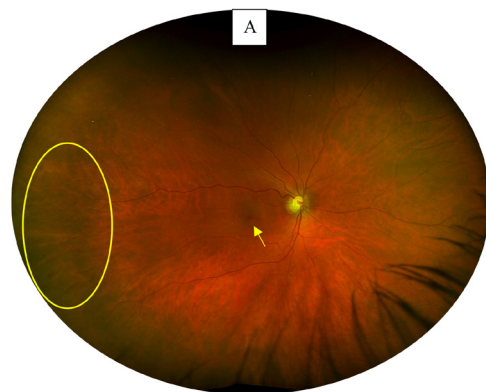


Figure 6: Color fundus photograph of the left eye demonstrating resolution of the retinal hemorrhage with no hemorrhages visible along the arcades and a stable posterior vitreous detachment.

Given the significant improvement in retinal findings, continued observation was recommended. The patient was again counseled on retinal detachment symptoms. A follow-up report documenting near-complete resolution of ocular findings was provided to the oncology team and repeat exam with OCT and widefield retinal imaging was planned for three months while systemic therapy continued.

DISCUSSION

The MAPK pathway is a central intracellular signaling cascade responsible for regulating cellular proliferation, differentiation, growth, and survival.¹⁻² Mutations in BRAF result in constitutive activation of this pathway and contribute to tumor development in multiple malignancies.³ Mutations in BRAF are identified in approximately 50% to 70% of cutaneous melanomas and have become an important therapeutic target in oncology.³⁻⁴ The development of BRAF inhibitors significantly improved outcomes for patients with advanced BRAF-mutated cancers, but resistance commonly develops through reactivation of MAPK signaling via secondary molecular mechanisms.⁴⁻⁵ Combination therapy targeting both BRAF and MEK has therefore become the preferred approach to improve treatment durability, delay resistance, and reduce paradoxical MAPK pathway activation.^{3, 6-7} Potent and specific inhibitors of MAPK pathway mediators include BRAF inhibitors (vemurafenib, dabrafenib, and encorafenib), MEK inhibitors (trametinib, selumetinib, cobimetinib, and binimetinib).³

Trametinib is approved, in combination with the BRAF inhibitor dabrafenib, for the treatment of unresectable or metastatic melanoma, advanced non-small cell lung cancer, and advanced anaplastic thyroid cancer that have a BRAF V600 mutation.² Ocular adverse events associated with MEK inhibitors have been reported in approximately 5% to 38% of patients across clinical trials, although the reported incidence varies due to differences in study populations, monitoring protocols, and terminology used to describe retinal findings.¹ Historically, these changes have been described as central serous retinopathy, serous retinal detachment, chorioretinopathy, or macular edema. These findings are now recognized as MEK inhibitor-associated retinopathy.¹

MEKAR typically presents shortly after treatment initiation, with retinal changes often developing within days to weeks of starting therapy.⁵⁻⁶ Although the exact mechanism remains incompletely understood, current evidence suggests that transient dysfunction of the retinal pigment epithelium (RPE) plays a central role. The MAPK pathway contributes to RPE homeostasis by regulating oxidative stress responses, maintaining tight junction integrity, and facilitating fluid transport across the outer blood-retinal barrier.³ Inhibition of MEK signaling may disrupt these functions, resulting in increased RPE permeability and accumulation of subretinal fluid. Other proposed mechanisms include disruption of extracellular signal-regulated kinase (ERK) signaling within

the RPE, leading to dysregulation of ion transport involved in maintaining the outer blood-retinal barrier, as well as changes in aquaporin 1, a fluid transport channel within RPE cells.³ The reversibility of MEK inhibitor-associated retinopathy may be related to recovery of MAPK/ERK signaling within the RPE and outer retina after transient pathway inhibition, leading to improvement in RPE homeostasis and resolution of subretinal fluid.³ However, resolution of subretinal fluid does not necessarily indicate complete recovery of RPE function.

