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Bilateral rhegmatogenous retinal detachments in a patient taking pazopanib: A case report

Nolan J. Adams, Felipe De Alba *

Department of Ophthalmology, Loyola University Medical Center, 2160 South 1st Ave, Maywood, IL, 60153, USA

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ABSTRACT

Purpose: To report a case of bilateral rhegmatogenous retinal detachments (RRD) associated with treatment with the systemic tyrosine kinase inhibitor pazopanib.

Observations: A 57-year-old man with history of renal cell carcinoma was treated with pazopanib therapy for four months. He presented to the ophthalmology clinic with bilateral rhegmatogenous retinal detachments, which resolved with pneumatic retinopexy with cryoretinopexy. Both retinas had transient post-operative cystoid macular edema and mild epiretinal membrane formation but remained stably reattached.

Conclusions and importance: This case report provides further evidence of the possibility that tyrosine kinase inhibitors used for cancer treatment could lead to the development of RRD. There were previous reports on the development of unilateral RRD after pazopanib use, but this is the first instance known to the authors of bilateral RRD. The mechanism behind this possible increased risk is unknown, but could be based on interactions between pazopanib and tyrosine kinases known to exist in the vitreous humor.

1. Introduction

Pazopanib is a tyrosine kinase inhibitor that is Federal Drug Administration approved for treatment of advanced renal cell carcinoma and advanced soft tissue sarcoma.[1,2] It inhibits tumor angiogenesis by blocking several tyrosine kinases, including vascular endothelial growth factor receptors (VEGFR).[2] Known side effects include hepatotoxicity, hypertension, and hemorrhagic events.[1] There have been two reports of unilateral rhegmatogenous retinal detachments associated with pazopanib,[3,4] as well as multiple ocular adverse events in other similar oral tyrosine kinase inhibitors/anti-VEGF drugs such as sorafenib and sunitinib.[5] We report the first case of bilateral rhegmatogenous retinal detachments associated with pazopanib.

2. Case report

A 57 year old Caucasian male with past medical history remarkable for hypertension and 60-pack year smoking history was diagnosed with clear cell type renal cell carcinoma in April 2014, following an episode of gross hematuria. A computerized tomography scan at that time showed bilateral lung nodules, which were confirmed by fine needle aspiration to be metastatic clear cell type renal cell carcinoma. The diagnosis was confirmed after right nephrectomy revealed a 12 x 9 × 6 cm mass. Following surgery, patient developed bilateral pulmonary emboli and was placed on subcutaneous anticoagulation therapy, which was later converted to oral warfarin.

After recovery from the pulmonary emboli, the patient began systemic therapy with high dose interleukin-2 (HD IL-2) treatment in July 2014. He underwent one cycle of HD IL-2 therapy, with 10/14 doses followed by 4/14 doses due to expected side effects. Patient was lost to follow up until January 2015 due to depression, and treatment was further delayed due to insurance issues. In March 2015, CT scan showed mixed response to HD IL-2 treatment. The patient was started on pazopanib 800mg daily in April 2015 and tolerated well with mild anorexia and fatigue.

Four months after beginning pazopanib treatment, the patient presented to the ophthalmology clinic with sudden onset of a large dark spot with loss of inferior vision in the right eye for five days. The patient's only ocular history was well controlled dry eye syndrome and moderate myopia with current spherical equivalent −2.50 in the right eye and −4.75 in the left eye. He had no history of trauma to either eye, no prior ocular surgeries, and no family history of eye disease including retinal detachments. On exam, the patient was noted to be phakic in both eyes with quiet anterior chambers. He had posterior vitreous

* Corresponding author. Loyola University Medical Center, 2160 South 1st Ave, LUH North Entrance, Suite 2601, Maywood, IL, 60153, USA.
E-mail address: fdealba@lumc.edu (F. De Alba).

