RETINAL PIGMENT EPITHELIAL TEARS AFTER INTRAVITREAL BEVACIZUMAB INJECTION FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

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Purpose: To study retinal pigment epithelium (RPE) tears after off-label intravitreal bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA) injection for neovascular age-related macular degeneration. Eyes with a vascularized pigment epithelial detachment (PED) that developed an RPE tear were compared with eyes with a vascularized PED but without an RPE tear.

Methods: Nine retina specialists across the United States and in Europe participated in this retrospective case series. All eyes that received intravitreal bevacizumab injection for choroidal neovascularization (CNV) over 12 months (October 2005 to September 2006) were included. Eyes without all three confirmed tests (fluorescein angiography, fundus photography, and optical coherence tomography) were excluded from analysis. Statistical analyses were performed on multiple characteristics of eyes with a vascularized PED that did and did not develop an RPE tear.

Results: Among 2,785 intravitreal bevacizumab injections for 1,064 eyes, RPE tears were found in 22 eyes in 22 patients (2.2%). A vascularized PED was present in 21 of 22 eyes that developed an RPE tear (17.1% of PED eyes; 15, 100% occult CNV; 6, predominantly occult CNV). Mean interval from bevacizumab injections to RPE tears was 37.3 days. Mean follow-up time was 124.9 days. Mean subfoveal PED size was larger for eyes with tears than for those without tears (13.97 mm^2 vs 9.9 mm^2, respectively; $P = 0.01$; odds ratio, 1.09). There was substantially smaller mean ratio of CNV size to PED size for eyes with tears than for those without tears (27.9% vs 67.6%, respectively; $P = 0.005$). Mean pre–bevacizumab injection best-corrected Snellen visual acuity was 20/162, and mean post–RPE tear best-corrected visual acuity was 20/160 ($P = 0.48$).

Conclusion: Large PED size is a predictor for RPE tears, and a small ratio of CNV size to PED size (<50%) is more common in eyes with RPE tears. Vision may be preserved despite RPE tears.

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Acute retinal pigment epithelium (RPE) tears are known to develop in eyes with neovascular age-related degeneration (AMD), especially in association with a pigment epithelial detachment (PED), either spontaneously or after conventional laser therapy.[1–9] In addition, RPE tears may develop after verteporfin photodynamic therapy (PDT)[10–15] and pegaptanib (Macugen; Eyetech Pharmaceuticals, New York, NY) therapy.[16,17] Recently, a few cases of RPE tears after bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA) therapy were described in a number of reports.[18–23] However, none of these case series had subgroup analyses and risk profiles of RPE tears associated with intravitreal bevacizumab therapy.

Our case series reports the cumulative experience of 9 retina specialists in 7 centers with RPE tears after intravitreal bevacizumab therapy for neovascular AMD; they performed 2,785 bevacizumab injections in widely diverse geographic locations over a 12-month period. Detailed subgroup analyses and a risk profile associated with this complication after bevacizumab therapy are also presented.

Methods

This study was a retrospective case series involving nine retina specialists located across the United States (West Coast, Midwest, and East Coast) and Europe. Retrospective chart review was performed for patients who had received off-label intravitreal bevacizumab injection for neovascular AMD within a 12-month period (October 2005 to September 2006) at the 7 study centers. All eyes that developed RPE tears after intravitreal bevacizumab injection for neovascular AMD within the study period were identified and included for analyses. Because it is a well known fact that RPE tears are usually associated with a PED, statistical analyses were performed for all eyes with a vascularized PED that developed an RPE tear in contrast to 80 eyes with a vascularized PED but without an RPE tear after intravitreal bevacizumab therapy in the same 7 centers. All eyes in both groups had $\geq$3 months of follow-up during the study period. The presence or absence of PED and RPE tears was confirmed by not only fundus photography (FP) and fluorescein angiography (FA) but also optical coherence tomography (OCT). Only eyes with photographic documentation by all three imaging modalities for identifying the PED and RPE tears were included for analysis. Those eyes with suspected PED or RPE tears but lacking documentation by all three modalities were excluded. The characteristics of choroidal neovascularization (CNV) and the presence of PED were established according to standard angiographic criteria. PED was further confirmed by the elevated hyperreflective RPE layer shown by OCT. RPE tears were confirmed by hypofluorescence of the elevated RPE flap and intense hyperfluorescence of the bare choroid demonstrated by FA, as well as interruption of the hyperreflective RPE layer with elevation of the torn RPE flap shown by OCT. Frequently, increased choroidal depth of signals corresponding to the area of RPE tear was visualized by OCT for eyes with RPE tears.

Statistical analysis was performed for pre– and post–intravitreal bevacizumab injection best-corrected Snellen visual acuity (BCVA) utilizing the Wilcoxon signed rank test. Mean and standard deviations were calculated for surface area (mm^2) and greatest linear diameter (μm) of the subfoveal PED and CNV lesions. The interval from bevacizumab injection to RPE tear (days) and follow-up duration (days) were calculated. The onset of RPE tear was defined as the time point that the RPE tear was first revealed by photographic documentation during a follow-up examination. The timing of a patient's history of any acute visual loss was also taken into account, but photographic documentation of the RPE tear by all three modalities discussed above was required. The follow-up intervals varied from 1 week to 4 weeks after each bevacizumab injection. Patients were examined sooner than their scheduled follow-up appointments upon any complaint of visual loss or new visual symptoms (e.g., decreased vision or increased metamorphopsia). Dosages and numbers of bevacizumab injections as well as locations of RPE tears were recorded.

