Retinal pigment epithelial tears after intravitreal bevacizumab injection for exudative age-related macular degeneration

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We report a series of retinal pigment epithelial (RPE) tears after intravitreal bevacizumab therapy for choroidal neovascularization associated with age-related macular degeneration (ARMD). Retinal pigment epithelial tears were estimated to occur at an incidence of 1.6% in this patient population at our institution. Ophthalmologists should be aware of this rare but serious finding associated with exudative macular degeneration therapy.

Key words: Age-related macular degeneration, bevacizumab, choroidal neovascularization, exudative, vascular endothelial growth factor

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Acute retinal pigment epithelial (RPE) tears are a rare but well-documented sequela of exudative age-related macular degeneration (ARMD). In the past decade, with the advent of new therapeutic modalities for exudative ARMD, they have also infrequently been observed in association with therapy. Several reports in the literature document acute RPE tears after photodynamic and anti-vascular endothelial growth factor (VEGF) therapy for exudative ARMD.[1,2] Non-selective VEGF inhibition, in the form of ranibizumab (Lucentis, Genentech, South San Francisco, CA, USA) and off-label bevacizumab (Avastin, Genentech, South San Francisco, CA, USA), has

recently been in use as a treatment for exudative macular degeneration. It has been shown to be remarkably potent, effective and in the process of becoming widely adopted.[3,4] The medical literature is beginning to document acute RPE tears associated with this form of therapy as well.[5-8] We report here a series of five patients who developed RPE tears soon after receiving intravitreal bevacizumab and attempt to establish the relative incidence of this complication in a patient population with exudative macular degeneration.

Case Reports

Case 1

An 89-year-old female underwent intravitreal bevacizumab injection for ARMD-related choroidal neovascularization in her left eye. Three months previously, she had undergone combined intravitreal triamcinolone and photodynamic therapy for the same lesion without significant clinical response. Her visual acuity at the time of bevacizumab injection was 20/400 and she demonstrated a persistent vascularized serous pigment epithelial detachment. She presented four weeks after bevacizumab injection with a complaint that her vision had dropped in the affected eye. Her visual acuity was found to be 6/200 and examination revealed a large RPE tear with persistence of serous fluid [Fig. 1].

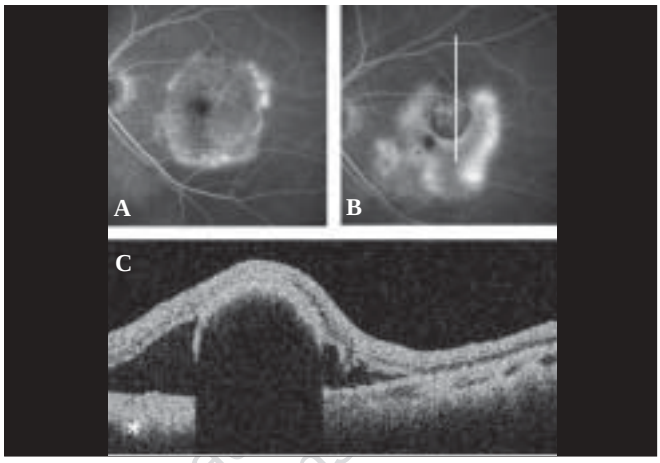

Figure 1: (A) Vascularized serous pigment epithelial detachment before bevacizumab injection. (B) Four weeks post bevacizumab injection, late phase angiography demonstrates a retracted and torn retinal pigment epithelium with serous leakage below. A retinal pigment epithelium tear was evident on OCT (C), characterized by an increased depth signal (asterisk), elevation of the retinal pigment epithelium band and serous detachment

Case 2

An 83-year-old female with no history of previous therapy underwent a bevacizumab injection for recent loss of vision from macular hemorrhage and serous pigment epithelial detachment in her right eye related to ARMD. She returned six weeks later with worsening of distortion of image. Her visual acuity had dropped by one line to 20/70. Her clinical examination demonstrated the presence of an RPE tear [Fig. 2].

