



## Case report

Exacerbation of pigment epithelial detachment following aflibercept: A case of bevacizumab rescue<sup>☆</sup>Samaneh Davoudi<sup>a</sup>, Ramak Roohipourmoallai<sup>a,b</sup>, Cynthia M. Guerin<sup>a</sup>, Siva S.R. Iyer<sup>a,\*</sup><sup>a</sup> Department of Ophthalmology, University of Florida College of Medicine, Gainesville, FL, USA<sup>b</sup> Department of Ophthalmology, Morsani College of Medicine, University of South Florida, Tampa, FL, USA

## ARTICLE INFO

## Keywords:

Aflibercept  
 Age-related macular degeneration  
 Anti-vascular endothelial growth factor  
 Bevacizumab  
 Pigment epithelial detachment  
 Visual acuity

## ABSTRACT

**Purpose:** We describe a 61-year-old female patient with a retinal pigment epithelial detachment (PED) of the left eye in the setting of neovascular aged-macular degeneration (nAMD) with unanticipated responses to aflibercept and bevacizumab.

**Observations:** A reduction of PED size from 423  $\mu\text{m}$  to 309  $\mu\text{m}$  and vision improvement (20/150- to 20/40) were observed after five consecutive monthly injections of bevacizumab. A switch to aflibercept for the following two consecutive months showed an unanticipated incremental decline in vision (20/80- at month 1, 20/150- at month 2), increased PED size (749  $\mu\text{m}$ ), and the development of subretinal fluid (SRF). After a switch back to bevacizumab, the subretinal fluid resolved. After nine consecutive monthly injections of bevacizumab, final vision in the left eye was 20/25, and final PED height was 84  $\mu\text{m}$ .

**Conclusions:** Different anti-VEGFs may induce varied and unpredictable responses among the most recalcitrant cases of nAMD. Unpredictably, PED size in our patient worsened with aflibercept treatment.

**Importance:** Treatment for nAMD with large PEDs has poor level 1 evidence for guidance, and customized treatment should be considered.

## 1. Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness and visual impairment in older populations despite recent advances in treatments. Vision loss in the form of exudative AMD can occur suddenly when a choroidal neovascularization (CNV) leaks fluid or blood into the sub-retinal pigment epithelial (RPE) or subretinal space. Retinal pigment epithelial detachment (PED) may be seen in near two-thirds of eyes with neovascular AMD (nAMD).<sup>1,2</sup> Based on the available literature, ranibizumab and aflibercept are effective in treating eyes with PED associated with neovascular AMD (nAMD),<sup>2</sup> and aflibercept is considered as a good option in recalcitrant PED cases.<sup>3</sup>

## 2. Case report

A sixty-one year old female presented to clinic with one month of worsening vision in the left eye. She had a past ocular history of bilateral Salzmann's nodular degeneration, nuclear sclerosis, irregular astigmatism, right eye nonexudative AMD, and left eye exudative AMD. She had

not had any prior ocular operations or treatments.

At presentation, BCVA in the left eye was 20/150, decreased from 20/30 from the year prior. On retinal exam, her left eye had a large central PED (702  $\mu\text{m}$ ), large drusen, and no evidence of hemorrhage (see Fig. 1). She was given intravitreal injections of bevacizumab [1.25 mg/0.05mL] once monthly for five consecutive months, with improvement left eye vision to 20/40 and PED height to 309  $\mu\text{m}$  (see Fig. 2a and b). She was then switched to aflibercept with intention to further reduce the PED size and improve vision. She was given intravitreal injections of aflibercept [2 mg/0.05mL] once monthly for two consecutive months. After the first treatment, her vision declined in the treated eye from 20/40 to 20/80- with an increase in PED size from 309  $\mu\text{m}$  to 603  $\mu\text{m}$  (see Fig. 2b and c). Following the second treatment of aflibercept, her vision further declined to 20/150- with a large increase in PED size to 749  $\mu\text{m}$ , and development of new subretinal fluid (SRF) (147  $\mu\text{m}$ ) (see Fig. 2c and d). She was then switched back to once monthly intravitreal injections of bevacizumab at the standard previous dosage. After two monthly injections, her vision returned to 20/30 with significant improvement of PED (250  $\mu\text{m}$ ) and resolution of SRF (see Fig. 2d and e). Following nine

<sup>☆</sup> None of the authors have any proprietary interests or conflicts of interest related to this submission.

