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Casre report

Retinal Pigment Epithelium Tear Following Aflibercept for Exudative Macular Degeneration Tachyphylactic to Anti-Vascular Endothelial Growth Factor A Agents

Asahi MG, Gallemore E and Gallemore RP*

Retina Macula Institute, USA

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Abstract

Purpose: To report two cases of retinal pigment epithelium (RPE) tears following treatment with aflibercept of exudative macula degeneration associated with pigment epithelial detachment (PED) tachyphylactic to anti-vascular endothelial growth factor (VEGF) A agents such as bevacizumab or ranibizumab.

Methods: Retrospective case series of patients with exudative macular degeneration with PED who were managed with anti-VEGF A agents that developed RPE tear following the first aflibercept injection. The patients were followed with optical coherence tomography and fluorescein angiography.

Results: In our two cases, RPE tear developed after being switched from bevacizumab or ranibizumab to treatment with aflibercept. Both cases were rescued with monthly ranibizumab injections. In each case vision and macular edema improved with continued treatment.

Conclusion: RPE tears may occur following injection with aflibercept for treatment of exudative AMD tachyphylactic to bevacizumab or ranibizumab. Continued anti-VEGF treatment can be effective rescue therapy.

Keywords: Aflibercept; Anti-VEGF; Choroidal neovascularization; Exudative macular degeneration; Pigment Epithelial Detachment; RPE tear; Tachyphylaxis

Introduction

Retinal pigment epithelium (RPE) tear is a well known complication in exudative macular degeneration [1] with the potential of 15-20% of vascularized PEDs to develop RPE tears after anti-VEGF therapy [2]. RPE tears

have been well documented with bevacizumab and ranibizumab and few case reports have documented RPE tears following intravitreal aflibercept injection (Eylea; Regeneron Pharmaceuticals, Tarrytown, NY, USA; Bayer AG, Leverkusen Germany). Here, we report a case of RPE tear after switching from bevacizumab to aflibercept due to tachyphylaxis and a case of RPE tear after switching from ranibizumab to aflibercept due to tachyphylaxis.

***Correspondence:** Ron P Gallemore, Retina Macula Institute, 4201 Torrance Blvd Suite 220, Torrance, CA 90503, USA, Tel: 310-944-9393; Fax: 310-944-3393; E-mail: rongallemoremd@gmail.com

Case Reports

Case 1: A 68-year-old woman presented with “jumping images” in the left eye over the past few weeks. Exam revealed angioid streaks with a hemorrhagic PED (Figure 1A top). Best corrected vision measured 20/30-2 in the left eye. FA studies were suggestive of occult CNV (Figure 1A middle, bottom) and OCT studies revealed the PED with retinal edema (Figure 2A). She underwent treatment with bevacizumab and after three consecutive injections 4-6 weeks apart, the PED and retinal edema had nearly resolved and vision recovered to 20/25+2 (Figure 2B). After thirteen consecutive treatments with bevacizumab, she developed tachyphylaxis with recurrence of the PED and a slight vision decrease to 20/25-1 (Figure 2C). Given the availability of aflibercept with potential improved efficacy and a reduction in the frequency of injection, she was treated with aflibercept.

Four weeks after the intravitreal aflibercept injection, there was a decrease in size of the PED and an improvement of vision to 20/25-1. On the fifth week however, following the initial treatment with aflibercept, she developed an RPE tear and her vision dropped to 20/200+1 as seen on OCT (Figure 2D) and FA studies (Figure 1B middle, bottom). She was subsequently switched to ranibizumab, after which the edema gradually decreased and the vision recovered to 20/30-2 following 8 sequential injections every 4-6 weeks (Figure 1C and Figure 2E).

Case 2: A 67-year-old man presented with exudative macular degeneration with occult choroidal neovascular membrane (Figure 3A, top). OCT studies also show he had a PED in the temporal macula in the right eye (Figure 3A, bottom). He received monthly injections and vision improved to 20/50+1. He developed apparent tachyphylaxis to subsequent injections of ranibizumab, as noted by an increase in the size of the PED on OCT studies and a decrease in vision to a VA of 20/70-1 and was switched to aflibercept. Subsequent two month follow up revealed an RPE tear with collapse of the PED clearly shown on subsequent FA studies (Figure 3B). His vision, however, improved to 20/60+2 as the tear was extrafoveal. We resumed treatment with

ranibizumab given the tear on aflibercept and after 8 injections, the CNV continued to regress and vision improved to 20/40-2 (Figure 3C).

Discussion

We report two cases of RPE tear following the first injection of aflibercept for treatment of exudative macular degeneration tachyphylactic to bevacizumab and/or ranibizumab. While RPE tears have been reported with anti-VEGF therapy in the past, aflibercept has now become the first line therapy for more complex cases of exudative macular degeneration, including cases of PED associated with exudative macular degeneration [3]. It is appropriate to highlight this potential complication during the current era of anti-VEGF therapy where switching to and utilization of more potent agents, such as aflibercept, is more common and this complication may become more frequent. In both of our cases, the RPE tear occurred after the initial aflibercept injection - likely due to the effect of the drug. While most reports have reported RPE tear following the first to third injection, with the mean RPE tear occurring after 1.3 injections [2], our patients were treated with multiple injections of other anti-VEGF such as bevacizumab and/or ranibizumab prior to being switched to aflibercept followed by a RPE tear.