Digital FP and FA were utilized by all study centers. Digital systems that were utilized were limited to the MRP (MRP Group, Inc., Lawrence, MA), OIS (Ophthalmic Imaging Systems, Inc., Sacramento, CA), or Zeiss Visupac (Carl Zeiss International, Oberkochen, Germany) software, and the camera models were limited to the Topcon 50 series (TOPCON Corporation, Tokyo, Japan) or Zeiss FF 450 (Carl Zeiss International). The lesion sizes of the subfoveal PED and the underlying CNV (mm^2) were analyzed and compared between eyes with and those without RPE tears by each center. Cases were submitted to the primary author for review and confirmation. Other contrasted features for the two groups included age, sex, race, right eye versus left eye, prior therapy (e.g., pegaptanib, corticosteroid, PDT, laser, or combination therapy), and history of exudative AMD in the fellow eye (e.g., active or inactive neovascular AMD, diskiform scar, or PED). Fisher exact test and Mann–Whitney test were performed for the above-mentioned analyses. Univariate and multivariate lo-

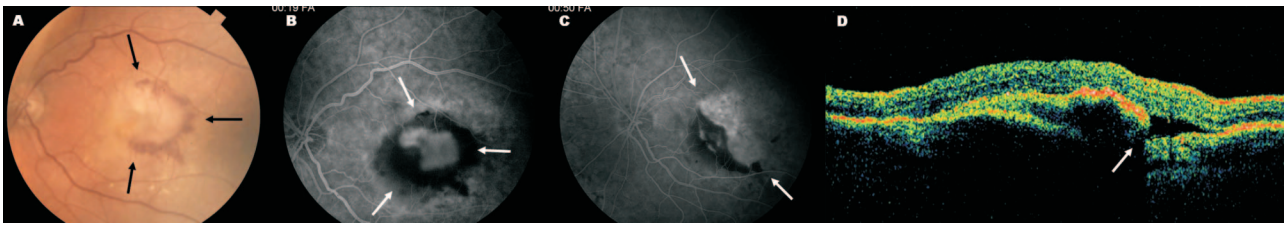

Fig. 1. Case 1. Fundus photography (**A**) and middle-phase fluorescein angiography (FA; **B**) of the left eye of a 78-year-old woman showed a subfoveal vascularized pigment epithelial detachment surrounded with hemorrhage (arrows). Best-corrected visual acuity in the left eye was 20/400. Follow-up FA (**C**) and optical coherence tomography (**D**) showed a temporal retinal pigment epithelium tear with a nasal flap retraction (arrows) 50 days after intravitreal bevacizumab (2.5 mg) injection in the left eye.

gistical regression analysis was performed for the variables of interest (PED size, CNV size, and PED-to-CNV size ratio). The statistical program used for data analyses in this study was SPSS (Version 12.0; SPSS, Inc., Chicago, IL).

This study was compliant with the requirements of the Health Insurance Portability and Accountability Act.

Technique for Intravitreal Injection

All participating retina specialists followed well established standard protocols for intravitreal bevacizumab injections. All intravitreal injections consisting of either 1.25 mg/0.05 mL or 2.5 mg/0.1 mL bevacizumab were carried out in a standard aseptic fashion. All bevacizumab preparations obtained from the manufacturer (Genentech, Inc.) were processed with proper aseptic techniques to achieve the desired dosages according to strict US Food and Drug Administration and US Pharmacopeia Chapter 797 guidelines by well qualified compounding or hospital pharmacies in the United States or Europe.

Selected Case Reports

Case 1

A 78-year-old woman received pegaptanib therapy for a subfoveal vascularized PED with surrounding dense hemorrhage in the left eye in November 2005. On January 17, 2006, BCVA in the left eye was 20/400. There was persistent turbid submacular fluid and hemorrhage associated with a subfoveal vascularized PED in the left eye shown by FP (Fig. 1A) and FA (Fig. 1B). She received an intravitreal bevacizumab (2.50 mg/0.1 mL) injection in the left eye on January 20, 2006. Follow-up examination 50 days later with FA (Fig. 1C) and OCT (Fig. 1D) of the left eye showed nasal retraction of an RPE flap associated with an acute temporal RPE tear, resulting in exposed choroid at the central and temporal portions of the PED but sparing the central fovea. There was decreased subretinal fluid. The size of the subfoveal complex decreased from 5,000 μm to 4,112 μm. During her latest examination on March 14, 2006, BCVA was 20/30-2 in the left eye.

Case 6

An 89-year-old man with a submacular diskiform scar in the left eye presented with a subfoveal vascularized PED bisecting the fovea in the right eye shown by FP (Fig. 2A), FA (Fig. 2B), and OCT (Fig. 2C) on November 11, 2005. BCVA was 20/60 in the right eye and counting fingers in the left eye. He received an intravitreal bevacizumab (1.25 mg) injection in the right eye on November 14, 2006. BCVA in the right eye improved to 20/50 1 week later. Fifty-two days later on January 6, 2007, a small superior temporal RPE tear developed in the right eye; it was shown by FP (Fig. 2D) and was much better visualized by FA (Fig. 2E) and OCT (Fig. 2F [increased depth of signals through the RPE defect]). Despite the RPE tear, BCVA remained 20/40 during the last follow-up examination 130 days later.