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consecutive months of treatment with bevacizumab, her vision improved to 20/25 and PED size returned to less than pre-aflibercept measurements (84  $\mu\text{m}$ ) (see Fig. 2e and f).

**Material and Methods:** Chart review. Informed consent was obtained from the patient and was in accordance with HIPPA regulations.

### 3. Discussion

PED, diagnosed in two-thirds of eyes with nAMD, is associated with poor visual prognosis, including loss of more than three lines in 50% of patients within one year.<sup>1</sup>

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy is an effective treatment in most eyes with PED secondary to nAMD. Similar visual acuity outcomes have been reported with different treatment algorithms.<sup>2</sup> Large focused clinical trials compared the use of ranibizumab or aflibercept therapy for the treatment of eyes with PED and nAMD. Post hoc analyses suggested that ranibizumab or aflibercept are effective in treating eyes with PED associated with nAMD.<sup>2</sup> There is no large clinical trial to date that has evaluated the effect of bevacizumab on PED treatment compared to other anti-VEGF agents. However, aflibercept is often considered in PED-recalcitrant cases after bevacizumab or ranibizumab treatment has failed.<sup>3</sup>

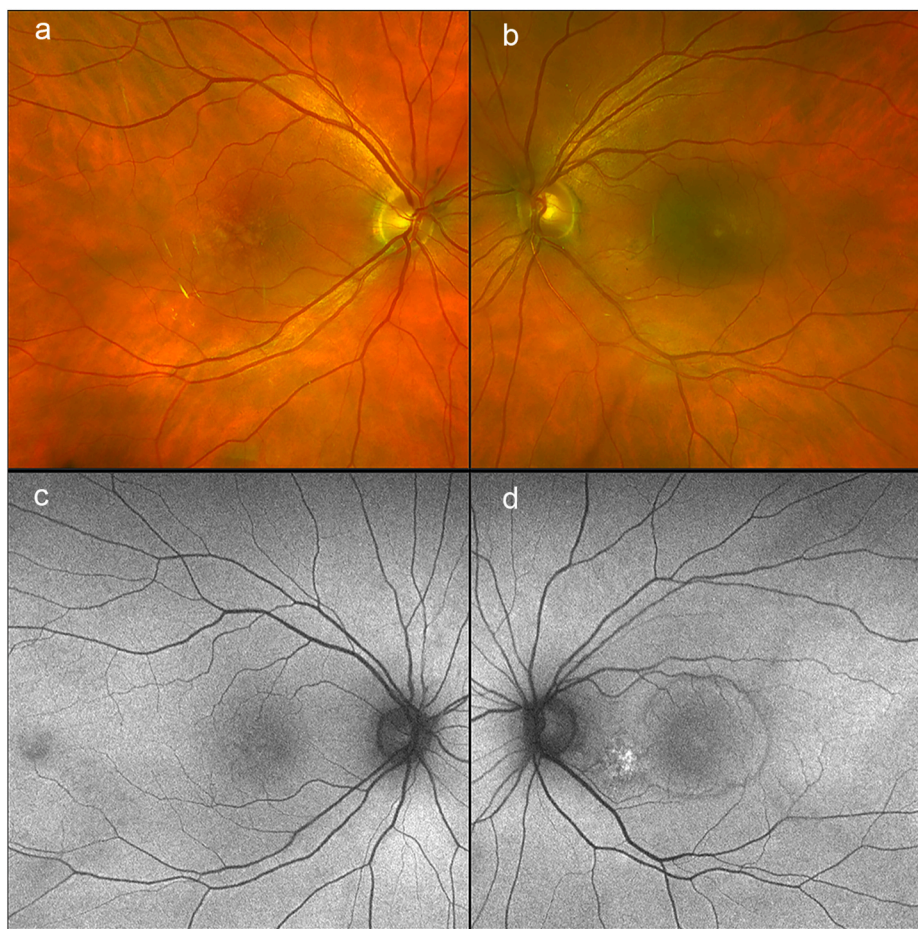
Our patient had PED associated nAMD with persistent PED despite monthly bevacizumab treatment over a five-month period. Although she responded favorably to the bevacizumab treatments, switching to aflibercept to further improve the size of her residual PED resulted in its unexpected exacerbation along with vision decline. A second treatment with aflibercept caused further worsening in both macular architecture

and vision in addition to new SRF, only to be reversed with a switch back to bevacizumab. In our patient, this pattern strongly supported bevacizumab having a rescue role, with aflibercept not only being ineffective but deleterious in the timeframe observed. We did not anticipate this response based upon available information from the literature, as there have been no prior reported cases.

