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Retinal Pigment Epithelium Tear

Aleksandra V. Rachitskaya, MD,

Cleveland Clinic Cole Eye Institute, 9500 Euclid Avenue / i32, Cleveland, OH 44195

Raquel Goldhardt, MD

Bascom Palmer Eye Institute, University of Miami, 900 NW 17th Street, Miami, FL 33136

Abstract

Retinal pigment epithelium tear is a potentially vision threatening complication of retinal pigment epithelial detachment associated with neovascular age-related macular degeneration. Retinal pigment epithelium tear has been reported to occur spontaneously and after treatment with anti-vascular growth endothelial factor agents. The current study summarizes the presentation, diagnosis, management, and outcomes of retinal pigment epithelium tears.

Keywords

retinal pigment epithelium tear; retinal pigment epithelial detachment; age-related macular degeneration; anti-vascular growth endothelial factor treatment

Introduction

Retinal pigment epithelium (RPE) tear is a vision threatening complication of retinal pigment epithelial detachment (PED) associated with neovascular age-related macular degeneration (AMD). This overview examines the presentation, risk factors, diagnosis, prognosis, and management of the RPE tears.

Retinal pigment epithelial detachment

PED occurs between the basal lamina of the RPE cells and the inner collagenous Bruch's membrane.¹ PED has been reported in AMD as well as in other chorioretinal diseases such as polypoidal choroidal vasculopathy, central serous chorioretinopathy, Vogt-Koyanagi-Harada syndrome, malignant hypertension and eclampsia.^[1] In AMD, PEDs are classified as serous, fibrovascular, and drusenoid. (Figure 1) Serous PED can be vascularized or non-vascularized, the former associated with choroidal neovascularization (CNV). CNV associated with vascularized serous PED can be an occult CNV membrane or a retinal angiomatous proliferation (RAP) lesion. [2–4] On optical coherence tomography (OCT), a

(corresponding author) Aleksandra V. Rachitskaya, MD Cleveland Clinic Cole Eye Institute, 9500 Euclid Avenue / i32, Cleveland, OH 44195, Tel 216-445-9519, Fax 216-445-2226, rachita@ccf.org.

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serous vascularized PED appears optically empty. Fluorescein angiography shows late hyperfluorescence and indocyanine green (ICG) angiography shows a focal or plaque CNV.[2] A RAP lesion shows as a focal area of intense hyperfluorescence (“hot spot”) corresponding to the neovascularization on ICG.[3] Fibrovascular PED is associated with occult CNV.[1,4] In contrast to serous PED, the elevation of fibrovascular PED is irregular and fluorescein angiography (FA) shows stippled or granular heterofluorescence or even hypofluorescence early, that in late-phase frames demonstrates intensification with leakage beyond the boundaries of early fluorescence.[1] Drusenoid PED is described as an RPE detachment with scalloped borders and an irregular surface and typical slow rate of enlargement of large soft drusen.[1]

Spontaneous retinal pigment epithelium tears in AMD

RPE rip or tear is a vision-threatening complication of a PED that occurs at the junction of the detached and flat pigment epithelium. The tear is followed by retraction of the pigment epithelium, revealing bare Bruch’s membrane.[5] RPE tears occur most commonly in AMD but have been reported in trauma, angioid streaks, and myopia.[6–8] In AMD, RPE tears can occur spontaneously.[5,9] Studies of AMD and PEDs showed that 10%–11.9% of eyes developed spontaneous RPE tears.[9,10] RPE tears have also been reported after argon laser and photodynamic therapy in AMD eyes.[9,11]

The patients who develop RPE tears usually present with acute decrease in vision. In cases of spontaneous RPE tears, vision loss is usually severe especially if there is foveal involvement.[5,9] Interestingly, RPE tears exhibit a high degree of bilaterality.[12]

RPE tears in eyes with neovascular AMD and PED treated with bevacizumab and ranibizumab

Incidence of RPE tears in eyes treated with bevacizumab and ranibizumab—

Patients with neovascular AMD frequently have a concurrent PED. Most experts agree that any subretinal or intraretinal fluid associated with a PED should be treated, and a PED without any evidence of subretinal or intraretinal fluid can be observed.[13–15] A patient with PED, regardless of whether or not she is going to be treated, needs to be educated about the association of neovascular AMD, PED, and RPE tears.

