TEARS OF THE RETINAL PIGMENT EPITHELIUM

An Old Problem in a New Era

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Background/Purpose: Recent attention has focused upon several reports of retinal pigment epithelium (RPE) tears following vascular endothelial growth factor (VEGF)–modulating therapy. The authors review the clinical features, etiologies, imaging characteristics, and pathogenesis of RPE tears and their relationship with intravitreal anti-VEGF treatments.

Methods: The authors conducted a comprehensive literature search of RPE tears or rips of any etiology using the PubMed database. They have also included a retrospective analysis of an additional five cases of RPE tears following anti-VEGF therapy, four after bevacizumab and one after ranibizumab.

Results: Thirty-three cases of RPE tear after treatment with pegaptanib, bevacizumab, or ranibizumab have been previously reported in the literature. The authors have collected and analyzed the clinical features for 25 of these cases for which this information was available. The authors have also included analysis of an additional five cases. Common features of each of these 30 cases included advanced age of the patient, the presence of fibrovascular pigment epithelial detachment (PED) or PED associated with choroidal neovascularization (CNV), and diagnosis of the tear within 4 to 8 weeks of the first or second injection.

Conclusions: RPE tears may develop during the course of anti-VEGF therapy for age-related macular degeneration–related PED. Patients with high-risk lesions, especially large irregular PED associated with CNV, should be counseled and monitored for this complication, which may limit visual prognosis.

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Tears of the retinal pigment epithelium (RPE) were first described by Hoskin et al as a complication of pigment epithelial detachments (PED) in the setting of wet age-related macular degeneration (AMD).[1] Since then, RPE rips, henceforth known as RPE tears, have been described spontaneously in association with central serous retinopathy,[2] angioid streaks,[3] and trauma[4] and as a result of various treatments for neovascular AMD.[5–22] Clinically, a well-demarcated area of bare choroid is visible immediately adjacent to a hyperpigmented area, which represents the redundant, retracted RPE (Figure 1). The overlying neurosensory retina remains intact and a localized exudative detachment of the neurosensory retina may be present.

A vascularized RPE detachment associated with AMD is the most common setting for development of a tear, which is often crescent-shaped and parallel to the temporal edge of the PED. RPE tears are often accompanied by hemorrhage or exudates; bleeding may be severe and may break through into the vitreous.

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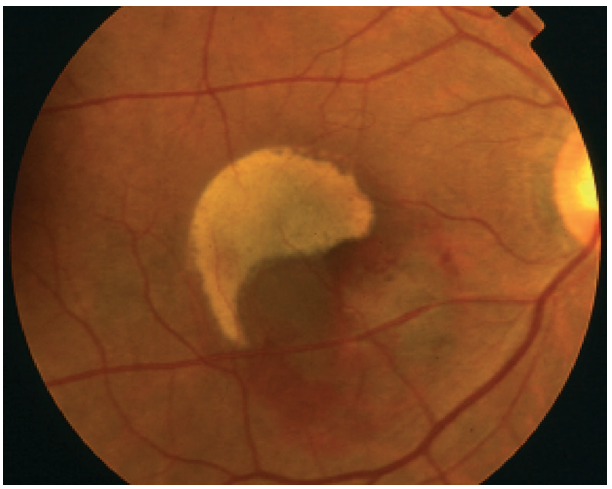

Fig. 1. Spontaneous retinal pigment epithelium tear in an elderly patient with pigment epithelial detachment from age-related macular degeneration. A large crescentic area of bare choroid is present in the central macula with adjacent area of relative hyperpigmentation nasally.

Patients usually report sudden and severe loss of vision.[1,23] Generally, RPE tears portend a poor visual prognosis, often 20/200 or less, even if they do not involve the subfoveal region.[23,24] Rarely, eyes with RPE tears not involving the fovea or through the fovea may retain good visual acuity.[24,25] There is a remarkable symmetry with RPE tears and Chuang and Bird have reported that bilateral RPE tears occurred in 53% of their patients in a 10-year study.[26]

Over time, the area of bare Bruch's membrane may remain exposed, be replaced by normal-appearing RPE, or become covered by fibrous tissue.[1] Delayed fibrosis may obscure the appearance of an acute RPE tear and make diagnosis of a chronic rip difficult, especially if the associated PED has resolved. After performing serial examinations on a cohort of patients, Chuang and Bird concluded that RPE tears could be reliably identified in 94% of cases after 1 year, 77% after 2 years, and in none after 6 years.[27]

No effective treatment exists for RPE tears. One small prospective study of 12 patients reported a decreased rate of vision loss in eyes with laser prophylaxis of drusen when the fellow eyes had AMD-related RPE tear.[28] However, larger, more recent prospective trials have failed to demonstrate a prophylactic benefit of laser to decrease the incidence of CNVM and vision loss.[29–32]

Imaging Characteristics

RPE tears have a distinctive appearance on fluorescein angiography. They show a sharply demarcated area of hyperfluorescent window defect, corresponding to the area of absent RPE, adjacent to an area of blocking hypofluorescence, corresponding to the area of redundant RPE.[1] Alternating light and dark bands of the RPE may be appreciated by FA and represent redundant, folded, or pleated RPE (Figure 2). In the setting of AMD, other features may be seen, such as pooling into the associated PED or leakage from persistent CNV. Indocyanine green (ICG) angiography of RPE tears shows normal choroidal fluorescence in the area of bare choroid and varying degrees of hyperfluorescence in the area of the scrolled or retracted RPE.[33]

Interestingly, RPE tears do not typically display leakage of fluorescein that would be expected to accompany loss of the outer blood–retinal barrier in the area of bare choroid exposed by the retracted RPE. Some have suggested that this may be due to concomitant atrophy of the choriocapillaris in the setting of AMD.[24] However, leakage may be appreciated due to persistent CNVM within the bed of the RPE tear.