While aflibercept has been shown to be just as effective as ranibizumab in the regression of a choroidal neovascular membrane (CNVM) [4], it may be more potent than bevacizumab and ranibizumab, leading to greater tractional forces within a PED as it occurs. VIEW trials suggest a superior morphologic efficacy of aflibercept in reducing intraretinal and subretinal fluid and reducing RPE elevation [3]. Aflibercept binds additional growth factors—VEGF-A, VEGF-B and placental growth factor—unlike bevacizumab and ranibizumab, which bind to VEGF-A alone [5]. The continued contraction of the CNVM eventually results in anatomic failure of the RPE, causing a tear of the RPE [6]. Another contributing factor is that a microrip of the RPE can occur due to hydrostatic forces alone producing a break at the margin of the PED [7]. Other proposed contributing factors include a natural progression of the PED itself, an effect of the needle

Figure 1: Fundus photos (top) and early and late phase fluorescein angiography (middle and bottom) of case 1 with angioid streaks and hemorrhagic PED in the left eye prior to treatment (A), (B) following aflibercept with RPE tear denoted by arrow, and (C) following eight treatments of ranibizumab as rescue therapy with RPE tear

entering the eye causing a deformation of the globe and changes in intra-ocular pressure resulting in tearing the RPE, and vitreomacular traction at the injection site [8].

Due to the deleterious loss in visual acuity following an RPE tear, we recommend assessing for established RPE tear risk factors prior to treatment with aflibercept to prevent the occurrence of an RPE tear. Although a patient's history alone cannot assess the risk of RPE tear in a patient, characteristics on OCT and FA studies be utilized to assess whether a changing to aflibercept is a high risk. OCT studies should be assessed to determine whether a PED is present and if present, determining the size of the PED. In one study, PED lesions greater than 400 microns have been reported as a predictor of RPE tears [9], while in another, 580 microns was

reported as the upper limit for PED height [10]. Large linear diameter and increased surface area have also been reported as risk factors for development of RPE tear [11]. OCT studies can also detect microrips, which lower the threshold of RPE resistance and can lead to anatomic failure of the RPE [6]. If a hyperfluorescent "ring" sign around the border of the PED is picked up on FA studies, this can increase risk of RPE tear as this may suggest a developing seam or fault line in the PED [2]. New PEDs should also be treated with caution as the newer PEDs have immature vessels, which are more susceptible to anti-VEGF therapy, leading to a more dramatic response [10].

We propose that a patient with a history of multiple anti-VEGF treatment itself can also be a risk factor due

Figure 2: Horizontal OCT cuts of macula in patient with occult CNV and PED at (A) baseline and (B) following three bevacizumab injections, (C) 13 bevacizumab injections, (D) following single aflibercept injection (with RPE tear denoted by *) and (E) following eight ranibizumab injections.

Figure 3: Mid to late phase fluorescein angiography (top) and OCT studies (bottom) at (A) baseline, (B) following single aflibercept injection with RPE tear denoted by arrow and (C) eight ranibizumab injections with RPE

to change in architecture of the neovascular fronds and those who develop tachyphylaxis are at even greater risk. Vitreous levels of VEGF versus connective tissue growth factor (CTGF) determine the nature of neovascular fronds, where greater VEGF levels correlated with active retinal neovascular fronds, whereas greater CTGF levels correlated with predominantly fibrotic neovascular membranes [2]. Continued anti-VEGF treatment may result in CTGF to predominate over VEGF, leading to a more fibrotic neovascular membrane with more contractile properties and greater risk of RPE tear [2].

The development of tachyphylaxis can result in growth of new vessels in the choroidal neovascular membrane within the RPE monolayer, which can provide additional tangential traction within the PED and increase risk of RPE tear. The cases presented here suggest that patient's who are treated with multiple anti-VEGF injections may have a PED predisposed to an RPE tear, and those who develop tachyphylaxis are at even greater risk due to extra tangential tractional forces within the PED. We suggest that these forces combined with forces from the more potent aflibercept can dramatically increase risk of RPE tear.

Given the increased risk of RPE tear in patients who develop tachyphylaxis after multiple anti-VEGF injections being switched to aflibercept, we recommend re-assessing the patient's risk for RPE tear based on risk factors (finding of a new PED, large PED size, hyperfluorescent ring on FA studies, multiple anti-VEGF, or tachyphylaxis prompting switch to first aflibercept injection in a patient with history of multiple anti-VEGF injections) and re-evaluating the decision to switch to aflibercept. The clinician should consider re-evaluating the PED two weeks later and consider a decrease in treatment interval or switching to ranibizumab given our success and data suggesting ranibizumab having better visual acuity improvements in patients with exudative macular degeneration and RPE tears [12].

Should an RPE tear develop, continued anti-VEGF therapy is recommended. Studies suggest there appears to be a long-term anatomical benefit with continued anti-VEGF therapy due to reduced development of fibrosis and apparent decreased risk of large end-stage exudative disciform scars [2]. Invasive surgical therapies to manage RPE tears including full macular translocation, RPE-choroid graft translocation are being investigated [2]. As with any surgical procedure, they carry potential for serious complications such as retinal detachment. As such, we recommend assessment of risk factors to prevent RPE tears from occurring and screening patients with OCT prior to each treatment to assess the size of PED, risk of RPE tear, and assess response to previous treatment.

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