Case 9

A 93-year-old woman presented with visual loss due to subfoveal classic CNV without a PED involving the upper portion of the macula in the left eye shown by FP (Fig. 3A) and FA (Fig. 3B). BCVA in the left eye was 20/100. She received an intravitreal bevacizumab (1.25 mg) injection in the left eye in October 2005 and developed an RPE tear with inferior submacular hemorrhage superior to the fovea revealed by FP (Fig. 3C), FA (Fig. 3D), and OCT (Fig. 3E) 118 days later. An additional intravitreal bevacizumab (1.25 mg) injection for persistent CNV through bare choroid in March 2006 led to progressive decline in neovascular activity shown by subsequent FP (Fig. 3F) and FA (Fig. 3G). BCVA decreased to 1/200 after 5 months of follow-up.

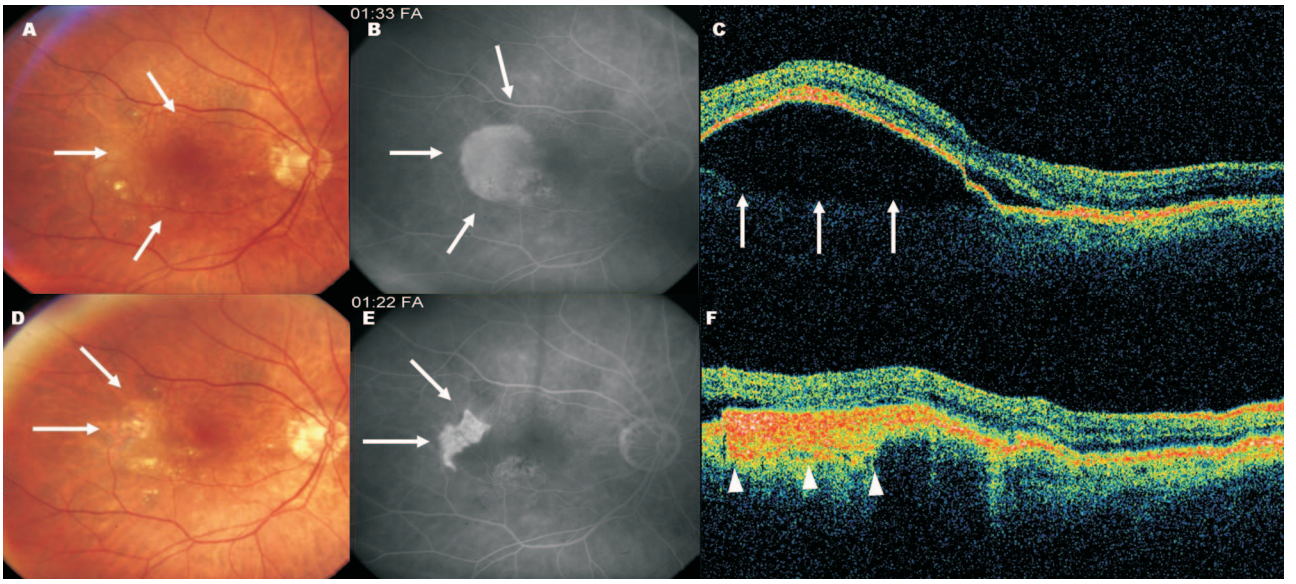

Fig. 2. Case 6. An 89-year-old man with history of a submacular diskiform scar in the left eye and a subfoveal vascularized pigment epithelial detachment (arrows) bisecting the fovea in the right eye shown by fundus photography (FP; **A**), fluorescein angiography (FA; **B**), and optical coherence tomography (OCT; **C**) (arrows) developed a retinal pigment epithelium (RPE) tear (arrows) superior temporal to the fovea during follow-up (shown by FP [**D**], FA [**E**], and OCT [**F**]) 52 days after receiving an intravitreal bevacizumab (1.25 mg) injection in the right eye. Increased depth of signals through defective RPE on the OCT image is shown by arrowheads.

Case 14

A 77-year-old Chinese woman presented with a 1-week history of deceased vision in the right eye in February 2006. BCVA in the right eye was 20/150. There was a subfoveal vascularized PED with surrounding scattered macular soft drusen in the right eye clearly seen by FP (Fig. 4A) and FA (Fig. 4B). There was minimal response and absence of complications associated with a pegaptanib injection in the right eye in February 2006. However, follow-up FP (Fig. 4C), FA (Fig. 4D), and OCT (Fig. 4E) showed substantial reduction in neovascular activity and a large temporal RPE tear 6 days after an intravitreal bevacizumab (1.25 mg) injection in the right eye on March 31, 2006. There was nasal retraction of a large RPE flap in the right eye. BCVA in the right eye deteriorated to 5/150 during her last visit 2 months later.

