Case Report

Cabozantinib-Associated Exudative Retinal Detachment and Choroiditis: A Case Report

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Abstract

Purpose: To describe the first reported instance of an acute chorioretinal inflammatory response to cabozantinib.

Methods: Case report.

Results: A 54-year-old Asian male presented with blurred vision 2 weeks following the commencement of cabozantinib for metastatic renal cell carcinoma. Ophthalmic examination revealed bilateral exudative retinal detachments and choroiditis in a pattern similar to Vogt–Koyanagi–Harada disease. Further investigations revealed latent tuberculosis (TB), and management of this ocular adverse event was with cabozantinib cessation, high-dose oral prednisone, single-agent anti-TB therapy, and methotrexate. Return of visual function and ocular anatomy occurred within 1 month.

Conclusions: Modern pharmacotherapy for metastatic cancer may increase survival, but a range of ocular and systemic adverse events are frequently seen. Screening and early intervention can mitigate adverse events and treatment burden, while maximizing benefits for this disadvantaged patient group.

Keywords: Cabozantinib, Exudative retinal detachment, Renal cell carcinoma, Uveitis, Vogt–Koyanagi–Harada-like reaction

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Introduction

Cancer may impact vision either directly (i.e., neoplasia in the eye or visual pathways) or indirectly (e.g., paraneoplastic or adverse treatment effects).[1,2] Ophthalmic sequelae with immune checkpoint inhibitors have been reported reinforcing the need for caution when using these agents on patients with impaired physiologic reserve. Ophthalmic reactions may affect any tissue from the anterior segment (e.g., keratitis, conjunctivitis, and anterior uveitis) to the posterior segment (e.g., retinal vasculitis, choroidal effusions, and optic neuropathy).[1] Herein, we describe a complex oncology case with acute ophthalmic findings and a wide differential diagnosis.

Case Report

A 54-year-old Filipino male with a 10-year history of type 2 diabetes mellitus, ischemic heart disease, and former smoking was diagnosed with left renal clear-cell carcinoma (RCC). He underwent a left nephrectomy with curative intent. Eleven years later, he developed RCC metastases to the lung, mediastinum, and spine. Treatment was endobronchial resection, local (spine) radiotherapy, and chemotherapy (sunitinib, changed to axitinib and subsequently to nivolumab for adverse effects (AEs) and/or treatment failure).

After a 7-month "treatment holiday," cabozantinib (Exelixis, CA, USA) 60 mg/day was started as systemic rescue therapy for metastatic RCC. Two weeks later, headaches and peripheral neuropathy developed, followed by eye pain and blurred vision in his right (OD) and then left (OS) eyes. There was no antecedent corticosteroid use or ocular trauma/surgery.

Uncorrected visual acuity was 20/100 OD and 20/50 OS. Nongranulomatous anterior uveitis (2+ cells) with 1+ anterior

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vitreous cells was noted. Exudative retinal detachment (ERD) involving the macula with choroidal folds and thickening was seen in the right eye with temporal peripapillary intraretinal edema in the left eye [Figure 1]. Intraocular metastatic disease was excluded.

Initial treatment included cessation of cabozantinib (in conjunction with his medical oncologist) and hourly topical prednisolone 1% drops while investigations were carried out (i.e., rule out infectious etiology, before using systemic immunosuppression). While syphilis and Borrelia serology were negative, latent tuberculosis (TB) was diagnosed by positive QuantiFERON gold.

Two weeks later, VA had deteriorated to 20/200 OD and 20/80 OS. Although the anterior chamber inflammatory signs had lessened with topical treatment, the ERD OD had increased in height and OS had developed multifocal ERDs with choroidal thickening [Figure 2]. Fundus autofluorescence demonstrated a well-circumscribed area in the superotemporal macula OD with a hyperautofluorescent border containing multiple punctate hyperautofluorescent dots. Fluorescein angiography revealed bilateral disc leakage and multiple pinpoint areas of leakage within the areas of ERD. Indocyanine green angiography demonstrated hypofluorescent spots most evident OD suggestive of choroidal inflammation [Figure 2].

High-dose oral steroid (75 mg) was commenced with single agent (rifampicin) latent TB cover (4-month planned course). In conjunction with a rheumatologist, oral methotrexate 25 mg/week was commenced to minimize the duration and AEs of steroids on his glycemic control. One month later, there was a dramatic resolution of the bilateral ERDs and choroidal thickening with gradual return of normal retinal pigment epithelium integrity [Figure 3a and b]. Choroidal depigmentation consistent with "sunset glow fundus" was seen in the quiescent stage [Figure 3c and d]. VA returned to 20/30 OU. Due to the treatment burden, he ceased methotrexate and rifampicin against medical advice but agreed to taper steroids and continue close follow-up.

