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Central retinal vein occlusion in the setting of fibroblast growth factor receptor inhibition

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ABSTRACT

Purpose: To report a case of central retinal vein occlusion (CRVO) in a patient being treated with a fibroblast growth factor receptor (FGFR) inhibitor.

Observations: A 54-year-old female patient with endometrial cancer presented with CRVO and cystoid macular edema while receiving lenvatinib/pembrolizumab combination therapy. The patient received treatment with intravitreal bevacizumab, after which her visual acuity improved markedly, permitting the continuation of her chemotherapy regimen without recurrence of ocular adverse events.

Conclusions and Importance: Like mitogen-activated protein kinase inhibitors, FGFR inhibitors have the potential to be associated with retinal vein occlusion. In this case, visual recovery was possible with intravitreal anti-vascular endothelial growth factor therapy, and toxicity did not recur with drug reinitiation and continuation over five years of follow-up.

1. Introduction

Fibroblast growth factor receptor (FGFR) inhibitors downregulate mitogen-activated protein kinase (MAPK) pathway signaling and have emerged as effective cancer therapeutics. Targets of the MAPK pathway are expressed in the retina,[1] and both FGFR inhibitors and mitogen-activated protein kinase kinase (MEK) inhibitors (which act on the same pathway) can induce a characteristic serous retinopathy.[2] Retinal vein occlusion is recognized as a rare occurrence with MEK inhibitors.[3] Taken together, these observations raise the question of whether vein occlusion is *also* associated with FGFR inhibitors. Herein, we describe a patient with central retinal vein occlusion (CRVO) while on the FGFR inhibitor lenvatinib.

2. Case report

A 54-year-old female received combination lenvatinib/pembrolizumab therapy for metastatic microsatellite stable G2 endometrioid adenocarcinoma. Lenvatinib is a tyrosine kinase inhibitor that selectively inhibits FGFR 1–4, VEGF R1-3, PGDFRα, RET and KIT. Pembrolizumab is a monoclonal antibody against PD1. The patient had no past medical or ocular history at the time of starting treatment. Six months into treatment, she had blurred vision of the right eye: visual acuity (VA) was count fingers at 1 foot OD, and 20/20 OS. Dosing at the time was lenvatinib 14mg PO daily/pembrolizumab 200mg IV q 3 weeks. Examination of the right fundus revealed optic disc edema with hemorrhages, macular edema, dilation and tortuosity of all central retinal vein branches, with extensive posterior and peripheral hemorrhages (Fig. 1, upper left panel). Optical coherence tomography (OCT) revealed cystoid macular edema and subretinal fluid of the right eye (Fig. 1, lower left panel). There was no clinical evidence of inflammation. Complete blood count, comprehensive metabolic panel, lipid panel, coagulation screen, hemoglobin A1c, Factor V, phospholipid Ab IgM and IgG were all within normal limits. Of note, the patient had also developed drug-induced hypertension that was controlled on amlodipine 25mg daily.

The patient was diagnosed with CRVO, lenvatinib was discontinued, intravitreal bevacizumab (1.25mg/0.05mL) was injected.

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Pembrolizumab was continued uninterrupted. At one month, a second dose of intravitreal bevacizumab was administered with continued clinical improvement. Lenvatinib (10mg) was restarted. Over 62 months follow-up, the patient had a complete response, and vision is maintained at 20/25 without recurrence of any ocular adverse events (Fig. 1).

3. Discussion

Fibroblast Growth Factor Receptor (FGFR) 1–4 inhibitors are known to downregulate MAPK pathway signaling (Fig. 2).[4] Targets of this pathway are expressed in the retina,[1,5] perhaps explaining the characteristic serous retinopathy which occurs with FGFR inhibitors, as well as other more direct inhibitors of the MAPK pathway, such as extracellular signal-regulated kinase (ERK) inhibitors and MEK inhibitors.[2,6] This case suggests another commonality between these drug classes: CRVO is associated with MEK inhibitors,[3,7] and here we present a case of CRVO likely attributable to FGFR inhibition.