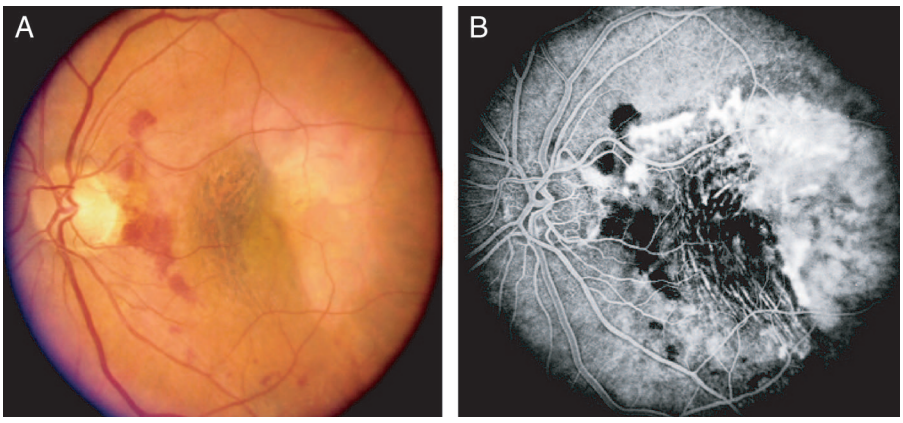

Fig. 2. Color fundus photograph and fluorescein angiogram showing a retinal pigment epithelium (RPE) tear at the temporal edge of a fibrovascular pigment epithelial detachment with associated subretinal hemorrhage in a patient with wet age-related macular degeneration (**A, B**). Note the alternating light and dark bands indicating the retracted, pleated, or folded RPE.

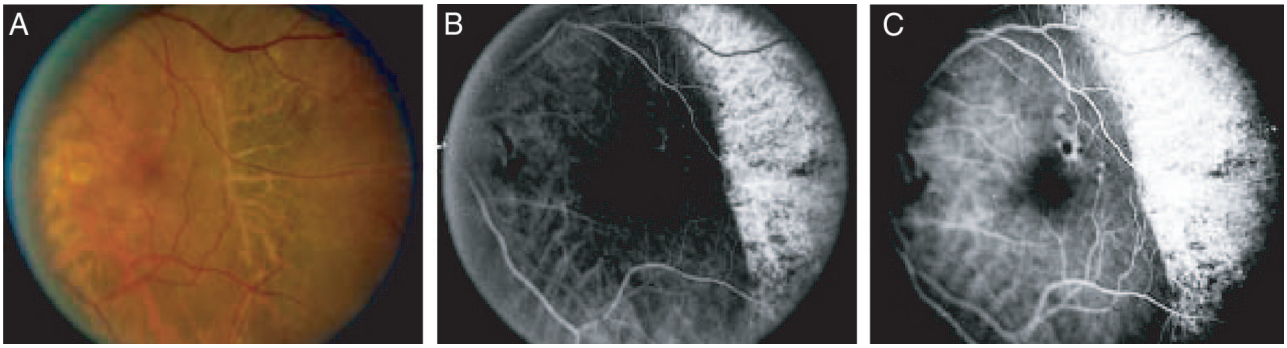

Fig. 3. Large spontaneous tear of the retinal pigment epithelium (RPE) in a patient with high myopia and posterior staphyloma. Note well-demarcated area denuded of RPE in the temporal macula (**A**), which shows transmission hyperfluorescence on fluorescein angiography (**B, C**) and the absence of leakage in the central macula or other evidence of choroidal neovascularization.

Optical coherence tomography (OCT) is useful in confirming the presence of an RPE tear.[34] The critical feature of a rip is a focal disruption in the RPE layer. A large area of RPE loss may also be appreciated. In the setting of AMD-related PED, the detached, torn RPE often retracts and may have three different appearances: a pleated, tentlike, or dome-shaped configuration.[35] The redundant RPE is often irregular in contour and will demonstrate a thicker hyperreflective reflex. It is unclear whether this represents an alteration in the RPE or an artifact related to increased reflectivity from adjacent exposed choroid. These three OCT configurations should raise suspicion of an RPE tear when a frank disruption of the RPE layer is not visualized in a particular optical linear scan. The neurosensory retina appears intact over the tear, with or without subretinal fluid. Tears tend to occur at the base of the PED, near or at the intersection of attached and detached RPE.[1] Detection of the detached and/or torn RPE layer by OCT can aid in differentiating RPE tears in AMD from geographic atrophy, especially if the RPE tear is chronic.

Ultrahigh resolution OCT of an RPE tear following blunt trauma showed disruption of the inner and outer segments of the photoreceptors as well as thinning of the outer nuclear layer centrally over the detached RPE.[36] However, it is unclear if this is a feature common to RPE tears from other etiologies, especially in the more common setting of AMD.

Fundus autofluorescence imaging of an RPE tear revealed loss of autofluorescence corresponding to the area of the RPE defect.[37] In the area of rolled RPE, the average signal was no different than that of the unaffected macula.