Two years later, there has been no recurrence of his posterior segment inflammation with one episode of recurrent anterior uveitis responding to topical steroids. His vision has remained near baseline at 20/30 OU. Current anti-RCC immunotherapy is lenvatinib (Eisai-Co. Ltd, Tokyo, Japan), without further ocular AEs. The patient provided informed consent to publish their anonymized case.

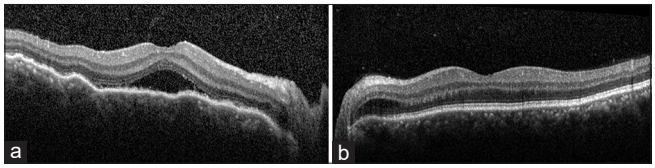

Figure 1: Optical coherence tomography (OCT, Spectralis, Heidelberg Engineering, Heidelberg, Germany) images demonstrating choroidal thickening/folds and exudative retinal detachment in the right eye (a) and intraretinal edema in the left eye (b)

Discussion

Herein, we describe the first reported case of a Vogt–Koyanagi–Harada (VKH) disease-like reaction to cabozantinib. We are confident that this VKH-like reaction was due to cabozantinib as no other inciting event aligns with the timing of ocular inflammation.

Cabozantinib is a multiple tyrosine kinase receptor inhibitor (VEGFR2, c-MET, and RET receptors) that enhances

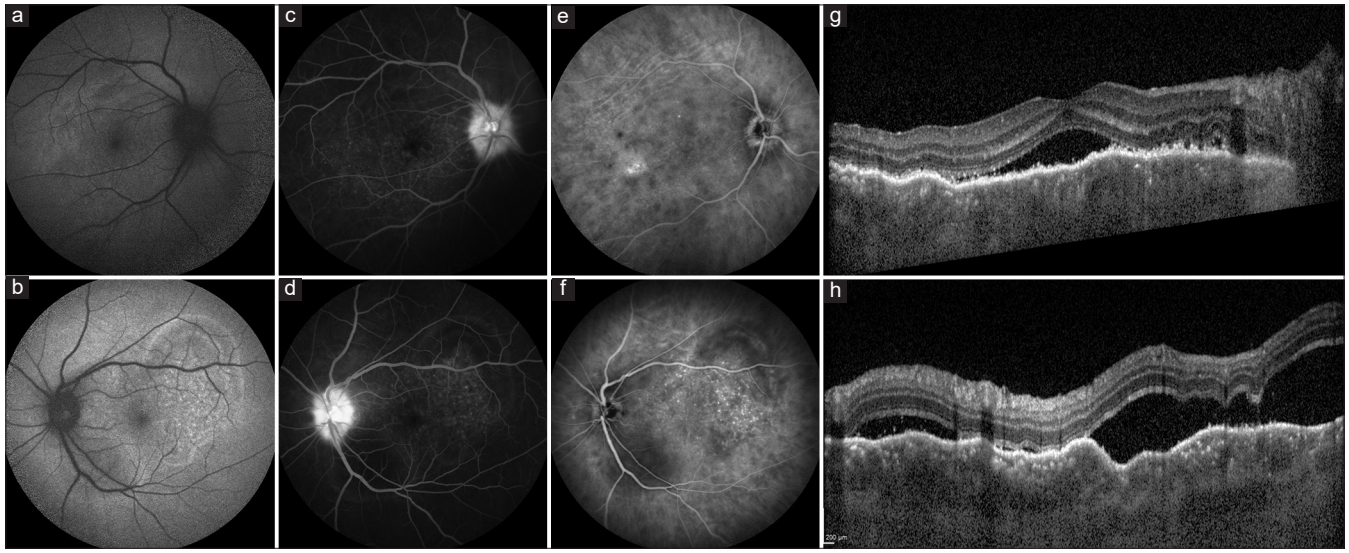

Figure 2: Multimodal retinal imaging of the right (top row) and left (bottom row) eyes. Blue light autofluorescence (a and b) delineating areas of hyperautofluorescence, most marked in the left eye. Fluorescein angiography (c and d) showing bilateral disc leakage and multiple pinpoint areas of leakage. Indocyanine green angiography (e and f) demonstrating multiple hypofluorescent spots (right more than left) suggesting choroidal/choriocapillaris inflammation. Optical coherence tomography (g and h) showing increasing choroidal thickening and folds and bilateral multifocal exudative retinal detachments