RPE tears after the use of anti-vascular growth endothelial factor (VEGF) treatments, including bevacizumab (Avastin; Genentech/Roche, South San Francisco, CA) and ranibizumab (Lucentis; Genentech/Roche), were originally reported in case reports and small case series.[6] (Figure 2) Pegaptanib sodium injection (Macugen; Eyetech Pharmaceuticals, New York, NY), an anti-VEGF medication used less frequently, has been associated with RPE tears as well.[16–18] In addition to case reports on the RPE tears associated with bevacizumab and ranibizumab, there have been several larger retrospective studies and one small prospective study. The role of anti-VEGF medications in enhancing RPE tears has been speculative and is based on the higher reported incidence of RPE tears in eyes with PED and neovascular AMD undergoing treatment in contrast to the incidence of RPE tears seen in AMD and PED natural history studies. Additionally, temporal relationship of anti-VEGF agent injection and development of the tear has led some investigators to

conclude that anti-VEGF medications are associated with RPE tears. When counseling a patient, a physician should summarize the evidence-based literature on the topic and highlight that none of these studies have been conclusive.

In pre-anti-VEGF literature, approximately 10% of eyes with AMD and PEDs develop spontaneous RPE tears. [9,10] Despite multiple reports, not all studies support the observation that anti-VEGF treatments increase a risk of an RPE tear. A study that retrospectively analyzed patients from ANCHOR, MARINA, and PIER found no statistically significant difference in the incidence of RPE tears within a 2-year treatment period in patients who received ranibizumab (0.5 mg or 0.3 mg) versus control treatment (PDT or sham injection).[19] In this analysis, however, most RPE tears in ranibizumab-treated patients were identified within 3 months of initiating treatment, whereas the majority of late-onset RPE tears occurred in control patients.[19]

When analyzing the studies on the incidence of RPE tears, it is important to pay attention to the methodology employed and in particular to the denominator used to calculate the incidence. The denominator differs significantly among studies and one can consequently erroneously compare apples and oranges. In some studies, it is the total number of eyes or the number of patients, in others it is the number of injections, with the latter usually being higher. In some cases it is all patients treated for neovascular AMD whether or not they have a PED, whereas in other cases it is only the patients with both AMD and PED.

Understanding the results of the studies allows a physician counsel her patients appropriately. When looking at a group of patients with neovascular AMD treated with anti-VEGF injections of ranibizumab or bevacizumab, the incidence of RPE tears ranged from 0.61% to 12.3%.[19–23] One study showed that 0.8% of all bevacizumab injections for neovascular AMD were associated with RPE tears.[24] The large range observed is explained partially by the different number of patients with PEDs among the study subjects with neovascular AMD. The study that had the lowest incidence had only 19 patients (out of 164) who were documented to have both AMD and PED.[21] The study that had the highest incidence of RPE tears among patients treated for neovascular AMD, had 132 eyes (out of 226) with PED.[22] One should be aware of this selection bias when examining the data. It might be advisable to look at the number of patients with PED and neovascular AMD treated with anti-VEGF medications who develop RPE tears. These results would be more applicable in the clinic when discussing the treatment options with a patient presenting with neovascular AMD and PED. The percentage of eyes with neovascular AMD and PED that developed RPE tears ranges from 5% to 19.7%.[17,20–22,25] Although some studies indicate incidence higher than in natural history studies, not all the reports support these findings.

