

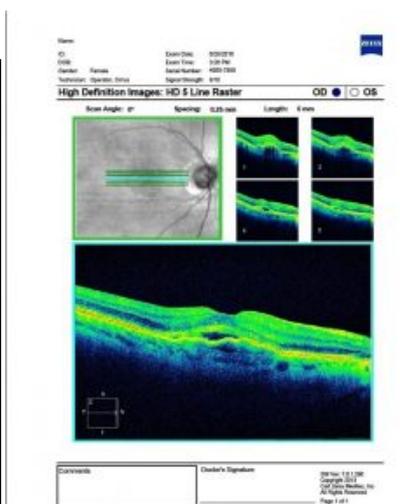
## When Early Intervention Fails to Improve Outcomes in Neovascular AMD | 1

In the Summer 2017 (Volume 42, Number 3) issue of *Optometric Education*, we presented a teaching case report titled “Normotensive Glaucoma Follow-Up with Incidental Finding of Choroidal Neovascular Membrane.” The case highlighted the need for student clinicians to be flexible and modify their exam plan when novel clinical findings emerge. The patient had presented for a Humphrey visual field test and glaucoma follow-up and was incidentally found to have a minimally symptomatic choroidal neovascular membrane resulting from conversion of non-neovascular to neovascular age-related macular degeneration (AMD) (**Figures 1 and 2**).



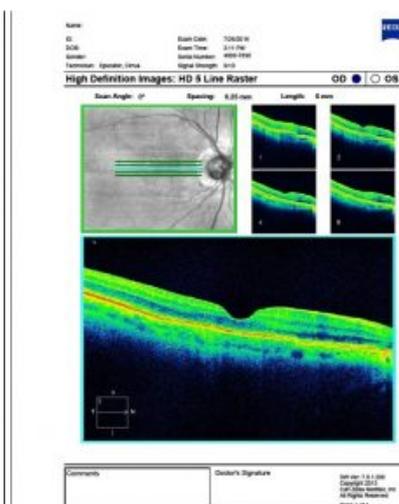
**Figure 1.** Fundus photo OD on 06/28/16 showing a mottled appearance of the macula with several small and intermediate drusen and large central-superior subretinal hemorrhage.

[Click to enlarge](#)



**Figure 2.** Optical coherence tomography five-line raster scan of the macula OD on 06/28/16 showing drusen and pigment epithelial detachment with overlying subretinal fluid causing macular elevation.

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**Figure 3.** Optical coherence tomography five-line raster scan of the macula OD on 7/26/16 showing reduction in the height of the pigment epithelial detachment and resolution of subretinal fluid.

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The neovascular membrane was presumably discovered relatively early because the patient first began experiencing blurred vision only one week prior. She was seen same day in the retina service and found to have a fibrovascular pigment epithelial detachment (FVPED) with exudation, subretinal fluid (SRF) and large central subretinal hemorrhage (SRH). She subsequently received an intravitreal injection of bevacizumab (Avastin). Following a loading dose of three monthly bevacizumab injections, the scotoma, SRF and SRH resolved (**Figure 3**). After the fourth monthly injection, because the patient had presented with a large SRH, a “treat and extend” rather than an “as needed” treatment strategy was selected.

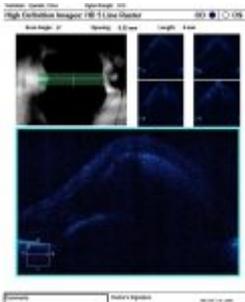
### Case Update



**Figure 4.** Fundus photo on 11/16/16 showing new large central subretinal hemorrhage and bullous sub-retinal pigment epithelium hemorrhage.

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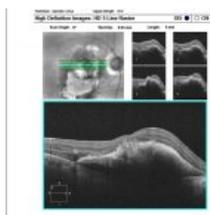
**Figure 5.** Optical coherence tomography five-line raster scan of the macula OD on 11/16/16 showing massive worsening of the pigment epithelial detachment with fluid, retinal pigment epithelial tear and subretinal hyper-reflective material. [Click to enlarge](#)

Unfortunately, despite the early intervention with significant anatomic improvement, the patient’s visual outcome was poor. Findings remained stable at the five-week extension visit, i.e., the SRF or SRH had not recurred. Therefore, another bevacizumab injection was given, and a six-week extend period was pursued. Despite the stabilization of the condition, three weeks after the fifth injection, the patient urgently presented with a dramatic reduction in vision and new large scotoma. Her uncorrected visual acuity had dropped from 20/40 at the previous visit to 20/400 (eccentrically). Ophthalmoscopic exam showed a new large central SRH involving the entire macula and a retinal pigment epithelium (RPE) tear with bullous sub-RPE hemorrhage (**Figure 4**). Macular optical coherence tomography (OCT) supported the exam findings, showing dramatic worsening of the PED and new RPE tear with subretinal hyper-reflective material (**Figure 5**).