Etiologies

RPE tears are most commonly seen in association with CNV from AMD. CNV from other causes may predispose to RPE tear. Cases of spontaneous RPE rip associated with CNV from angioid streaks and from presumed ocular histoplasmosis syndrome (POHS) have been reported.[3,38] One patient with a classic subfoveal CNV from pathologic myopia developed an RPE tear after treatment with PDT.[39] We have identified a highly myopic eye with posterior staphyloma without CNV that developed a large spontaneous rip at the margin of the staphyloma (Figure 3).

In the setting of AMD, the most common lesion associated with RPE tears is a PED. RPE tears may also be associated with PED from central serous chorioretinopathy (CSC) (Figure 4). ICG and OCT imaging show that PED are frequently present in this condition.[2,40] Treatment of CSC with corticosteroids may increase the risk of RPE tears by rapidly increasing leakage associated with the PED[41,42] or possibly by increasing fibrin exudation which may cause traction.[43] RPE tear may also occur in association with large PED secondary to idiopathic polypoidal choroidal vasculopathy.[44]

Rare cases of RPE tear from proliferative vitreoretinopathy with primary rhegmatogenous retinal detachment have been described.[45,46] Two cases of RPE tears after glaucoma surgery have been reported, both complicated by postoperative hypotony and choroidal edema or detachment.[47]

Another rare etiology is trauma.[4,36,48] In all reported cases, the RPE tear was detected upon initial examination within days of the trauma, making it more plausible that they resulted directly from the trauma and not associated with secondary CNV. Some have proposed that this etiology is rare because the force must be within a narrow range: great enough to disrupt the RPE layer, but less than that required to break the RPE and Bruch's membrane, causing a choroidal rupture.[4]

Although RPE tears occur spontaneously in AMD,

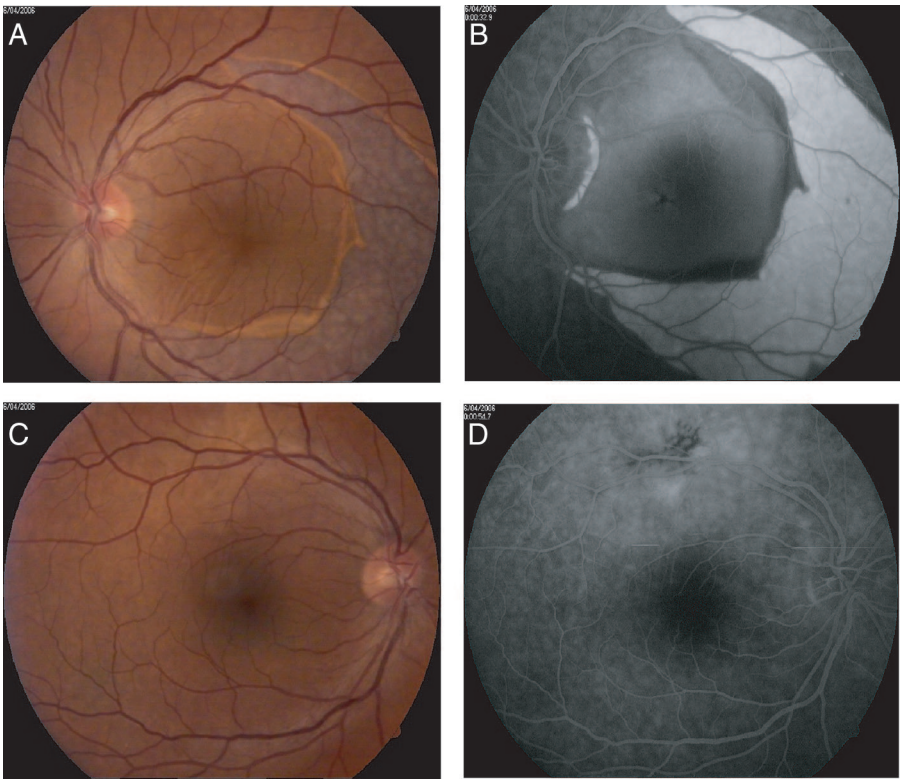

Fig. 4. Spontaneous retinal pigment epithelium (RPE) rip in central serous chorioretinopathy (CSC). A large crescentic tear of the RPE in the left eye (**A**) with window defect corresponding to the area of exposed choroid on fluorescein angiography (**B**). Note small focus of leakage near the superior arcade in the right eye (arrow), suggestive of CSC in the fellow eye (**C, D**). Photographs courtesy of Mark McCombe, MD (Melbourne, Australia).

they have also been linked to various treatments for AMD. A number of cases of RPE tear associated with krypton red laser photocoagulation of CNV from AMD have been described.[5,24,38] In several of the cases, the tear was observed to occur during the treatment, strongly implicating an iatrogenic etiology. In others, the development of the rip occurred from weeks to months after the treatment, making a causal role for the treatment less clear. In a prospective trial of laser photocoagulation of pigment epithelial detachments, RPE tears occurred at a similar rate of 10% in the treatment and control groups, although the sample sizes were small.[49] In addition many of the PEDs were serous, which have a lower risk for tears than fibrovascular PED or PED overtly associated with occult CNVM.