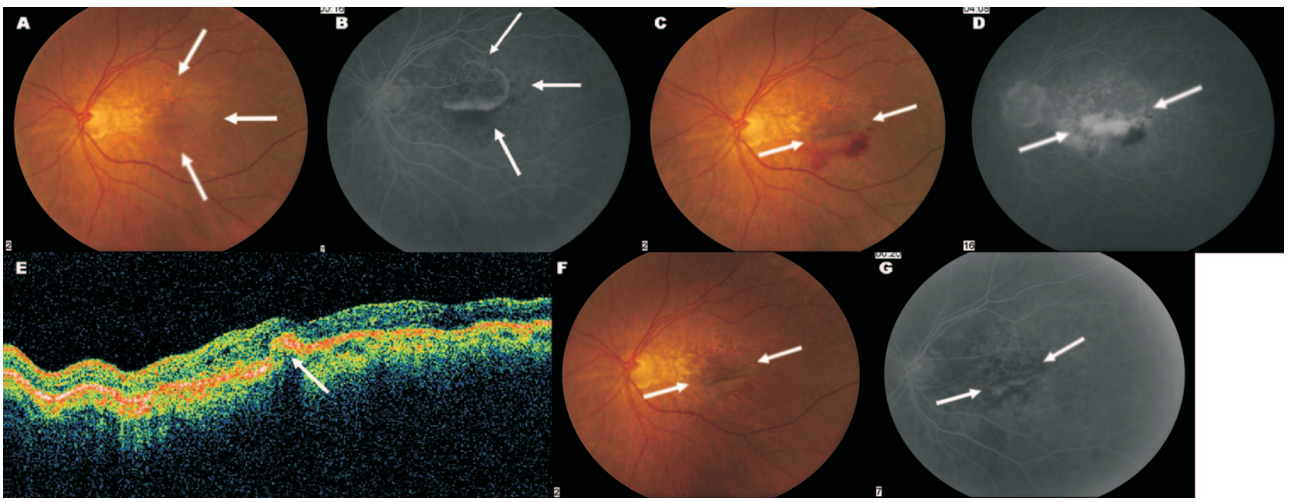

Fig. 3. Case 9. A 93-year-old woman presented with a large classic subfoveal choroidal neovascular process (arrows) without a pigment epithelial detachment in the left eye shown by fundus photography (FP; **A**) and fluorescein angiography (FA; **B**). She developed a superior retinal pigment epithelium tear (arrows) with inferior submacular hemorrhage shown by FP (**C**), FA (**D**), and optical coherence tomography (**E**) 118 days after receiving an intravitreal bevacizumab (1.25 mg) injection in the same eye. Repeated intravitreal bevacizumab injection led to progressive decrease in neovascular activity (arrows) through bare choroid as shown by subsequent FP (**F**) and FA (**G**).

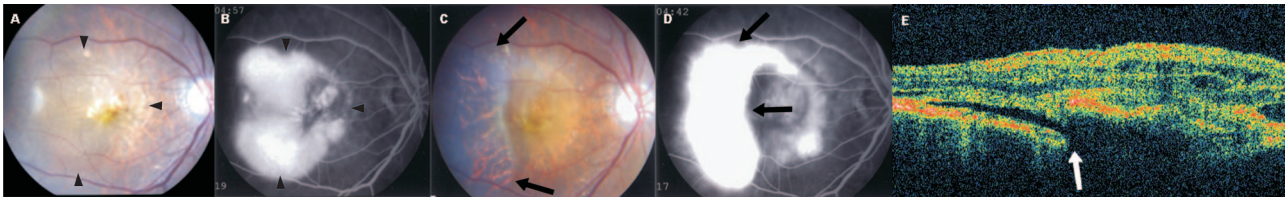

Fig. 4. Case 14. A 77-year-old Chinese woman presented with a subfoveal vascularized pigment epithelial detachment (arrowheads) in the right eye shown by fundus photography (FP; **A**) and fluorescein angiography (FA; **B**). There was no response to pegaptanib therapy in the right eye. She developed a prominent temporal retinal pigment epithelium (RPE) tear (arrows) 6 days after intravitreal bevacizumab injection with a nasal RPE flap retraction sparing the fovea of the same eye shown by FP (**C**), FA (**D**), and optical coherence tomography (**E**).

Results

Demographics and Frequencies

There were 1,064 eyes of 1,038 patients who underwent 2,785 intravitreal bevacizumab injections for neovascular AMD at 7 centers during the study period. One thousand two of 1,064 eyes had confirmed preinjection FA, FP, and OCT at baseline, postinjection OCT at every visit, and FA with FP on a periodic basis. Thus, 62 eyes that lacked all the above confirmed tests were excluded from analysis. One hundred twenty-three (12.3%) of 1,002 eyes had a PED. No preinjection RPE tears were found in 1,002 eyes. Postinjection RPE tears were identified in 22 eyes in 22 patients (2.2% of all confirmed eyes). A vascularized PED was present in 21 of 22 eyes that developed an RPE tear (17.1% of all PED cases among confirmed eyes). Of 22 eyes with RPE tears, 15 had a subfoveal vascularized PED with 100% occult CNV, 6 had a vascularized PED with predominantly occult CNV, and 1 had classic CNV without a PED. Of the 22 patients, 11 were white men, 10 were white women, and 1 was an Asian woman. There were 11 right eyes and 11 left eyes. Mean age ± SD was 80.2 ± 7.4 years (range, 65–93 years). Mean interval from bevacizumab injections to RPE tears ± SD was 37.3 ± 28.70 days (range, 4–118 days). Three eyes (13.6%) developed RPE tears within 7 days after bevacizumab therapy, whereas 19 eyes (86.4%) developed RPE tears >1 week after bevacizumab therapy. Mean follow-up time ± SD was 124.9 ± 58.34 days (range, 42–240 days). FA and OCT documented a rapid decrease in submacular fluid and neovascular activity for all 22 eyes, sparing the central fovea in 17 eyes (77.3%).