The patient was treated with an intravitreal injection of aflibercept (Eylea) 2 mg and scheduled for a two-week follow-up visit. At follow-up, she reported only minimal improvement in vision. Visual acuity was finger counting at three feet (eccentrically). Ophthalmoscopic exam showed persistent subretinal and sub-RPE hemorrhage, and OCT showed no appreciable change. Treatment with Eylea was continued at two- to four-week intervals in an effort to resolve the hemorrhage and reduce the risk of re-bleeding (**Figures 6-7**). Despite several months of aflibercept treatment (total of 8) and resolution of the large hemorrhage, vision improved only minimally to 20/200 due to the RPE tear and development of central dense subretinal fibrosis (**Figure 8**). The utility of ongoing intravitreal treatment was questioned given the abnormal retinal anatomy. The patient, however, chose to continue because she felt her scotoma had improved significantly. She currently receives aflibercept injections at six- to eight-week intervals to maintain her current level of vision and reduce the risk of another catastrophic macular bleed.

**Discussion**

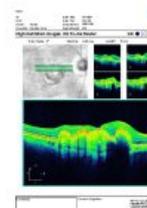
AMD is a multifactorial disease with a poorly understood pathogenesis. Age is a major risk factor, and smoking remains the only known modifiable risk factor.<sup>1</sup> Genetics also plays a role as 52 genetic variants across 34 loci have been associated with development of AMD.<sup>2</sup> Conversion to neovascular AMD is characterized by the uncontrolled expression of pro-angiogenic vascular endothelial growth factor (VEGF), which leads to the development of new abnormal blood vessels from the choroid.<sup>3</sup> While the emergence of intravitreal anti-VEGF therapies for neovascular AMD has been a significant advance in eye care in recent years, 10-15% of patients do not respond to anti-VEGF therapy and lose >15 ETDRS letters of visual acuity.<sup>4</sup> It is unclear why patients respond to anti-VEGF treatment differently, and current practice involves treating poorly responsive patients more aggressively, i.e., more frequently, or with increased dosing and/or a different anti-VEGF drug, often with variable responses.<sup>3</sup>



**Figure 6.** Optical coherence tomography five-line raster scan of the macula OD on 12/06/16 showing reduced height of the pigment epithelial detachment and retinal pigment epithelium tear. [Click to enlarge](#)



**Figure 7.** Fundus photo OD on 1/31/17 showing old subretinal hemorrhage inferior and resolving subretinal pigment epithelium hemorrhage parafoveally and retinal pigment epithelium tear. [Click to enlarge](#)



**Figure 8.** Optical coherence tomography five-line raster scan of the macula OD on 07/11/17 showing persistent retinal pigment epithelium tear with subretinal fluid and subretinal hyper-reflective material. [Click to enlarge](#)

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Tears of the RPE are characterized by a separation of the RPE basement membrane from the adjacent layers of Bruch's membrane.<sup>5</sup> Visual acuity is often significantly affected, with an average visual acuity of 20/150.<sup>6</sup> On ophthalmoscopic exam, an RPE tear is visualized as a well-demarcated area of bare choroid immediately adjacent to a hyperpigmented, rolled-appearing area.<sup>7</sup> With a reported incidence of 0.06%-0.8%, RPE tears are an infrequent sequela of intravitreal anti-VEGF therapy.<sup>5</sup> Eyes with AMD, with or without choroidal neovascularization, particularly those with PEDs large in height, and eyes that have undergone previous treatment, including laser photocoagulation, photodynamic therapy or intravitreal corticosteroid or anti-VEGF injection, are most susceptible to developing RPE tears.<sup>8</sup> Increased pre-injection lesion size and increased SRF also increase a patient's risk for developing a tear of the RPE.<sup>9</sup> While an RPE tear following treatment of choroidal neovascularization may be visually devastating, the benefits of vision-preserving treatment outweigh the relatively low risk of the potential complication.

A common assumption, particularly among student clinicians, is that a patient "will be OK" once he or she has been referred to the appropriate specialist, ophthalmic or otherwise. This case highlights that, even with early detection and intervention demonstrating significant anatomical improvement, patients with neovascular AMD may still have poor visual outcomes. AMD is a multifactorial disease, and VEGF is only one part of its pathobiology. Fortunately, numerous new therapeutic interventions are in the pipeline. They include oral tyrosine kinase inhibitors,<sup>10</sup> bone marrow-derived stem cells,<sup>11</sup> nanoparticle-loaded biodegradable injectable implants,<sup>12</sup> and RPE transplantation.<sup>13</sup> An improved understanding of the role of genetics in the management of retinal disease accompanies the potential new treatment options.<sup>14</sup> It is encouraging that these promising interventions may someday improve the care of patients with AMD.

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