A number of reports have linked photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis) for the treatment of neovascular AMD with RPE tears.[6–9] These eyes had subfoveal CNV and developed RPE tears from days to months after one or two PDT treatments. In the VIP study, acute severe vision loss after the treatment with PDT for occult CNV was reported in 4.4% of cases.[50] In a subsequent analysis, 3 of 14 cases of acute vision loss following PDT in this study were attributed to RPE tear.[51] PDT has been shown to have a number of effects, including damage to the endothelial layer of the choriocapillaris and altered expression of growth factors.[52]

RPE tears have also been reported following treatment of exudative macular degeneration with intravitreal injection of VEGF-modulating therapies, including pegaptanib[10–12] (Macugen, Eyetech Pharmaceuticals), bevacizumab[13–19] (Avastin, Genentech), and ranibizumab[20–22] (Lucentis, Genentech). These will be discussed in greater detail below.

Pathogenesis

Hemodynamic factors may play an important role in the pathogenesis of tears of the RPE in AMD. Retrospective analyses of pre-tear characteristics identified PEDs that increased in size as a risk factor for RPE rip.[23,44] An abrupt increase in the amount of sub-RPE fluid could stretch the RPE, leading to a

"blowout" tear.[53] Increased fluid could result from a diseased RPE layer that cannot process normal amounts of fluid or relatively normal RPE cells that are challenged with an increased volume of fluid, e.g., from an occult CNV.[1,54] Hydrophobic deposits such as drusen and basal laminar deposits may act as a hydrophobic barrier to outward passage of fluid at Bruch's membrane. The detached RPE could also have compromised pump function.

Based on similar clinical observations, Krishan et al proposed a model for RPE tears based on a metal plate with central deflection.[55] According to this model, mechanical stress at the base of the PED would increase at a substantially greater rate than the force at the center of the PED as the height of the PED increased. This model accounts for the propensity of tears to occur at the base of the PED. Cantrill and colleagues postulated that angulation of the pigment epithelium at the base of the PED weakens the layer, predisposing to rupture in this area.[56] We and others have observed a propensity of RPE tears to occur at the temporal edge of the PED, but the underlying mechanism for this is unknown.[24]

Based on the observation of RPE tears occurring during photocoagulation, Gass and others have proposed that the heat generated by photocoagulation caused a shearing force responsible for the RPE tear.[5] Changes in the amount of sub-RPE fluid would not be expected to occur over such a short time period, arguing that tractional forces from contraction along the RPE layer may have a more prominent role in this setting. Such direct tractional forces may also be an important cause of RPE tears that occur after other types of treatment of CNV, such as PDT and anti-VEGF therapies.

Most PED associated with rips are vascularized, indicating the presence of underlying CNV.[57] Signs of vascularization include a larger size of the PED, associated presence of heme and/or exudates, and kidney-shaped or notched configuration. The presence of irregular fluorescence or a hot spot with FA or ICG may also indicate vascularization. Contraction of the associated CNV after treatment may exert force on the RPE layer that contributes to the tear. Radial choroidal folds may indicate the presence of underlying traction and a greater risk of rip.[58] Tractional forces may also have a more direct role in the pathogenesis of RPE tears from other causes such as trauma,[4] PVR,[45,46] and vitreomacular traction.[59]

Gass has reported spontaneous rips of chronic serous PED due to thinning of the RPE.[43] Small asymptomatic edge tears may be appreciated. A similar mechanism may explain our case of RPE rip associated with posterior staphyloma causing stretching or thinning of the RPE (Figure 3).

The actual location of the tear in the RPE/Bruch's membrane complex has been debated. Evidence exists to support a cleavage plane between RPE and underlying basement membrane or between RPE basement membrane and inner collagenous layer of Bruch's membrane. Hoskin et al observed that tears occur more commonly in areas of homogenous hyperfluorescence on fluorescein angiography, which the authors believed represented RPE without basement membrane.[1] However, histopathologic examination in two cases of spontaneous AMD-related RPE tears showed the inner layer of Bruch's membrane detached and redundantly folded, suggesting the cleavage plane occurred within Bruch's membrane.[60]

Interestingly, there may be an underlying biologic predisposition to RPE tear given the high degree of bilaterality in some series. Nearly 35% (15/43) of patients with vision loss from RPE tear developed vision loss from RPE tear in the fellow eye within 3 years.[61] Over a 10-year study period, 24 of 45 patients with bilateral vision loss from AMD had evidence of RPE tears in both eyes.[27] This could represent an underlying structural or physiologic risk factor predisposing the RPE or Bruch's membrane to rip or may relate to the symmetric nature of AMD.

The Association with Anti-VEGF Therapy

Tears of the RPE have been reported in association with VEGF-modulating intravitreal therapies for the treatment of neovascular AMD. Pegaptanib sodium, an aptamer that selectively inhibits the165 isoform of VEGF, was the first VEGF-modulating treatment approved by the Food and Drug Administration (FDA) for use in neovascular AMD.[62] A total of 10 cases in three series of RPE tears occurring shortly after intravitreal injection with pegaptanib sodium have been reported.[10–12] In all these cases, RPE tears occurred from days to weeks after intravitreal injection in eyes with fibrovascular PED (Table 1). The clinical, fluorescein angiographic, and OCT appearance of these cases are indistinguishable from spontaneous RPE tears.

Although not FDA approved for eye care, bevacizumab, a humanized antibody that inhibits all isoforms of VEGF, has been used extensively in the treatment of CNV in the setting of AMD.[63] A number of cases of RPE tears following intravitreal injection of bevacizumab have been reported (Table 1). [13–19] As with those associated with pegaptanib treatment, all eyes harbored a fibrovascular PED or PED associated with occult CNV and most tears occurred within

weeks of the first or second injection. Again, the RPE tears showed identical characteristics to spontaneous RPE rip in the setting of AMD. We have also observed four cases of RPE rip following injection of bevacizumab treatment for fibrovascular PED in eyes that did not receive any other type of treatment for AMD (Figures 5 and 6 and Table 1).