Although MEKAR shares several clinical features with central serous chorioretinopathy (CSCR), including subretinal fluid accumulation, blurred vision, and metamorphopsia, MEKAR is more commonly bilateral, whereas CSCR is generally unilateral and associated with a different underlying pathophysiology.⁸⁻⁹ MEKAR is commonly characterized by multiple discrete areas of subretinal fluid involving the fovea and posterior pole, whereas CSCR more often demonstrates localized serous detachments with gravitational tracking of fluid.⁸ Choroidal thickness typically remains unchanged in MEKAR, while choroidal thickening is a recognized feature of CSCR.¹⁰ OCT findings in MEKAR have been categorized into four morphologic patterns: dome, caterpillar, wavy, and splitting configurations. Dome-shaped lesions represent localized fluid accumulation between the interdigitation zone (IZ) and RPE, which is more commonly observed in CSCR.⁸ Smaller dome lesions primarily displace the outer retinal layers toward the vitreous, while larger dome lesion may involve displacement of both inner and outer retinal structures.⁸ The caterpillar pattern appears as a shallow, linear, plateau-like fluid collection that produces localized inward displacement of the interdigitation zone and adjacent outer retina.⁸ The wavy pattern consists of linear small dome-shaped fluid accumulations that create an undulating appearance of the IZ and outer retinal layers.⁸ The splitting pattern demonstrates a broader separation between the RPE and IZ, with subretinal fluid extending beyond the boundaries typically observed in other configurations.⁸ Additionally, the ellipsoid and interdigitation zones generally remain preserved during both fluid accumulation and resolution in MEKAR, whereas CSCR may result in persistent photoreceptor disruption.⁸

Unlike CSCR, patients with MEKAR generally do not demonstrate evidence of retinal or choroidal vascular leakage on fluorescein angiography or indocyanine green angiography.⁸⁻¹⁰ When fluorescein pooling is present, it typically corresponds to areas of serous retinal detachment rather than active leakage, supporting transient RPE dysfunction rather than primary choroidal vascular pathology.⁸⁻¹⁰ Early age-related macular degeneration (AMD) may also be considered in the differential diagnosis, as both conditions can demonstrate RPE irregularities or elevations. However, AMD is typically associated with chronic findings such as drusen, pigmentary changes, or preexisting structural abnormalities.⁹

Additional ocular complications associated with MEK inhibitor therapy include pigment epithelial detachments, retinal vein occlusion, uveitis, conjunctivitis, dry eye disease, ocular hypertension, optic nerve abnormalities, and, less commonly, cystoid macular edema.^{1,3} Although uncommon, retinal vascular events have been reported with both MEK inhibitor monotherapy and combination regimens and may result from oxidative stress and a prothrombotic state, which can increase the risk of retinal vein occlusions.¹¹

Currently, there are no universally established recommendations for routine ophthalmic screening in all patients receiving MEK inhibitors.^{1,12} However, a baseline comprehensive eye exam, including dilated fundus evaluation and macular OCT, may be beneficial to document retinal findings before treatment initiation and identify preexisting pathology.¹ The literature suggests obtaining a baseline ophthalmic exam within 1 month of starting a MEK inhibitor, followed by exams every 3 to 6 months.¹² Management of MEKAR should be individualized based on the extent of retinal involvement, visual symptoms, and the patient's oncologic needs. Treatment interruption, dose reduction, or discontinuation should generally be considered for patients with significant visual impairment or extensive retinal involvement.¹

CONCLUSION

The increasing use of targeted cancer therapies highlights the importance of recognizing associated ocular toxicities. MEK inhibitor-associated retinopathy is a typically reversible retinal adverse effect that may develop shortly after initiation of therapy and can often be managed without discontinuing systemic treatment. Prompt identification through a comprehensive exam and multimodal imaging allows appropriate monitoring, preserves visual function, and supports continuation of potentially life-prolonging oncologic therapy.

Disclosures

No identifiable health information was included in this case report. The author declares no conflicts of interest. The author declares no funding sources.

Take Home Points

1. MEK inhibitor-associated retinopathy is a recognized ocular toxicity that may present most commonly with transient subretinal fluid accumulation, often occurring early after initiation of therapy.
2. MEK inhibitor-associated retinal changes are frequently reversible and may resolve with observation and without interruption of treatment
3. Close collaboration between eye care providers and oncology teams is necessary to appropriately manage ocular adverse effects while avoiding unnecessary interruption of effective and potentially life-prolonging cancer therapy.

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