Classification of RPE tears—It is possible that the differences in incidence of RPE tears have to do with difficulty of identifying the small tears.[26] A classification system has been proposed and consists of Grade 1 tears (diameter smaller than 200 μ m), Grade 2 tears (diameter between 200 μ m and 1-disk diameter), Grade 3 tears (diameter greater than 1-disk diameter), and Grade 4 tears (Grade 3 tears that involve the foveal center).[26] Grade 1 tear is the hardest to recognize. FA usually shows a only a thin defect at the margin of the PED with a subtle ring sign of transmission hyperfluorescence (positive ring sign) and OCT

shows a tented up or peaked PED with a microscopic RPE defect. Lower grade tears have better visual acuity and response to anti-VEGF therapy. Grade 4 tears have a poor prognosis with or without anti-VEGF therapy. As the grade of the RPE rip increases, FA exhibits a larger area of window hyperfluorescence corresponding to the area of absent RPE adjacent to an area of blocking fluorescence corresponding to the redundant RPE. OCT shows a larger patch of RPE loss with redundant RPE taking on a dome-shaped configuration. Lower grade tears are more likely to have resolution of sub-retinal fluid with therapy and less likely to develop subretinal fibrosis or disciform scars with or without therapy. It was also noted that tears might progress to the more advanced grade.

Eyes at risk—It has been noted that PEDs which are increasing in size might be at a higher risk for RPE tear development.[10] A history of PED tear in one eye is a risk factor for PED tear in the other.[12] In eyes undergoing treatment with anti-VEGF medications, baseline large PED basal diameter and vertical height (in particular a baseline PED height above 550 microns) along with the presence of a Grade 1 tear, or positive ring sign, were identified as high-risk factors for the subsequent development of an RPE tear. [17,20,22,25,27,28] Additionally, PEDs of shorter duration (< 4.5 months) were more likely to progress to RPE tears.[22] The severity of subretinal fluid at baseline was found to be significantly greater in the tear group, but baseline cystoid macular edema was not significantly different between groups.[17,25] Using near-infrared reflectance imaging combined with OCT, radial hyperreflective lines corresponding to wrinkled changes in the RPE were seen prior to RPE tear development. These hyperreflective lines that spread like a funnel across the PED apparently emanated from the site of CNV. [29]

Does drug or dose matter?—The majority of the eyes (72.2%) develop RPE tear after one anti-VEGF injection.[20,22] However, in many retrospective studies, the subjects had prior treatments for neovascular AMD.[17,20,24]

The data on the effect of different types and doses of anti-VEGF medications is inconclusive at this point. There are multiple reports on RPE tears temporally associated with bevacizumab and ranibizumab treatments. The cases of RPE tears after aflibercept (Eylea; Regeneron, Tarrytown, NY) are limited to case reports.[30] A retrospective study showed that RPE tears may form after intravitreal injection of either 1.25 mg or 2.50 mg of bevacizumab with the higher dose of 2.50 mg not associated with a greater frequency of RPE tears.[20] A study examining 0.3 mg and 0.5 mg doses of ranibizumab used in ANCHOR, MARINA, and PIER studies found no difference in the incidence of RPE tears. [19] In a prospective study, 4 tears occurred in the high dose of 2.0mg ranibizumab treatment arm, whereas only 1 in 0.5 mg treatment group.[25] However, the number of tears in this study was small to draw any conclusions.

Time course—There appears to be two patterns of RPE tears: acute tears within a few days after injection and delayed tears weeks after injection. In a retrospective bevacizumab study, three eyes (13.6%) developed RPE tears within 7 days, whereas 19 eyes (86.4%) developed RPE tears more than 1 week after bevacizumab therapy.[20] In another bevacizumab study, the range was 4 days to 8 weeks.[24] In a study using pegaptanib, bevacizumab, or ranibizumab injections, the mean time from injection to tear was 49 days

with the range of 7 to 133 days.[17] As previously noted, in ANCHOR, MARINA, and PIER studies, RPE tears in the eyes with neovascular AMD that were treated with ranibizumab were identified within 3 months of initiating treatment, whereas the onset of tears in eyes not treated with anti-VEGF therapy was later.[19]

Visual acuity post RPE tear—The visual acuity after an RPE tear treated with anti-VEGF is variable. In several studies the difference in visual acuity before and after the formation of RPE tear was not statistically significant; in one, the mean pre-bevacizumab injection best-corrected Snellen visual acuity was 20/162, and mean post-RPE tear best-corrected visual acuity was 20/160.[20,22] In other studies, the visual outcome varied significantly, with the best outcome improving from 20/150 to 20/60 and the worst outcome showing visual decline from 20/30 to 20/200.[24]