Currently, literature suggests that anti-VEGF therapy is safe and efficacious for PED and nAMD.<sup>2</sup> There are few prospective studies that demonstrate optimal therapy for PEDs associated with nAMD.<sup>2</sup> Without treatment, significant loss of visual acuity is encountered in 40%–50% of eyes over a mean of 9–10 months.<sup>4</sup> In addition, some studies have noted secondary loss of visual acuity after anti-VEGF treatment in eyes with fibrovascular PED.

Aflibercept is a soluble decoy receptor that binds VEGF-A, VEGF-B, and placental growth factor (PlGF) with a greater affinity than the body's native receptors.<sup>5</sup> Aflibercept is called a decoy receptor because VEGF does not bind to its original receptors and mistakenly binds with aflibercept, thereby reducing VEGF's activity.<sup>5</sup> Bevacizumab is a humanized monoclonal antibody that targets VEGF-A, an isoform of VEGF that stimulates endothelial cell proliferation and subsequent migration.<sup>5</sup> Aflibercept has the greatest binding affinity to VEGF receptors compared to ranibizumab and bevacizumab.<sup>5</sup> After the induction period, bimonthly intravitreal aflibercept injection has been shown to be as safe and effective as ranibizumab monthly injection in the treatment of nAMD in phase III of VIEW 1 and VIEW 2 studies.<sup>6</sup>

Based on the mechanism of the agents used, we expected to have a better response to aflibercept in our patient. It is possible, however, that the most recalcitrant cases of wet AMD with PED may have different,



**Fig. 1.** Fundus photography (a,b) and fundus autofluorescence (c,d) showing macular drusen in the right eye (a, c) and a large pigment epithelial detachment (PED) in the left eye (b). Hyperautofluorescence is evident in the nasal macula of the left eye with a subtle ring of hypoautofluorescence delineating the edge of the PED (d).

unpredictable anti-VEGF responses. In addition, although anti-VEGF is the standard of care of nAMD,<sup>7</sup> some cases are refractory with persistent fluid, while others develop tolerance or tachyphylaxis (a decrease in anatomical response over time after responding initially to treatment).<sup>8</sup> Since this patient was on bevacizumab for five months, a tolerance or tachyphylaxis was initially considered, as an improvement plateau was achieved after five treatments. A switch to ranibizumab was not considered given supportive literature of aflibercept in recalcitrant PEDs.<sup>3</sup> The switch back to bevacizumab over ranibizumab was made because there was a partial acceptable response with bevacizumab in the beginning. Her response after the switch back to bevacizumab was also positive, however, suggesting that perhaps rather than tachyphylaxis, a maximal benefit from bevacizumab may have been achieved. Her clinical symptoms and PED height size never increased on bevacizumab. It is also possible that if the patient had received aflibercept for a longer time (more than two treatments), an improvement may have eventually been detected because the full positive effects of aflibercept may have not yet manifested. However, in the patient's best interest, both progression of PED size and significant decline of visual acuity warranted a change of treatment.

Another treatment option for this patient would have been to increase the dose of bevacizumab before switching to aflibercept. There is evidence, though limited, in both the retrospective and prospective literature supporting the concept that higher dosages of various anti-VEGF agents, delivered either as more frequent dosing or as a greater dosage, may lead to a more rapid or more improved anatomical response.<sup>2</sup> However, there is no evidence that higher dosages of anti-VEGFs correlate with an improvement in vision. As with the administration of higher dosages of anti-VEGF agents, switching anti-VEGF agents in eyes with treatment-resistant PED may result in additional anatomical improvement, without vision improvement.

The randomized Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) study reported, in each of the head-to-head comparisons of ranibizumab with bevacizumab in nAMD treatment, that the agents had equivalent effects on visual acuity at all time points throughout the first year of follow-up.<sup>9</sup> This study did not compare the effect of ranibizumab with bevacizumab on PED treatment or recalcitrant PED.