RPE tears have also been reported after treatment with ranibizumab,[20–22] a recombinant humanized anti-VEGF antibody that has been FDA approved for the treatment of all angiographic subtypes of neovascular AMD.[64] We have observed a large RPE tear 1 month after a single intravitreal injection of ranibizumab in a 74-year-old woman with a large fibrovascular PED that had been previously monitored without treatment for several years (Figure 7 and Table 1). Interestingly, her fellow eye demonstrated an acute fibrovascular PED and was treated successfully with Lucentis with subsequent collapse of the PED and improvement of her vision.

All cases of RPE tear associated with anti-VEGF treatment occurred in the setting of neovascular AMD (Table 1). All lesion subtypes, when reported, were fibrovascular PED or PED associated with CNV, emphasizing the high-risk nature of these lesions. The average age of patients was 78.3 years with a median age of 78 years. Since all patients had AMD, the advanced average age is expected. However, it is interesting that only 2 of the 31 patients for whom age was reported were under age 70 years. The mean pre-tear and post-tear visual acuities were 20/93 and 20/194, respectively. The average number of injections before development of the rip was 1.35. The mean time between the last injection and the diagnosis of the RPE tear was 4.51 weeks (median time 4 weeks).

Before our appreciation of RPE tears as a complication of treatment for neovascular AMD, patients with RPE tears typically presented with the complaint of abrupt and significant vision loss. Interestingly, many of the cases in the literature and in this report were discovered incidentally during follow-up examination and retained stable vision. Four of the five ranibizumab cases for which pre- and post-tear visual acuities were reported failed to demonstrate a decrease in vision associated with the RPE tear. The development of intravitreal anti-VEGF therapy has allowed for better maintenance, and in some cases improvement, of vision, largely due to the ability of these agents to reduce vascular permeability and angiogenesis. The concomitant improvement or resolution of subretinal fluid and/or regression of the PED associated with anti-VEGF treatment may mask the acute decrease in vision from the RPE tear (Figure 6). In addition, it has also brought an increase in the frequency of retinal examination in these patients, thus allowing more opportunity to detect less symptomatic RPE tears than in previous years. Thus, RPE tears in this setting may be less visually disabling than those that occur spontaneously. This also underscores the need for careful examination before subsequent intravitreal injections. Whether further anti-VEGF therapy after RPE tear is beneficial is a topic for further study but may be considered with persistent fluid, heme, or exudation.

Given the increasing role of VEGF-modulating therapies for AMD, whether such treatments have a causal role in the development of tears of the RPE becomes an important question. No other modality of treatment for neovascular AMD was given concomitantly or previously in all the reported cases of RPE tear associated with anti-VEGF therapy, with the exception of three cases (Table 1). Additionally, most rips occurred within days to weeks of initiation of anti-VEGF therapy, further raising suspicion for a precipitating role. Because RPE tears occur spontaneously in the setting of AMD, this temporal relationship may simply be coincidence. Because many of the RPE tears were asymptomatic, the timing of the detection may reflect the follow-up interval rather than the exact onset of the event.

The estimated incidence of RPE tear in eyes with fibrovascular PED following pegaptanib sodium treatment was 27% in one study, although this was calculated using retrospective analysis and a small sample size.[12] With additional experience, we have observed a 15% incidence (9/59) of RPE tears following anti-VEGF pharmacotherapy in eyes with a PED associated with CNV that was not previously treated with argon laser photocoagulation or PDT. This is closer to the reported 10% incidence of spontaneous RPE tear in eyes with AMD-related PED over a 1-year follow up, although the authors of this study concede that this figure may underestimate the true incidence.[65] Spandau and Jones reported a 6% incidence of RPE rip in their series of 63 patients receiving intravitreal bevacizumab for exudative AMD with a serous PED.[43] The discrepancy between these figures may be explained by different underlying patient populations. The pegaptanib study and the survey herein considered only fibrovascular PED or those clearly associated with an occult CNV, which clearly have a higher risk of tearing than serous PED. In an Internet-based, self-reported survey of practitioners, the rate of RPE rip as a complication of intravitreal bevacizumab was only 0.06%.[66] In this study, no information about the criteria for diagnosis or the indication for treatment,