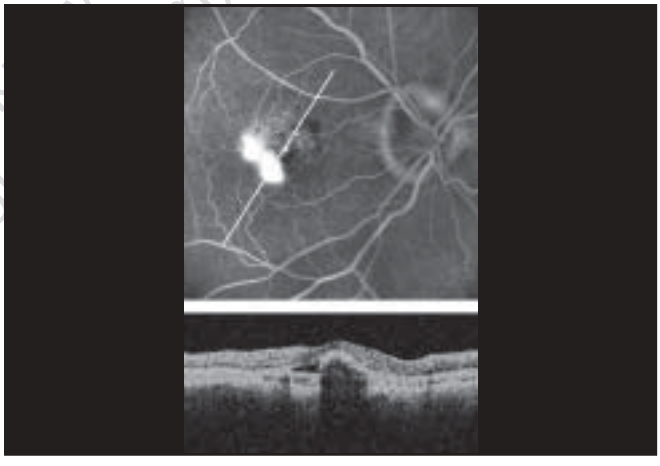

Figure 2: Six weeks post bevacizumab injection, prominent hyperfluorescence inferotemporal to the choroidal neovascular complex is noted from bare choriocapillaris. Oblique OCT section through the lesion confirms the presence of a retinal pigment epithelial tear

Case 3

An 85-year-old female with loss of vision from an ARMD-associated occult choroidal neovascular complex and macular hemorrhage underwent an intravitreal bevacizumab injection. Her visual acuity at the time of injection was 20/200. She underwent two additional intravitreal bevacizumab injections, each six weeks apart. When she returned six weeks after the third bevacizumab injection, she was found to have developed an RPE tear. Her vision remained at 20/200.

Case 4

An 88-year-old female who had four months previously been treated for exudative macular degeneration in her left eye with combined intravitreal pegaptanib (Macugen, OSI Pharmaceuticals, Melville, NY, USA) and photodynamic therapy was found to have persistent activity of a classic choroidal neovascular complex. Her visual acuity was counting fingers and she underwent an intravitreal bevacizumab injection. At four weeks' follow-up, she was found to have a visual acuity of 20/400 with decreased activity of the neovascular complex. She was found, however, to have a small RPE tear at the border of the lesion.

Case 5

An 81-year-old female presented with vision loss in her right eye from exudative ARMD. Her visual acuity was 20/400 and she was found to have a classic choroidal neovascular complex associated with subretinal hemorrhage. Intravitreal bevacizumab was injected and the patient returned at four weeks for follow-up. She demonstrated resolution of retinal edema and hemorrhage but was noted to have developed an RPE tear at the inferior margin of the neovascular complex.

Discussion

As a complication of ARMD therapy, RPE tears were originally reported in the early 1980s in association with thermal laser photocoagulation of choroidal neovascularization. Gass hypothesized that laser-related thermal contraction of choroidal neovascular membranes and subsequent rupture of RPE intracellular adherence was to blame for the development of such tears.[9] In later years, laser-related thermal shrinkage of the choroidal neovascular complex was also blamed for RPE

tears after transpupillary thermotherapy.[10] In photodynamic therapy, it has been proposed that RPE tears occur because of a combined mechanism of RPE phototoxicity and thermal injury to the choroidal neovascular complex and RPE.[1,11]

More recently, with pegaptanib, a selective VEGF-blocking agent, it has been proposed that decrease in VEGF activity results in loss of VEGF-mediated tight junction gene transcription. This loss of tight junction formation decreases RPE intercellular adherence and when the RPE cells are stressed, as in these cases with exudative ARMD, this may lead to an RPE tear.[2] We believe that a similar pathophysiologic mechanism exists for anti-VEGF therapy with bevacizumab but the effect is potentiated by the drug's non-selective VEGF-blockade, which may inhibit the more physiologic forms and functions of VEGF in the retina and retinal pigment epithelium. Furthermore, as in the laser and photodynamic therapy-related RPE tears, contraction of the choroidal neovascular complex by these very potent anti-VEGF drugs is likely to play a contributory role. Pericytes are vascular support cells found in choroidal neovascular membranes and normal body tissue. They affect vascular permeability by their contractile response. It has been directly observed to be mediated by VEGF in collagen-embedded pericyte cell cultures.[12]

Although previous reports have documented RPE tears associated with bevacizumab, none have provided data on the relative incidence of this complication.[5-8] The cases we report here were pooled from a total of 322 different patients who received bevacizumab for treatment of exudative macular degeneration in our practice. This calculates to a 1.6% incidence of RPE tears. This number must be viewed with caution as patients were not studied prospectively and follow-up may not have been consistent, however, it provides us with an approximate incidence of this complication. This number would represent a conservative estimate and the actual incidence might be higher. All patients in our practice received a 1.25 mg dose of bevacizumab at each injection. Ophthalmologists should be aware that RPE tears may occur after intravitreal bevacizumab therapy for choroidal neovascularization associated with ARMD.

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