Due to concerns about the side effects of anti-VEGF, we cannot easily consider the double dosage of anti-VEGF injection. The CATT study found that rates of death, myocardial infarction, and stroke were similar for patients who received either bevacizumab or ranibizumab.<sup>9</sup> However, the proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab.<sup>9</sup>

It is well established that anatomical and vision improvement can be achieved with anti-VEGF therapy for nAMD. Most studies that have evaluated eyes with PED that were resistant to previous bevacizumab or ranibizumab therapy did not demonstrate an improvement in vision after a switch to aflibercept therapy, despite improved anatomical outcomes.<sup>2</sup> Though treatment should focus on achieving improvements in

visual acuity and not necessarily complete resolution of PED, there is no apparent correlation between anatomical and functional improvement in most eyes with PED and nAMD.<sup>2</sup>

Another study found that PEDs with significant hyporeflectivity (hollow or mixed) were more responsive than hyperreflective (solid) PEDs.<sup>10</sup> This suggests that the hyporeflective components may represent the presence of fluid exudate, while the hyperreflective components of mixed and solid PEDs represent fibrinous leakage or fibrovascular proliferation (indicating active neovascularization).<sup>10</sup> The increased response of lesions with some hyporeflective component may thus relate to a reduction in the exudative component of these reflective subtypes as a result of inhibition of VEGF-driven vasodilation and vascular leakage. Hyperreflective PEDs may sometimes involve a significant lipid or fibrous component in addition to a neovascular membrane.<sup>10</sup> These materials would be expected to be less responsive to aflibercept therapy. As our case only had hyporeflective components, we anticipated a better response to aflibercept. Our patient showed improvement after switching from aflibercept to bevacizumab. Perhaps there was also some repair of a dysfunctional RPE pump that occurred after the switch to bevacizumab that resulted in an increase in visual acuity and also a decrease in the PED size. There was however, not a specific demonstrable reason as to why the response was favorable with the switch.

#### 4. Conclusions

Although anti-VEGF agents have revolutionized the treatment of nAMD, we must often make adjustments in the treatment protocol based upon the patient's responses and needs. There is minimal level-one evidence to guide ophthalmologists when treating suboptimal responders to anti-VEGF monotherapy. Our case serves as a reminder that specialized care should involve the customization of treatment along with good evidenced-based guidance.

#### Patient consent

Patient consent was obtained for this publication.

#### Conflict of interest

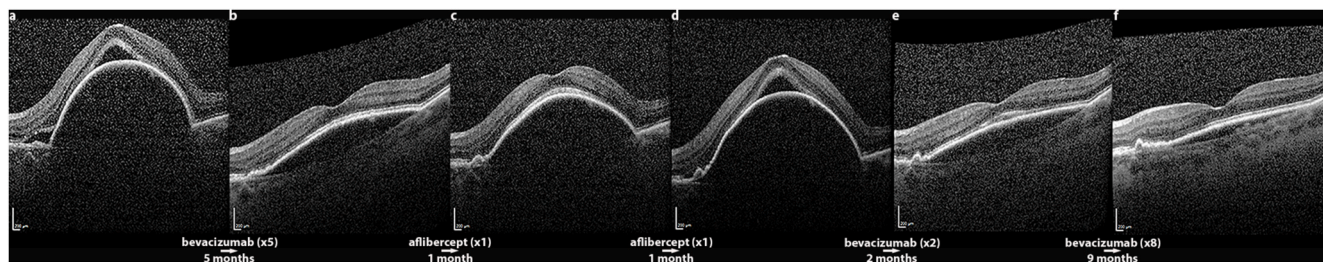
No conflict of interest exists.

#### Funding

Funding was received for this work.

#### Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have



**Fig. 2.** Spectral Domain Optical Coherence Tomography (SD-OCT) showing exacerbation of PED following aflibercept, and improvement with bevacizumab rescue. a-b reduction of PED size following 5 months of bevacizumab. c. Increase in PED following first month of aflibercept. d. Continued increase of PED and development of SRF following second continuous month of aflibercept. e. Significant improvement of PED and resolution of SRF 2 months post-bevacizumab switch. f. PED size reduced to less than pre-aflibercept following 9 additional consecutive months of bevacizumab treatment.

followed the regulations of our institutions concerning intellectual property.

### Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

IRB approval was obtained (required for studies and series of 3 or more cases).

Written consent to publish potentially identifying information, such as details or the case and photographs, was obtained from the patient(s) or their legal guardian(s).

### Acknowledgments and Disclosures

This study was funded by an unrestricted grant from Research to Prevent Blindness (SSRI).

The following authors have no financial disclosures: (SD, RR, CMG, SSRI).

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

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