Pazopanib Induces Retinal Tear: A Case Report

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Abstract
This is a case report about a renal cell cancer patient who developed retinal tear after anti-VEGF multi-tyrosine kinase inhibitor Pazopanib. Early recognition and referral to ophthalmology for management is necessary.

Keywords: Retinal; Pazopanib; angiogenesis

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Introduction

Pazopanib (Votrient), is one of the tyrosine kinase inhibitors. It inhibits angiogenesis via blocking VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-A, PDGFR-B, FGFR-1, and FGFR-3[1-3]. It is Federal Drug Administration approved for the treatment of metastatic renal cell cancer in the first line setting.

Case Presentation

A 63 year old Caucasian female with past medical history of migraine headaches, dyslipidemia and depression was diagnosed with renal cell cancer, clear cell type in late 2004. Patient underwent a laparoscopic nephrectomy and a kidney mass of 9 x 7 x 4 cm was removed. Pathology revealed T2 Furman Grade 2 disease. Patient was followed for years and a CT scan of chest 7 years later showed multiple bilateral pulmonary nodules, the largest was a 1.5 x 1.2 cm nodule at the right middle lobe. CT-guided biopsy was attempted, however it was not diagnostic. Therefore, patient underwent a right upper lobe wedge resection on October 12, 2012, which confirmed metastatic renal cell cancer to the lung.

She was considered an excellent candidate for high-dose interleukin-2 treatment as she only had pulmonary nodules without evidence of metastatic disease elsewhere. She finished three cycles of high-dose interleukin-2 treatment. Prior to her first dose of IL-2 treatment, she received stereotactic body radiation therapy to the lung nodule. She was found to have disease progression a few months later after IL-2 therapy. So Votrient was started on June 2013. She had side effects of fatigue and diarrhea. The dosage of Votrient was adjusted based on her tolerability and it was 400 mg initially then titrated up to 600 mg daily.

Four months after the onset of Votrient treatment, patient began having blurry vision. Upon visiting the ophthalmologist, patient was diagnosed with Rhegmatogenous Retinal Tear OD. Patient past ocular history was negative for any chronic diseases. On exam, patient had retinal detachment, superotemporal (horseshoe) tear and a macula off. Patient left eye exam was remarkable for nuclear sclerosis. Patient therefore had a pneumatic retinopexy performed on August 19, 2014 and was started on Maxitrol 0.1% 1 drop OD, four times a day. Post operatively, patient had decreased complaints of blurry vision. Because of this possible adverse event along with diarrhea, patient was switched from Votrient to Sutent.

Discussion

Retinal tears occur when the retinal tissue begins to peel away from supporting tissue. Rhegmatogenous retinal detachment, the type of retinal attachment the patient in above case had, occurs primarily when a small retinal tear allows for fluid to pass from vitreous space into subretinal space where the retinal pigment epithelium is located. Studies have illustrated that these tears are often preceded by anti-VEGF therapy, stating that an “increased risk of developing a retinal pigment epithelium tear after anti-VEGF therapy” is common in many patients [11]. This occurs because following the administration of anti-VEGF therapy, there is rapid involution and contraction of the neovascular tissue that is attached to the undersurface of the retinal pigment epithelium. Those forces will cause a contractile force of the Retina Pigment Epithelium forcing a tear on the retinal tissue [12]. Understanding the pathophysiology of retinal tears and its relationship with anti-VEGF therapy – it is highly probable that the repeated administration of pazopanib in therapeutic doses for RCC can lead to strain to the retinal pigment epithelium, inducing a tear and further progressing onto a rhegmatogenous retinal detachment.

A recent study was published evaluating the ocular effects of Sorafenib, which suppress the VEGF receptor that are expressed in ocular tissue [5,6]. Both Sorafenib and Votrient specifically targeting
VEGF signaling and thus both affecting the ocular tissue. There has been established research regarding VEGF receptors in ocular tissue, specifically looking in diabetic patients with retinopathy who have increases in VEGF expression especially in the retina [7]. Furthermore, there have been studies analyzing the effect of Votrient in mice retinal tissues – specifically studying pazopanib’s effect on inhibiting choroidal neovascularization. It was shown in multiple studies that pazopanib inhibits VEGF expression affecting retinal pigment epithelium cells and choroidal endothelial cells – primarily down-regulating the release of VEGF in the retina and impairing VEGF-induced signaling and chemotaxis [8]. Thus, a clear link is illustrated between pazopanib and its effect on retinal tissue. Furthermore, studies have shown that if pazopanib is “orally administered, it has good bioavailability to the retina/choroid” further giving proof to its profound effect on the retina and likely impact on treating ocular abnormalities, such as choroidal neovascularization by inhibiting angiogenesis [9,10]. Studies evaluating the drug’s concentration in the blood necessary to inhibit angiogenesis prove that pazopanib is an excellent, bioavailable drug able to attain high concentrations at relatively low doses. This attribute allows it to effectively target VEGFR, PDGFR, and c-Kit tyrosine kinases and inhibit angiogenesis in retinal tissue.

However, the link between pazopanib and retinal tears is difficult to be determined such as understanding the findings in this case. Case reports of retinal affects from Sorafenib have been reported, With pazopanib’s large bioavailability in ocular tissues, and its direct effect on VEGF receptors, it is very most likely that retinal tear is induced by pazopanib exposure in this case.

Concluding Remarks

This case illustrates a risk with using VEGF inhibitors, such as pazopanib, in causing retinal damage such as tears leading to detachment. There is an increased amount of anti-VEGF agents being used in renal cell carcinoma and other malignancies. With the increased usage, guidelines may be required for annual ophthalmology screening to monitor for retinal abnormalities. Early ophthalmology referral is needed for patients who have blurry vision or other vision changes. Close follow up will be required to determine if discontinuing the pazopanib and starting other TKIs may help deter further ocular abnormalities.

References

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