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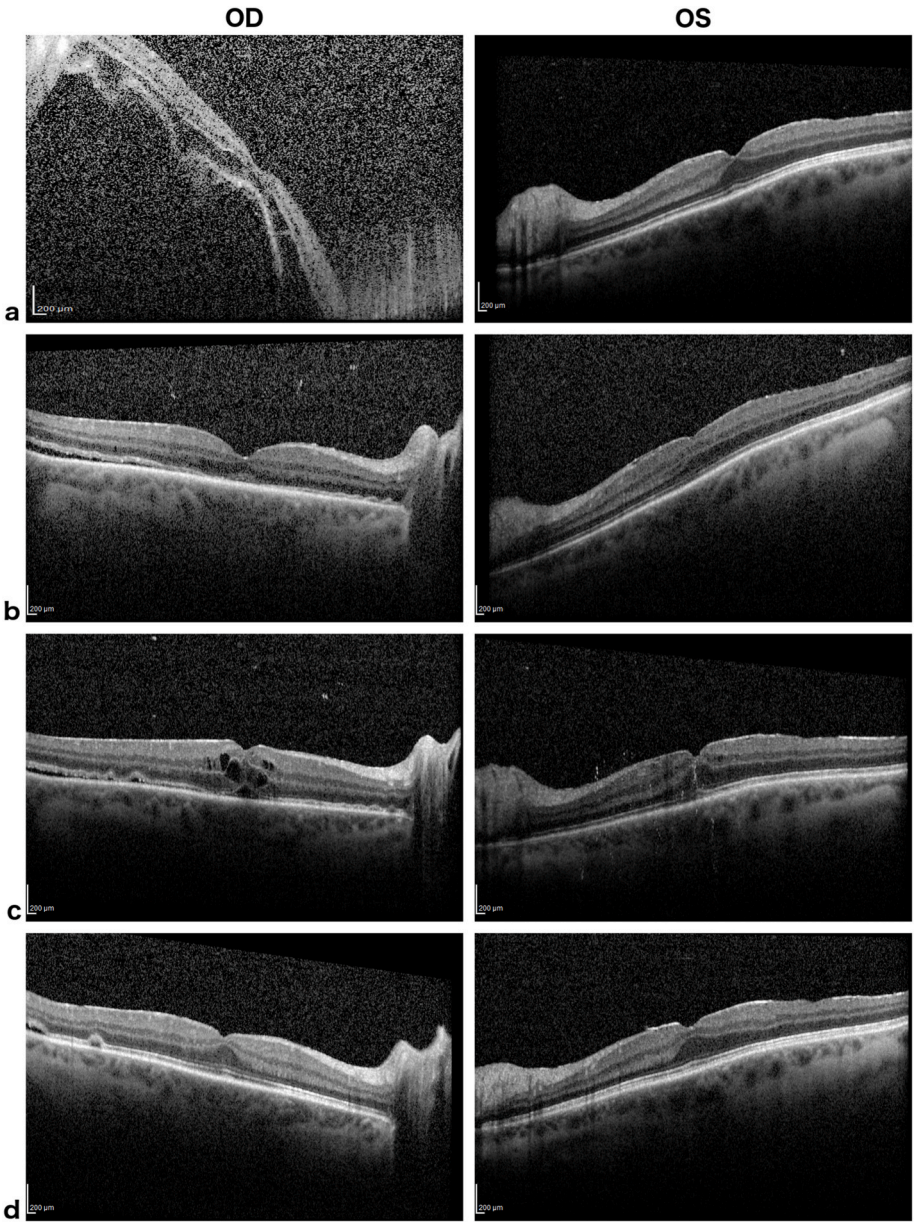

Fig. 1. OCT Scans of Treatment Progress a) 8/25/15: Rhegmatogenous Retinal Detachment (RRD) of the right eye with macula off, superior RRD of the left eye with macula on not visible; b) 9/1/15: resolution of RRD of the right eye with minimal sub-retinal fluid, stable appearance in the left eye; c) 9/9/15: Cystoid macular edema (CME) in both eyes; d) 5/27/16: CME resolution in both eyes with baseline epiretinal membrane.