Bevacizumab Dose

There was an average of 2.7 bevacizumab injections per patient for the entire series, ranging from 1.4 injections to 5.0 injections per patient for individual study sites. The bevacizumab dose was 1.25 mg/0.05 mL for 14 eyes with RPE tears and 2.50 mg/0.1 mL for 8 eyes with RPE tears. Sixteen eyes (72.7%) developed RPE tears after 1 bevacizumab injection, 5 eyes (22.7%), after 2 injections, and 1 eye (4.6%), after 3 injections.

Location of RPE Tears

RPE tears developed most often along the temporal margin of the PED and temporal to the fovea after intravitreal bevacizumab injection. The location of the RPE tear was temporal to the fovea in 11 eyes, superior to the fovea in 4 eyes, inferior to the fovea in 2 eyes, inferior temporal to the fovea in 3 eyes, superior temporal to the fovea in 1 eye, and circumferential around the inferior PED margin in 1 eye (Table 1).

Statistical Comparison of Eyes With and Without RPE Tears

There were no statistical differences ($P \geq 0.25$) between eyes with RPE tears and eyes without RPE tears for age (mean age, 78.9 years vs 79.6 years, respectively), sex (male patients: 52.4% vs 33.8%, respectively), right eye versus left eye (right eye: 52.4% vs 53.8%, respectively), and race (white: 99% in both groups).

There was lack of a statistical difference in the mean preinjection BCVA and the mean postinjection RPE tear BCVA (0.91 ± 0.40 logMAR [20/162] vs 0.90 ± 0.55 logMAR [20/160], respectively; and $P = 0.48$, Wilcoxon signed rank test). Table 1 outlines detailed pre– and post–bevacizumab injection findings for all 22 eyes. Mean greatest linear diameter of the subfoveal PED ± SD for eyes with RPE tears was 4,590 ± 1,520 μm (range, 1,090–7,360 μm). Mean subfoveal PED lesion size ± SD was larger for eyes with RPE tears than for eyes without RPE tears (13.97 ± 7.23 mm^2 [range, 3.6–29.74 mm^2] vs 9.90 ± 7.65 mm^2 [range, 0.2–49.07 mm^2], respectively; $P = 0.01$, Mann–Whitney test). Mean CNV lesion size ± SD was 2.73 ± 2.22 mm^2 (range, 0.33–8.07 mm^2) for eyes with RPE tears and 4.81 ± 5.08 mm^2 (range,

Table 1. Pre– and Post–Intravitreal Bevacizumab Injection Characteristics of RPE Tears

Patient	Age (y)	Race	Eye	Sex	PED	Preinjection VA	Postinjection VA	Latest VA	CNV Feature	Drug Dose (mg)	Interval of Injection to RPE Tear(d)	Follow-up Duration (d)	PED Size (mm^2)	CNV Size (mm^2)	Location of RPE Tear	Foveal Sparing
1	78	White	LE	F	Yes	20/400	20/100	20/200	100% Occult	2.5	50	100	12.6	1.10	Temporal	Yes
2	79	White	RE	F	Yes	20/300	20/70	20/200	100% Occult	1st, 2.5; 2nd, 1.25	7 (after 1st injection)	75	11.4	2.38	Temporal	Yes
3	84	White	LE	M	Yes	20/200	20/300	20/400	100% Occult with RAP	1st, 1.25;2nd, 1.25	45 (after 2nd injection)	154	9.34	4.37	Inferior temporal	No
4	65	White	RE	M	Yes	20/60	20/80	20/30 after subretinal surgery	100% Occult	1.25	4	120	16.48	0.46	Inferior	Yes
5	84	White	LE	F	Yes	20/60	20/200	20/200	100% Occult	1.25	28	90	22.92	0.48	Inferior temporal	Yes
6	89	White	RE	M	Yes	20/60	20/40	20/40	100% Occult	1.25	52	130	9.45	2.29	Superior temporal	Yes
7	73	White	RE	M	Yes	20/200	20/50	20/50	100% Occult	2.5	36	87	11.0	1.87	Temporal	Yes
8	90	White	RE	M	Yes	20/100	20/100	20/100	100% Occult	1st, 1.25; 2nd, 2.5	11 (after 2nd injection)	116	8.83	1.64	Inferior	Yes
9	93	White	LE	F	No	20/100	20/80	1/200	Classic	1st, 1.25; 2nd, 1.25	118 (after 1st injection)	155	NA	4.48	Superior	No
10	74	White	LE	F	Yes	20/200	20/50	20/70	100% Occult	1st, 2.50; 2nd, 2.50	27 (after 2nd injection)	75	6.2	0.87	Temporal	Yes
11	78	White	LE	F	Yes	20/30	20/40	20/40	Predominantly occult	1st, 1.25; 2nd, 1.25	19 (after 2nd injection)	152	3.6	0.33	Superior	Yes
12	81	White	RE	F	Yes	20/200	20/60	20/50	100% Occult	1st, 2.5; 2nd, 1.25	66 (after 1st injection)	95	7.69	2.17	Superior	Yes
13	76	White	LE	M	Yes	20/400	20/200	20/200	100% Occult	1st, 1.25; 2nd, 2.5	20 (after 1st injection)	190	17.9	2.98	Temporal	Yes
14	77	Asian	RE	F	Yes	20/150	20/150	20/150	100% Occult	1.25	6	42	21.79	1.64	Temporal	Yes
15	75	White	RE	M	Yes	20/80	20/100	20/100	Predominantly occult	2.5	14	120	9.81	2.46	Temporal	Yes
16	86	White	RE	M	Yes	5/200	5/200	5/200	100% Occult	1st, 1.25; 2nd, 1.25	63 (after 2nd injection)	63	20.0	8.07	Temporal	Yes
17	73	White	LE	M	Yes	5/200	5/200	5/200	100% Occult	2.5	48	210	23.4	1.75	Inferior arcuate	No
18	92	White	RE	F	Yes	20/400	20/400	20/400	Predominantly occult	1st, 2.5;2nd, 2.5; 3rd, 2.5; 4th, 2.5	43 (after 3rd injection)	42	18.1	1.03	Superior	No
19	83	White	LE	F	Yes	20/50	20/67	20/80	100% Occult	1.25	15	210	12.34	6.90	Temporal	Yes
20	69	White	RE	M	Yes	20/100	20/133	20/80	Predominantly occult	1.25	21	240	9.81	2.46	Temporal	Yes
21	78	White	LE	F	Yes	20/400	4/200	4/200	Predominantly occult	1.25	91	210	29.74	6.34	Inferiortemporal	No
22	87	White	LE	M	Yes	20/200	20/60	20/60	Predominantly occult	1.25	36	71	5.1	3.94	Temporal	Yes