When comparing the neovascular AMD groups that developed tear and those that did not, there was no statistically significant difference between the tear and non-tear groups in the median initial visual acuity (20/300 versus 20/80 respectively), however there was a significant difference in the median final visual acuity (20/400 versus 20/60, respectively). [17] Another study found significant difference in the median initial visual acuity (20/100 versus 20/70, respectively) and final visual acuity (20/200 versus 20/50, respectively).[25] The poor visual acuity was seen in cases of foveal involvement, in eyes with subretinal or vitreous hemorrhage, and grade 4 tear (diameter greater than 1-disk diameter with involvement of foveal center).[17,25,31]

Should anti-VEGF treatments be continued?—The important question is whether anti-VEGF therapy should be continued after the development of the RPE tear. The patients might be reluctant to continue with therapy. The evidence that continued treatment may help to maintain, if not improve, visual acuity and prevent further deterioration comes from both observations in the larger retrospective studies and from the smaller studies addressing the question specifically.[17,19,20,25,32–34]

Previous reports indicate that either spontaneous or post anti-VEGF treatment RPE tear resulted in poor visual acuity especially when patient were followed long-term.[5,9,35,36] In spontaneous RPE tears with 10 years of follow-up, two years after the acute event the visual acuity was worse than 6/60 (20/200) in all affected eyes.[36]

No study has looked at the role of repeat anti-VEGF treatment in RPE tears with similarly long follow-up time. However, it was noted that mean visual acuity was better in patients who developed RPE tears while receiving ranibizumab than in those who received control treatment in pooled results of ANCHOR, MARINA, and PIER studies, suggesting a potential benefit of continued ranibizumab therapy in patients with neovascular AMD who developed RPE tears. [19] A study that followed twenty RPE tear patients treated with repeat anti-VEGF therapy found that after the median of 7 injections (range, 3–15) within 12 months of follow-up the visual acuity improved in 6 eyes (28.57%), remained stable in 12 (57.14%), and decreased in 3 (14.28%).[32] A study with longer follow-up of 52 weeks supported these findings describing 5 patients with mean post-tear visual acuity improving from 20/160 to the mean final visual acuity of 20/60 after two to eight re-injections.[33]

It is hypothesized that the patients with RPE tears might do better than expected due to the treatment of CNV associated with decrease in subretinal fluid and suppression of neovascular activity despite the development of RPE tears.[20]

The visual outcomes even with continued anti-VEGF treatment could be unsatisfactory in some cases.[37] The eyes with foveal involvement improve less than those without. Nonetheless, the improvement is still sometimes noted. [32] The visual gains are also less likely with Grade 4 tears. [26] However, even eyes with submacular hemorrhage and RPE tear can improve with anti-VEGF therapy. The cases of submacular hemorrhage and RPE tears required more injections than those without RPE tears. [38]

Tissue remodeling in retinal pigment epithelium tear—The visual acuity after an RPE tear is determined not only by control of neovascularization, but also by tissue remodeling. (Figure 3) It has been reported that some, usually small, RPE tears can self-heal.[39,40] Larger lesions on long-term follow-up were observed to be replaced by a plaque of fibrous tissue.[36] Several studies utilizing auto-fluorescence and OCT have shown evidence of RPE proliferation, migration and repopulation. [39,41] However, the viability of the migrated RPE is not clear.[42] In fact, intraretinal RPE migration was noted in addition to RPE migration located directly on Bruch's membrane. The former does not form a functional RPE layer.[39] Two repair processes have been observed by OCT to be present in the area where RPE tears developed.[43] Persistent subretinal fluid after the development of an RPE tear lead to subsequent repair with thickened proliferative tissue at the area of RPE loss. With an early resolution of the sub-retinal fluid, the outer retina appeared to be directly attached to Bruch membrane. Interestingly, in this small study, the proliferative tissue that developed after the formation of the RPE tear was not correlated with the visual acuity deterioration.[43]