detachments (PVD) in both eyes and no evidence of vitritis. The right retina was noted with bullous rhegmatogenous retinal detachment (RRD) from 8:00 to 5:00 with horseshoe tear (HST) at 1:00 and macula off. The left retina was also noted to have RRD from 10:30 to 2:30 with HST at 12:00 and macula on. There was no lattice degeneration and no retinal holes in either eye. The patient's vision was count fingers at 1 foot in the right eye, 20/40 in the left eye. Treatment options were given, and the patient chose to undergo immediate pneumatic retinopexy with cryoretinopexy in the left eye. He was subsequently started on topical moxifloxacin and prednisolone four times a day. Two days later, the patient underwent pneumatic retinopexy with cryoretinopexy in the right eye. The retina was re-attached in both eyes clinically and the patient's vision improved post-operatively. His course was uneventful until he developed cystoid macular edema in both eyes two weeks post-operatively. He was started on ketorolac four times a day, with resolution of the intraretinal fluid four weeks later. Both eyes were noted to have pre-existing epiretinal membrane (ERM) not requiring vitrectomy. At 2 months, visual acuity was 20/30 in both eyes and continued to be stable through the last follow-up at 9 months. Confrontational visual fields were full at that appointment. Ocular Coherence Tomography (OCT) scans of the patient's progression are shown in Fig. 1.

The patient's pazopanib was discontinued following the retinal detachments. He was started on palliative radiation therapy one month later and transitioned to systemic therapy with vinorelbine in December 2015.

3. Discussion

Rhegmatogenous retinal detachments (RRD) occur when a tear in the retina allows fluid to move into the subretinal space. The neurosensory retina then separates from the underlying retinal pigment epithelium. This is often preceded by liquefaction of the vitreous humor.[6] The incidence of RRD is 1 in 10,000, and risk factors include aging, myopia, trauma, cataract surgery, and focal retinal atrophy.[6] There have been

two reports of rhegmatogenous retinal detachments associated with use of pazopanib.[3,4] Other reports on tyrosine kinase inhibitors include a retinal tear with sorafenib and serous retinal detachments with sunitinib.[7,8] A recent study found 75 reports of retinal detachments or retinal tears associated with oral anti-VEGF agents, although the reports didn't differentiate between RRDs or other types of retinal detachments, which makes it difficult to estimate the prevalence of RRDs in patients taking these medications.[5] In January 2014, the European Medicines Agency reported 12 cases of retinal detachments and retinal tears linked with pazopanib, leading to a requirement for the pazopanib package insert to include retinal detachment and retinal tear as possible adverse events, although these were again not specified as rhegmatogenous or non-rhegmatogenous.[9]

While causality can't be established in the case being reported, the timeframe of bilateral RRDs four months after starting pazopanib raises suspicion for this association. However, it is possible that these occurred incidentally in the same time frame given the patient's age (57) and presence of bilateral PVDs which may have induced these tears and subsequent detachments. No reports to date have shown an association with pazopanib and cystoid macular edema, which developed bilaterally in this patient after retinal detachment repair. This may have been an incidental finding, although clinicians should be aware to watch for this development as well in patients on oral tyrosine kinase inhibitors.

The tyrosine kinase inhibitors pazopanib, sorafenib, and sunitinib have inhibitory activity against multiple tyrosine kinases, including VEGF receptors.[2] There have also been studies showing that orally administered pazopanib has bioavailability in mouse retinal tissues.[10] However, it has not yet been shown how pazopanib could be implicated in the development of RRD. Given that the pathogenesis of RRD involves changes in the vitreous humor, it is possible that pazopanib's effects are mediated by its activity on tyrosine kinases in the vitreous humor. There have been multiple studies demonstrating the presence of several tyrosine kinases in the vitreous humor, including VEGF receptors, PDGF receptors, and c-KIT.[11] Future studies could research the interactions of these tyrosine kinase inhibitors on tyrosine kinases in the vitreous humor.

4. Conclusions

This case report provides further evidence of the possibility that tyrosine kinase inhibitors used in cancer treatment could lead to the development of RRD. There were two previous reports on the development of unilateral RRD after pazopanib use, but this is the first instance known to the authors of bilateral RRD. The mechanism behind this possible increased risk is unknown, but could be based on interactions between pazopanib and tyrosine kinases known to exist in the vitreous humor. Clinicians should be aware of this possible adverse event in patients taking pazopanib, and prescribers could consider obtaining a dilated fundus exam prior to starting this medication.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

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