RPE, retinal pigment epithelium; PED, pigment epithelial detachment; VA, best-corrected Snellen visual acuity; CNV, choroidal neovascularization; RAP, retinal angiomatous proliferation.

0.05–21.64mm^2) for eyes without RPE tears (P = 0.26, Mann–Whitney test). Mean ratio of CNV size to PED size ± SD was substantially smaller for eyes with RPE tears than for eyes without RPE tears (27.9 ± 38.7% vs 67.6 ± 105%, respectively; P = 0.005, Mann–Whitney test).

Prior therapy was performed before bevacizumab injection for eyes with RPE tears in the following manner: pegaptanib, 4 eyes; PDT and intravitreal triamcinolone treatment, 1 eye; pegaptanib and intravitreal triamcinolone treatment, 1 eye; and pegaptanib and intravitreal triamcinolone treatment and PDT, 1 eye. Although 68.2% of eyes with RPE tears in contrast to 58.8% of eyes without RPE tears were naive to treatment, there was a lack of statistical difference between the two groups in overall prior therapy (P = 0.62, Fisher exact test). Subgroup analysis of prior therapy also did not reveal any statistical differences between eyes with and eyes without RPE tears for intravitreal triamcinolone treatment (P = 0.18, Mann–Whitney test), PDT (P = 0.42, Mann–Whitney test), combination therapy (P = 0.97, Mann–Whitney test), and laser therapy (P = 0.83, Mann–Whitney test). However, there were more eyes with prior pegaptanib therapy in the group of eyes without RPE tears than in the group of eyes with RPE tears (P = 0.007, Fisher exact test).

Previous study suggested an increased tendency for an RPE tear in the case of a history of exudative AMD in the fellow eye. For our study, analysis of fellow eyes showed that 10 (47.6%) of 21 eyes with RPE tears in contrast to 39 (48.8%) of 80 eyes without RPE tears had a history of exudative AMD (active or inactive CNV, PED, or diskiform scar) in their fellow eyes. There was a lack of statistical difference between the two groups (P = 0.45, Fisher exact test).

Logistical Regression Analysis

Univariate logistical regression analysis with reference category equal to eyes with RPE tears showed the following odds ratios: PED size, 1.06 (95% confidence interval [CI], 1.00–1.13); CNV size, 0.9 (95% CI, 0.78–1.05); and CNV size-to-PED size ratio, 0.22 (95% CI, 0.03–1.40). Multivariate logistical regression showed the following odds ratios: PED size, 1.09 (95% CI, 1.01–1.18); CNV size, 0.85 (95% CI, 0.69–1.06); and CNV size-to-PED size ratio, 0.18 (95% CI, 0.20–3.53).

Bevacizumab Therapy After RPE Tears

Additional bevacizumab therapy was performed for 27.3% of eyes after development of RPE tears (Cases 2, 9, 10, 12, 13, and 18), leading to continued suppression of neovascular activity for all these eyes. Of note is visual preservation in Case 18 despite foveal involvement by the RPE tear.