Several centers have attempted macular translocation with 360 degree retinotomy or RPE-choroid graft translocation in order to provide viable RPE and reestablish the interaction between the RPE and photoreceptors. The surgeries resulted in improvement of vision, but the number of patients undergoing surgery is small. [44–47]

Pathogenesis: One proposed hypothesis of RPE tear formation popularized by Bird is that RPE tear occurs due to accumulation of fluid and increased hydraulic pressure resulting in tangential stress.[48] In this theory, there is constant deposition of lipid materials into the Bruch membrane that renders it increasingly hydrophobic and impermeable to the passage of fluid. In RPE tears, RPE pumps enough fluid to cause rupture of the PED due to increased pressure.[48]

Gass, on the other hand, believed that CNV plays a role in RPE tears.[49] This theory has been supported by showing that contracture of the fibrovascular proliferation seen on the back surface of PED on EDI-OCT might result in RPE tears. This contracture could also cause the RPE to retract and scroll. [50] A spectral-domain OCT study also showed pre-tear OCT revealing a vascularized PED containing hyperreflective material consistent with CNV. This CNV was adherent to the undersurface of the RPE and created contractile folds in the RPE contour. Contractile neovascular tissue spanned the PED, causing outward bowing of

the Bruch membrane and a peaked appearance to the overlying RPE monolayer.[51] The hypothesis that CNV-related fibrovascular contraction in the sub-RPE compartment results in RPE tear has been further supported by the histopathological studies of surgically excised specimens indicating RPE-basement membrane abnormalities and CNV membranes associated with clinically evident spontaneous pigment epithelial detachment.[52,53]

It has been also proposed that vitreomacular traction might play a role in formation of RPE tear. [54]

Future directions: The advances in imaging technologies allow us to obtain more clinically relevant information. Recently there have been several articles focusing on the automated classification of PED internal reflectivity as well as area and volume using OCT.[55,56] Automated imaging using internal reflectivity characteristics appears to be sensitive for detecting serous and fibrovascular PEDs.[55] An algorithm for qualitative appearance of the RPE deformation maps and the quantitative measurements of PED area and volume using spectral-domain OCT was shown to be highly reproducible as well.[56] Automated classification and quantification of PEDs may be a useful tool in future studies for stratifying PEDs according to risk and following disease progression. It could be particularly interesting in relation to the response of vascularized PEDs to anti-VEGF therapy.[55,56] Using the PED volume measurements, for instance, it has been shown that growth of PED might indicate neovascular activity and serve as an indicator for anti-VEGF treatment prior to development of fluid in the macula area.[57] The relationship of PED, neovascular activity, and its role in RPE tears remains to be studied.

Conclusion

RPE tears can complicate the natural history of PEDs associated with neovascular AMD. Poor visual acuity is more frequently seen in cases of foveal involvement. Pigment epithelial detachment height and the shorter duration of PED are potential risk factors for developing RPE tear. RPE tear can happen spontaneously or after treatment with anti-VEGF medications. The clear cause and effect between RPE tears and anti-VEGF agents has not been established. The trend is to continue with anti-VEGF treatment after the development of RPE tear. Patient education regarding the evidence-based outcomes remains the key in diagnosis and treatment of PEDs and RPE tears.

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Figure 1.

Types of retinal pigment epithelium detachment (PED) A. Serous PED. B. Fibrovascular PED, *courtesy of Philip A. Rosenfeld MD*. C. Drusenoid PED.

Figure 2.

RPE tear in an 85 -year-old male receiving anti-VEGF for exudative age-related macular degeneration with sudden decrease in vision in the right eye. A. Fundus photograph showing the presence of a parafoveal RPE tear and extensive subretinal hemorrhage. B. Spectral-domain OCT showing an area devoid of RPE reflectivity with adjoining area of high reflectivity corresponding to the scrolled margin of the RPE tear. C and D. Spectral-domain OCT showing the margins of the RPE tear.

Figure 3. Remodeling of an RPE tear. A. RPE tear with visual acuity 20/100. B. Remodeling with fibrous tissue. Final visual acuity 20/50. *Courtesy of Philip A Rosenfeld, MD*