In determining the extent to which the vein occlusion was attributable to lenvatinib, we considered other possibilities. First, CRVO are associated with systemic risk factors,[8] and perhaps the patient's lenvatinib-induced hypertension was a contributing factor. Notably, hypertension has been reported as an adverse event in almost one fifth of patients treated with lenvatinib.[9] Clearly, it is beyond the scope of this report to demonstrate the extent to which the CRVO was attributable directly to lenvatinib or indirectly by drug-induced hypertension, however this is an important factor to take account of in the patient's clinical presentation. A second possibility to consider is that treatment was given in combination with pembrolizumab, which has been associated with a host of ocular inflammatory phenomena, including vasculitis (which itself has the potential to instigate a vein occlusion).[10] However, our patient had no clinical evidence of intraocular inflammation nor vasculitis, and she continued pembrolizumab uninterrupted throughout her vein occlusion recovery. Lastly, our patient's malignancy creates a hypercoagulable state and heightens the risk of vein occlusion.[11,12] However, borrowing from the MEK inhibitor literature, the risk of MEK inhibitor-associated CRVO in a cancer patient is five times higher than would be expected for a cancer patient not on MEK inhibition,[13] and the same may be true of FGFRi.

There is a notable aspect of this case which overlaps with MEK inhibitor-associated CRVO. This is the fact that the clinical outcome, specifically the excellent visual rehabilitation, is consistent with previous reports of MEK inhibitor-associated CRVO.[13] The multicenter Central Vein Occlusion Group previously studied the natural history of 714

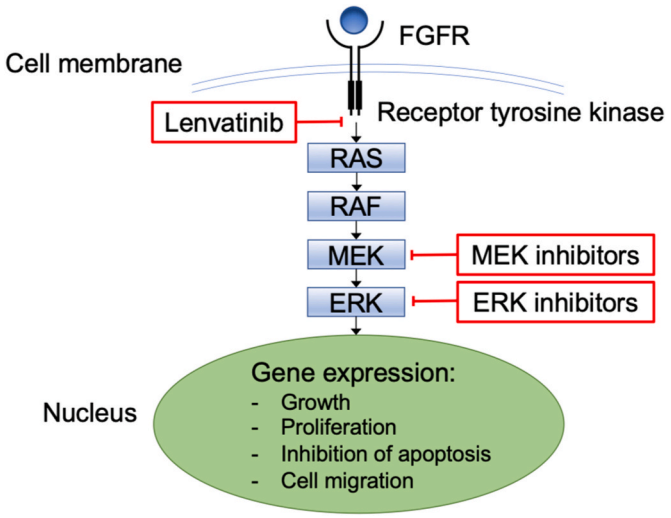

Fig. 2. Key components of the Ras-Raf-MEK-ERK signaling pathway.

eyes with CRVO, and reported that, for eyes presenting with visual acuity of 20/200 or worse, 79% of eyes remained with vision of 20/200 or worse, 19% improved to 20/50 to 20/200, and 1% improved to 20/40 at three years follow-up.[14] Since 2010 a number of trials have demonstrated significant improvement in visual outcomes following intravitreal injection of anti-VEGF, although real-world gains have been shown to be more modest.[15] Accordingly, visual improvement from count finger vision to 20/25 as described in this case is highly atypical. Yet visual recovery to baseline occurred in all three of our previously reported MEK inhibitor-associated CRVO patients, including one who similarly improved from count fingers to 20/25.[13] Given the small number of patients described in these reports, it is challenging to draw generalizable conclusions, nevertheless our case does exhibit similar clinical characteristics to CRVO occurring in the setting of MEK inhibition.