Discussion

Since the initial reports of excellent tolerance, substantial efficacy, and low cost of intravitreal bevacizumab for treating neovascular AMD and central retinal vein occlusion by Rosenfeld et al,[24,25] there has been widespread interest in the ophthalmic community for its off-label use as treatment of various retinal vascular conditions. Multiple subsequent clinical case series continue to demonstrate the substantial antiangiogenesis and antipermeability properties of bevacizumab in comparison with other commercially available agents.[26–29] Several recent reports have shown sound safety profiles of bevacizumab in animal and in vitro studies.[30–32] Much is known about the potentially serious cardiovascular and thromboembolic complications associated with intravenous administration of bevacizumab, but there have been few descriptions of ocular complications associated with intravitreal bevacizumab administration in the literature until small case series of RPE tears after intravitreal antivascular endothelial growth factor therapy by multiple investigators in recent reports.[18–23,33,34]

The current large case series showed that among all eyes receiving bevacizumab injections for neovascular AMD within the study period, 12.3% had a PED and 2.2% developed an RPE tear (corresponding to 17.1% of eyes with a PED). A review of the literature showed that our report of a PED in 12.3% of all eyes with neovascular AMD is consistent with the report of Meyer and Toth[8] of a PED in 10% of eyes with neovascular AMD. For RPE tears, natural history studies by Hoskin et al,[1] Casswell et al,[35] and Chuang and Bird[7] estimated that 10% of eyes with a PED developed RPE tears. In their prospective study on the clinical course of PED in the elderly, Pauleikhoff et al[36] reported an RPE tear incidence of 11.9%. Although any role of bevacizumab in enhancing RPE tears is speculative (consistent with the higher incidence of RPE tears in our study in contrast to the natural history studies on PED eyes [17.1% vs 10–11.9%, respectively]), additional study on their potential correlation is warranted. Furthermore, possible underestimation of the incidence of RPE tears after bevacizumab injections due to the retrospective nature of this study cannot be discounted. In fact, the initial presentation of RPE tears after bevacizumab injection can be rather subtle and unrecognized with delayed development in some eyes (e.g., Cases 6, 10, 13, and 17). A delay in the diagnosis of RPE tears for some

eyes related to the follow-up intervals also cannot be ruled out, although all patients were encouraged to contact the study centers for earlier examination before their next appointments in case of worsening visual symptoms. Similar to other case series of RPE tears,[18–23] all eyes except one with RPE tears after intravitreal bevacizumab injection in this study had an associated PED.

A key finding of this study relates to large PED size as a predictor for RPE tears after intravitreal bevacizumab therapy. The PED size was larger in eyes with RPE tears than in those without RPE tears (mean: 13.97 mm^2 vs 9.9 mm^2, respectively). This finding is consistent with the study by Pauleikhoff et al[36] that clearly showed that RPE tears developed only in eyes with large PED sizes. Regarding subfoveal CNV lesion sizes, there was a trend for smaller CNV sizes in eyes with RPE tears than in those without RPE tears, although the difference failed to reach statistical significance (2.9 mm^2 vs 4.45 mm^2, respectively). However, there was a substantial difference between the two groups in the mean ratio of CNV size to PED size (27.9% vs 67.6%, respectively). Despite the smaller ratio of CNV size to PED size among eyes with RPE tears, logistical regression with both univariate and multivariate analyses showed only large PED size to be a predictor for RPE tears after intravitreal bevacizumab therapy (odds ratio: 1.06 and 1.09, respectively).

The significance of a small ratio of CNV size to PED size among eyes with RPE tears is uncertain and may seem to be counterintuitive at first glance. One possibility is that it is a coincidental finding. Another possibility is that it is a result driven by a certain subgroup. However, there is a plausible explanation for such a profile among many eyes with RPE tears. A small ratio of CNV size to PED size implies that the CNV has more space to migrate under a much larger PED and therefore induces more stress on the RPE margin during its contraction in response to antiangiogenesis therapy (Fig. 5). It should be pointed out that most current multicenter clinical trials involving antiangiogenesis therapy for neovascular AMD excluded eyes with a PED, which may explain the absence or paucity of RPE tears in those trials.[37–41]

In a previous report, Goldstein et al[14] conjectured that eyes with a history of exudative AMD in their fellow eyes have a greater risk for developing RPE tears. Our study did not confirm this correlation. Although a large number of eyes with RPE tears in our study had a history of exudative AMD in their fellow eyes (10 eyes [47.6% PED cases]), statistical analysis showed a lack of difference in the frequency of exudative AMD involving the fellow eyes between eyes with RPE tears and eyes without RPE tears.

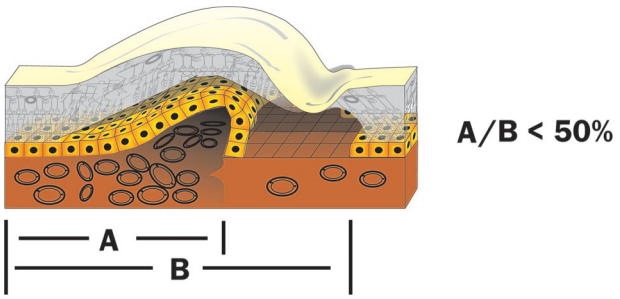

Fig. 5. The mean ratio of choroidal neovascularization (CNV) size to pigment epithelial detachment (PED) size was significantly lower among eyes with retinal pigment epithelium (RPE) tears than among eyes without RPE tears (27.9 vs 67.6, respectively). A, size of CNV; B, size of PED.