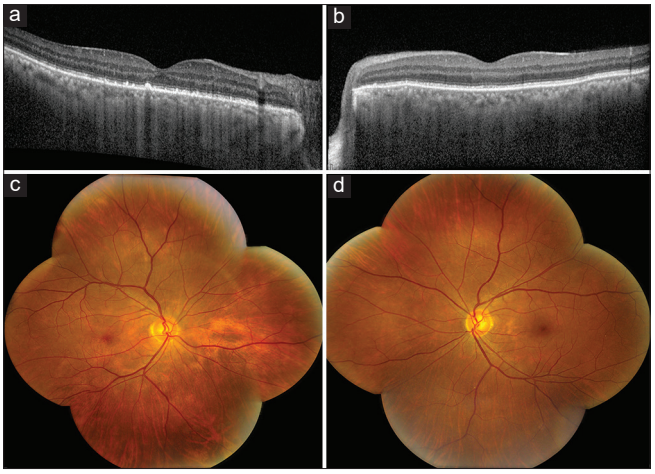

Figure 3: Multimodal imaging of late-stage disease. Optical coherence tomography images of right (a) and left (b) eyes showing resolution of exudative retinal detachment, normalization of choroidal contour and thickness with remaining irregularity of the retinal pigment epithelial layer and ellipsoid zone in both eyes (OU). Note: The external limiting membrane is intact OU suggesting anatomic preservation of photoreceptors. Color fundus photographs of the right (c) and left (d) eyes demonstrating "sunset glow" choroidal depigmentation, more marked in the right eye

antitumor T-cell responses/chemotaxis.[3,4] As second- or third-line immunotherapy, it increases progression-free survival in metastatic thyroid/renal carcinoma, particularly for bone metastases.[3,5,6] AEs of cabozantinib (>70%) include diarrhea (14.3%), nausea (6.5%), hand-foot syndrome (8.2%), fatigue (15.6%), and anemia/lymphopenia (6%).[6] Despite frequent AE, immunotherapy has revolutionized the dismal prognosis of metastatic RCC. This patient was alive and independent 6 years later due to these medications.

VKH disease is a T-cell-mediated idiopathic panuveitis syndrome with bilateral granulomatous uveitis, ERDs, and audiological and skin manifestations.[7] Multimodal retinal imaging is instrumental in confirming pathology and monitoring the progression/recovery of panuveitis. Similar ocular features have been described with trauma (i.e., sympathetic ophthalmia) or anticancer immunotherapy (e.g., immune checkpoint inhibitors, MEK inhibitors, and *BRAF* inhibitors).[1,2,8] The pathogenesis of this reaction is presumedly related to heightened immune response and T-cell activation to melanocyte antigens.[4,9] Cabozantinib may also induce relative choroidal hypoperfusion (VEGFR2 inhibition) with rebound choriocapillaris dilatation causing exudation.[10] Immune activation may be beneficial against metastatic cancers but causes multiple systemic inflammatory sequelae (e.g., thyroid, lung, pancreas, skin, gastrointestinal mucosa, and eyes).[9]

Treatment tolerability is an important consideration for patients with advanced cancers as treatment goals are survival and quality of life.[11] In this case, the patient was taking cabozantinib, systemic steroids, methotrexate, diabetes medications, and antimycobacterial agents. Although each had its pharmacological role, this became overwhelming for the patient who ceased all treatments. Thankfully, the withdrawal of cabozantinib with tapering oral steroids allowed resolution of ocular inflammation.

Patient education regarding immunotherapy AE is critical, including planning for AE (e.g., withdrawal of inciting agent). Close monitoring for cancer progression and assessment of other therapeutic options maximize survival and quality of life. In this case, steroids would likely exacerbate his diabetes, and steroid-sparing immunosuppression was started. Screening for infectious conditions before commencing immunosuppression remains critical as in this case (latent TB). Periocular depot corticosteroids are an option when systemic immunosuppression is contraindicated.[2]

Modern pharmacotherapy for metastatic cancer provides amazing possibilities for increased survival, but AEs are frequent and potentially severe. Anticipation, screening, and appropriate management can mitigate symptoms and treatment burden while maximizing benefits for this disadvantaged patient group.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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