4. Conclusions

FGFR inhibitors and MEK inhibitors both target the MAPK pathway, and both result in a serous retinopathy. CRVO has been reported as a rare occurrence with MEK inhibitors, and here we present a case of

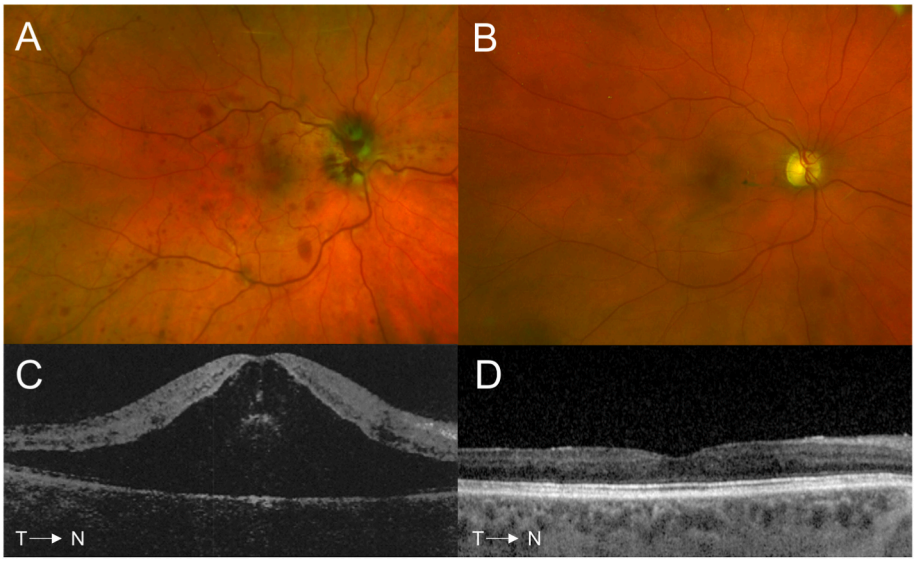

Fig. 1. Ophthalmic images at presentation and follow-up.

CRVO occurring in the setting of FGFR inhibition. Our case suggests that, as with CRVO occurring in patients on MEK inhibitors, there may a relatively favorable visual prognosis compared to the wider cohort of CRVO patients. The decision of whether to withhold these potentially life-saving chemotherapeutic agents when ocular adverse events occur is extremely challenging. Strikingly our patient restarted and remains on FGFR inhibition through her five-year follow up, without recurrence of ocular toxicity. Further reports are needed to determine visual prognosis and guide decision making.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editor of this journal.

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Authors contributions

All authors attest that they meet the current ICMJE criteria for Authorship. JHF conceived the work. WF, BZE, JC, VM, JK, DHA were involved in acquisition and interpretation of patient data. WF drafted the work. WF, BZE, JC, VM, JK, DHA, JHF performed critical revision of the work. WF, BZE, JC, VM, JK, DHA, JHF gave final approval of the work to be published and agree to be accountable for all aspects of the work.

Ethics approval and consent to participate

No ethical approval required.

Availability of data and materials

All data generated and analyzed during this study are included in this article.

Fundus photographs of the right eye at presentation (A) and at 62 months' follow-up (B). At presentation, visual acuity was count fingers at 1 foot, with fundus exam notable for optic disc edema and hemorrhages, venous dilation and tortuosity and diffuse intraretinal hemorrhages. At 62 months' follow-up, visual acuity was 20/25, with resolution of posterior pole pathology. Optic coherence tomography shows macular edema at presentation (C), with restoration of a normal foveal contour at follow-up (D).

Lenvatinib is a tyrosine kinase inhibitor that blocks signaling via fibroblast growth factor receptors 1–4. Accordingly, lenvatinib downregulates signaling along the Ras-Raf-MEK-ERK pathway, a chain of proteins that communicates a signal from the cell surface to the nucleus. MEK inhibitors and ERK inhibitors are downstream inhibitors of this same pathway.

Declaration of competing interest

None of the authors have a proprietary interest in the material presented in this study. Disclosures include WF: none. BZE: none. JC: none. VM: research (all funding to institution)/consultant/advisory board member support from Merck, Eisai, Karyopharm, AstraZeneca, Clovis, Moreo, Takeda, Zymeworks, Genentech, GSK, Dicephera, Faeth, Novartis, iTEOS. JK: research (all funding to institution)/consultant/advisory board member support from Immunogen, Merck, AstraZeneca, Clovis. DHA: none. JHF: none.

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