Table 1. Summary of Cases of RPE Tears After VEGF-Modulating Therapy

Reference	Treatment	Age, yr	Lesion Type	No. of Injections	Time to Diagnosis	Pre-tear Visual Acuity	Post-tear Visual Acuity
Dhalla et al[10]	Pegaptanib	78	Occult CNV with serous PED	1	1 wk	20/60	20/70
	Pegaptanib	77	Occult CNV with serous PED	1	8 wk	20/80	20/400
Singh and Sears[11]	Pegaptanib*	75	Turbid PED with occult CNV	1	6 wk	20/60	CF
	Pegaptanib	79	Turbid PED with occult CNV	1	6 wk	20/60	20/400
Chang et al[12]	Pegaptanib	81	Occult CNV with serous PED	1	6 wk	20/200	CF
	Pegaptanib	85	FV PED	1	8 wk	20/60	20/200
	Pegaptanib	78	FV PED	2	6 wk	20/400	CF
	Pegaptanib	82	Occult CNV with serous PED	2	8 wk	20/400	20/70
	Pegaptanib	75	Occult CNV with serous PED	1	6 wk	20/50	CF
	Pegaptanib	96	Occult CNV with serous PED	1	2 wk	20/50	20/70
Meyer et al[13]	Bevacizumab	64	Occult CNV with PED	1	4 d	20/60	20/80
	Bevacizumab	84	Occult CNV with PED	1	NR	20/60	NR
Nicolo et al[14]	Bevacizumab	59	Occult CNV with serous PED	1	60 d	20/32	20/20
Shah et al[15]	Bevacizumab	90	PED with occult CNV	3	2 wk	20/100	2/200
	Bevacizumab	85	RAP lesion with PED	2	10 d	20/60	3/200
Spandau and Jonas[16]†	Bevacizumab	NR	Serous PED from exudative AMD	NR	>1 wk	†	†
Gelisken et al[17]	Bevacizumab	70	Occult CNV with PED	1	4 wk	20/50	20/40
Gibran et al[18]	Bevacizumab‡	74	Subfoveal CNV	2	NR	20/125	20/320
Gamulescu et al[19]	Bevacizumab	84	Occult CNV with PED	1	1 wk	20/160	20/100
	Bevacizumab	86	Occult CNV with PED	1	1 mo	20/50	20/80
	Bevacizumab	74	RAP lesion with serous PED	1	1 mo	20/50	20/80
	Bevacizumab	75	PED with CNV	1	1 wk	20/63	20/100
Case 1 (Figure 5)	Bevacizumab	87	FV PED	1	5 wk	20/100	CF
Case 2 (Figure 6)	Bevacizumab	84	FV PED	2	8 wk	20/50	20/40
Case 3	Bevacizumab	75	Serous PED occult CNV	1	6 wk	20/80	20/100
Case 4	Bevacizumab	86	FV PED	2	8 wk	20/200	20/200
Lee et al[20]	Ranibizumab§	70	Occult CNV with PED	3	1 d	20/100	20/100
Carvounis et al[21]	Ranibizumab	78	AMD with PED	1	1 mo	20/200	20/200
	Ranibizumab	78	PED with hot spots	1	1 mo	20/200	20/200
Bakri and Kitzmann[22]	Ranibizumab¶	74	PED with hemorrhage	1	1 mo	20/60	NR
	Ranibizumab	70	Occult CNV with PED	2	1 mo	20/50	20/80
Case 5 (Figure 7)	Ranibizumab	74	FV PED	1	4 wk	CF	CF

Clinical characteristics of all reported and five previously unreported cases of retinal pigment epithelium (RPE) tear associated with pegaptanib, bevacizumab, or ranibizumab use. The interval between the last anti–vascular endothelial growth factor (VEGF) treatment and the diagnosis of the RPE tear is reported under "Time to Diagnosis." Unless otherwise noted, no other treatment for neovascular age-related macular degeneration (AMD) was given.

* Indicates previous treatment with tissue plasminogen activator.

† This study included four cases, but specific details were not reported. Visual acuity was reported as decreasing from 20/60 to 20/100 in one case and unchanged in the remaining three cases.

‡ Indicates previous treatment with pneumatic displacement of subretinal hemorrhage.

§ Indicates three injections with pegaptanib were given prior to three injections of ranibizumab.

¶ Previous treatment with photodynamic therapy.

CNV = choroidal neovascularization; PED = pigment epithelial detachment; CF = counts fingers; FV = fibrovascular; NR = not reported.

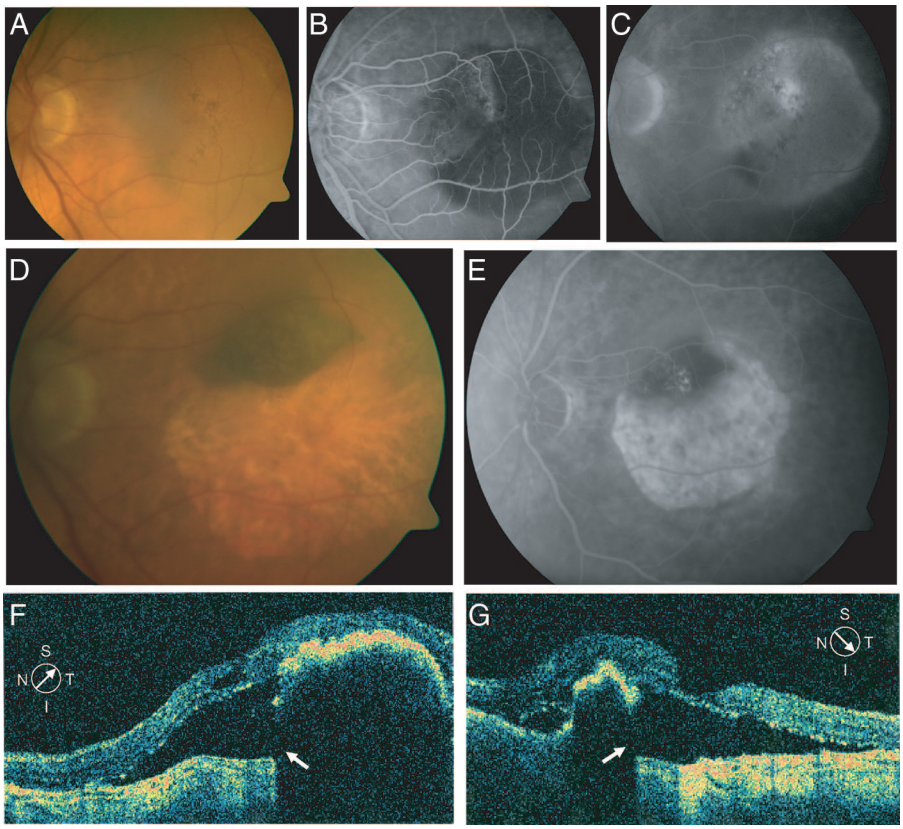

Fig. 5. Retinal pigment epithelium (RPE) tear after intravitreal bevacizumab. This 87-year-old man with a turbid fibrovascular pigment epithelial detachment (PED) (**A**) and irregular filling by fluorescein angiography (FA) (**B, C**), was given a single intravitreal injection of Avastin. At a 6-week follow-up visit, his visual acuity was noted to have decreased from 20/100 to 20/200. Examination at this time showed an RPE tear (**D**), confirmed by FA (**E**) and optical coherence tomography (**F, G**). Note the retracted irregular hyper-reflective RPE layer of the tented PED (**F, G**). Arrow denotes break or tear point in RPE; bare choroid and denuded RPE are present adjacent to each arrow. The patient deferred further treatment and the vision stabilized at counts fingers at last follow-up.

including the angiographic subtype of CNV, is provided, complicating direct comparison.

Despite the frequent dosing required for these treatments, all but two of the reported cases of RPE tears following anti-VEGF therapy occurred after the first or second injection. This observation argues that there

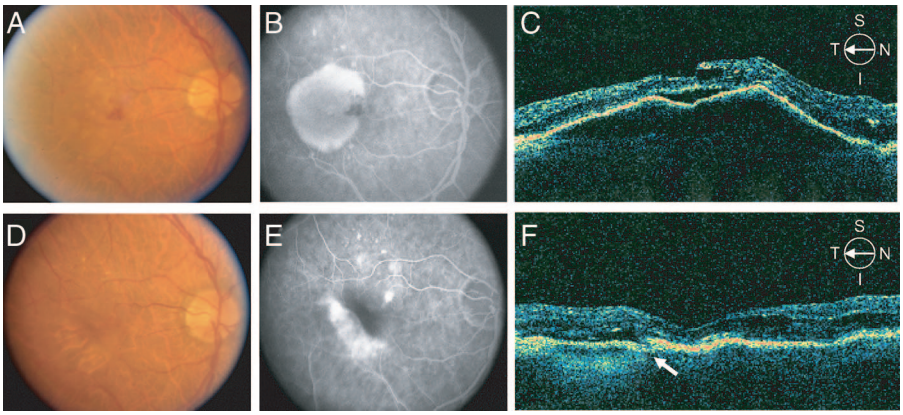

Fig. 6. Retinal pigment epithelium (RPE) rip after intravitreal bevacizumab with flattening of pigment epithelial detachment (PED). Pre-bevacizumab with PED with occult choroidal neovascularization and small focus of subretinal hemorrhage (**A, B**). Optical coherence tomography (OCT) shows irregular, highly elevated PED (**C**). After the second injection of bevacizumab, the patient developed an RPE tear at the temporal edge of the PED (**D, E**). Interestingly, the visual acuity improved from 20/50 before the tear to 20/40, which may be the result of the resolution of sub-RPE fluid with flattening of the PED by OCT (**F**). Arrow in **F** indicates location of RPE tear.

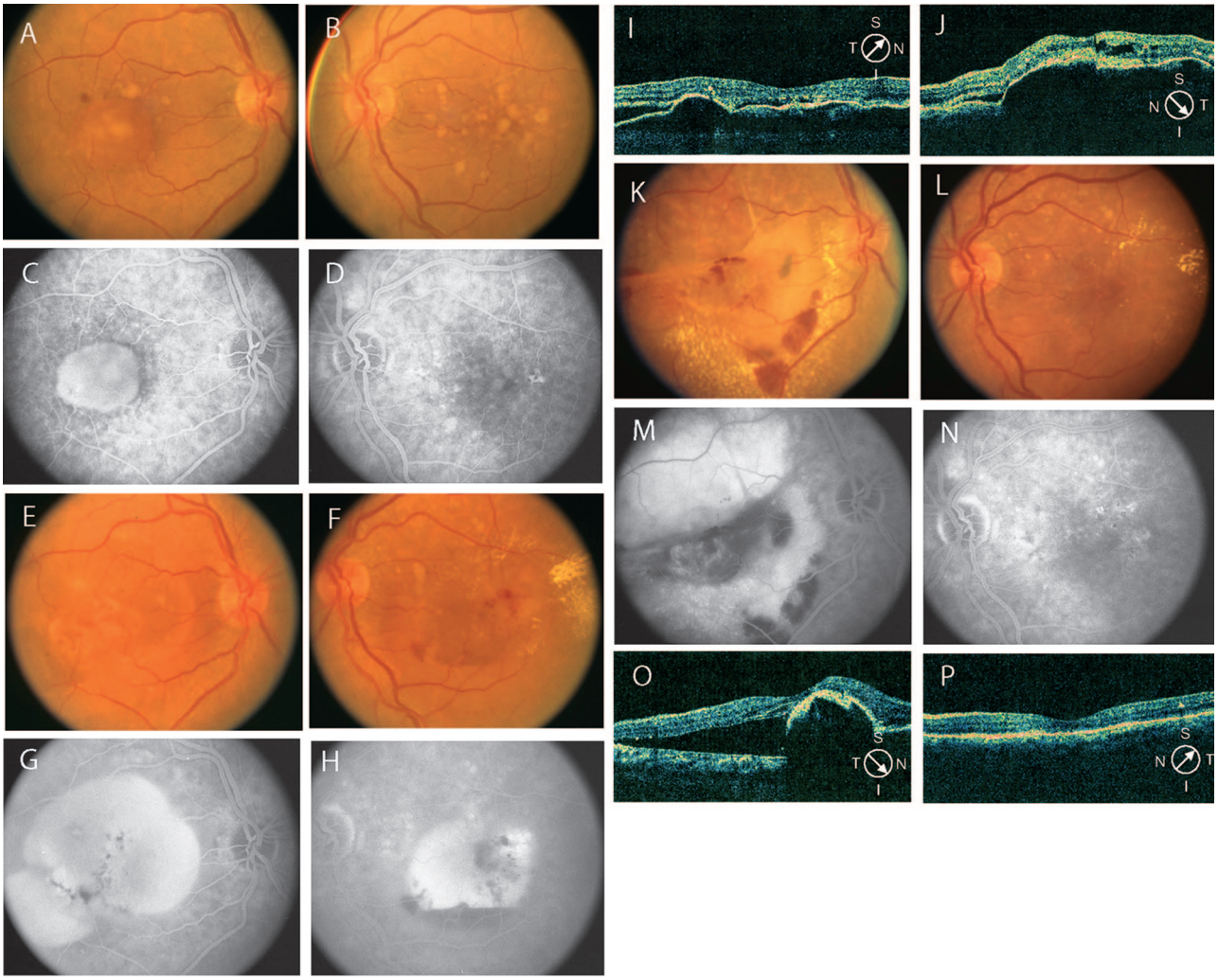

Fig. 7. Retinal pigment epithelium (RPE) tear following intravitreal ranibizumab. This 74-year-old woman initially presented with a serous pigment epithelial detachment (PED) in the right eye (**A, C**) and soft drusen in the left eye (**B, D**), for which she elected to be monitored. Four years later, the PED in the right eye had enlarged and become kidney-shaped (**E, G**), while her left eye developed a new serous PED with hemorrhage and exudates (**F, H**). Optical coherence tomography (OCT) confirmed a broad, irregular PED in the right eye (**I**) and a highly elevated PED in the left eye (**J**). She received two intravitreal injections of ranibizumab in the left eye, which collapsed the PED. After discussing treatment options with the patient, she elected ranibizumab therapy in the right eye, given a gradual decline to count fingers (CF) visual acuity in the right eye and the favorable response to treatment in the left eye. Four weeks after the first injection of intravitreal ranibizumab, her vision remained at CF, but a large RPE tear in the right eye was noted on examination (**K**) and confirmed by fluorescein angiography (FA) (**M**) and OCT (**O**). Note clinical improvement in the left eye (**L**), resolution of leakage on FA (**N**), and flattening of PED by OCT (**P**).

may be a population that is at risk for this complication, rather than an additive risk of each individual treatment. Since the high-risk characteristics of PED for RPE tear following treatment may be similar to those of spontaneous rips, anti-VEGF therapy may accelerate the natural history in those PED that were likely to tear spontaneously if not treated. Given the small numbers of cases, continued experience in this area may shed more light on whether anti-VEGF therapy increases the overall risk for RPE tear or if it precipitates this complication in an at-risk population.

Several potential mechanisms have been proposed, including fibrovascular contraction of the CNV, mechanical forces from vitreomacular traction[59] or extreme fluctuations in intraocular pressure,[19] or interruption of tight junction maintenance by VEGF.[67] Direct, mechanical disruption from needle penetration seems less likely, since RPE tears in some cases were not detected during the initial follow-up examination after the injection.[14,19]

We are unaware of any reports of consecutive bilateral RPE tears following anti-VEGF therapy. Given the high degree of bilaterality of spontaneous RPE tears, it is possible that the fellow eyes may be at high

risk for a similar complication. More data on this topic are needed to inform the decision to offer VEGF-modulating treatment to patients with RPE tears and vision loss following similar treatment in the fellow eye. Interestingly in our case of bilateral large fibrovascular PED, chronic in the right eye and acute in the left, a large RPE rip occurred in the former eye with severe vision loss while the fellow eye sustained resolution of the PED with marked improvement of vision status-post ranibizumab therapy (Case 5, Table 1 and Figure 7).

Identifying those eyes at risk of RPE tear may be an important action before initiating anti-VEGF therapy. Markedly elevated, irregular PED associated with signs of vascularization by examination or ancillary imaging (FA, ICG, OCT) including heme, exudate, CME, notching, hot spot, or irregular fluorescence may represent high risk lesions for RPE rip and vision loss. At the very least, the patient should be educated that there is a risk of vision loss with our novel, revolutionary anti-VEGF therapies such as bevacizumab and ranibizumab and that these drugs are not panaceas.

We performed this comprehensive literature review using the PubMed database (www.pubmed.org) and the following key words: RPE tear, RPE rip, PED, pegaptanib, bevacizumab, ranibizumab. An additional five cases of RPE tear associated with only anti-VEGF therapy seen by one retinal specialist (D.S.) were retrospectively identified and analyzed according to a Kaiser Permanente IRB-approved protocol. Intravitreal injections of bevacizumab (1.25 mg) or ranibizumab (0.5 mg) were administered according to standard protocol.[63,64]

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