Bevacizumab injection was the sole treatment for 15 eyes (68.2%) that developed RPE tears in this series, whereas other therapeutic modalities were performed before bevacizumab injection for 7 eyes (31.8%). Our data showed no statistical difference in overall prior therapy as well as individual prior therapy (i.e., intravitreal triamcinolone treatment, laser, PDT, and combination therapy) for eyes with or without RPE tears. However, prior pegaptanib therapy was the exception. Statistical analysis showed a converse relationship between prior pegaptanib therapy and RPE tears, because there were more eyes without RPE tears than eyes with RPE tears that underwent prior pegaptanib therapy. For the 6 eyes (27.3%) with RPE tears that underwent prior pegaptanib therapy, they developed RPE tears only after bevacizumab therapy but not during their prior pegaptanib therapy. These findings imply substantial mechanical contraction of the CNV after treatment with a panvascular endothelial growth factor inhibitor such as bevacizumab with potent antiangiogenic properties.

Regarding the bevacizumab doses, this study showed that RPE tears may form after intravitreal injection of either 1.25 mg or 2.50 mg of bevacizumab (1.25 mg for 14 eyes; 2.50 mg for 8 eyes). The higher dose of 2.50 mg was not associated with a greater frequency of RPE tears. There were similar percentages of eyes in the two dose groups that developed RPE tears (2.2% vs 2.6%, respectively). Statistical analysis showed no differences between the two groups in risk for RPE tears. The tendency for RPE tears was also not correlated with the cumulative doses of bevacizumab injections, because most (72.7%) formed after only 1 injection. Although these findings are surprising, there is a well recognized phenomenon among antiangiogenesis investigators in oncology that higher doses of certain antiangiogenesis

drugs do not always lead to a greater response than their lower doses, and the reverse may even sometimes occur (Potential Future Advances in Ophthalmology from Research in Tumor Angiogenesis by Judah Folkman, MD; September 10, 2006; 24th Annual ASRS Meeting and 6th Annual EVRS Meeting, Cannes, France).

Our data showed two patterns of RPE tears: acute tears within a few days after bevacizumab injection and delayed tears weeks after bevacizumab injection. The reason for the predominance of the delayed pattern (86.4% of eyes with RPE tears) is unclear. One plausible explanation is that neovascular tissue shrinkage may take more time to develop after bevacizumab injection than after conventional laser, which may induce immediate tissue contraction by delivering a concentrated dose of thermal energy to the CNV. The delayed development of the RPE tears may increase the chance of failed or belated diagnosis of the more subtle cases (e.g., Cases 6 [Fig. 2], 10, 13, and 17).

The precise mechanism for the formation of RPE tears after treatment of neovascular AMD is not known. For verteporfin PDT, Goldstein et al[14] speculated weakening of RPE intercellular adhesion due to temporary exudation shortly after treatment to play a role. Other investigators proposed biologic mechanisms including release of proinflammatory cytokines and angiogenic factors after PDT that may weaken the integrity of the RPE layer.[42,43] In the case of antiangiogenesis therapy such as bevacizumab injection, the most likely mechanism involves mechanical shrinkage of the treated CNV.[18–23] Meyer et al[18] also proposed vitreoretinal traction related to globe deformation and vitreous syneresis and incarceration induced by the needle injection. In addition, they speculated that bevacizumab modulates the permeability and biologic activities of the CNV. Another biologic mechanism proposed by Nicolo et al[23] involves decreased tight junction gene transcription due to the blockage of vascular endothelial growth factors by bevacizumab, leading to increased tendency for RPE cellular dehiscence. The tendency of RPE tears to form at the temporal margin of the vascularized PED due to an unknown mechanism shown by our study is consistent with the findings of a previous report.[44]

Finally, the reasons for visual preservation for most eyes with RPE tears in this study are uncertain. The most logical explanation is the lack of foveal involvement for most of the eyes with RPE tears in our study (Table 1), consistent with previous reports showing good visual function for such eyes.[5,7] However, one previous report showed that foveal involvement by the RPE tear does not rule out good visual function.[45] In fact, vision was maintained despite foveal involvement by the RPE tear in one eye in this study. Our study also documented rapid decrease in subretinal fluid and suppression of neovascular activity with bevacizumab therapy despite the development of RPE tears, another potential mechanism for visual preservation in our study. In addition, our data showed that repeated intravitreal bevacizumab injection after RPE tears did not worsen the tears but continued to suppress neovascular regrowth through denuded choroids, as occurred in 27.3% of cases.

The strength of this study is its presentation of a broad spectrum of collective findings on RPE tears after intravitreal bevacizumab therapy involving multiple clinicians and a large number of patients over diverse geographic locations, likely representative of the overall worldwide clinical experience on this ocular complication associated with bevacizumab therapy. However, the retrospective nature of this study involving multiple centers may have introduced unknown confounding variables. For instance, the association of bevacizumab with RPE tears was confounded by prior therapy with other modalities in one third of the eyes with RPE tears, although there was a lack of statistical difference in the frequency of overall prior therapy between eyes with RPE tears and those without RPE tears in this series. Similar to most other retrospective and prospective studies involving multiple centers, the lack of a single digital system and camera model among all of the study centers might have introduced confounding variables to the outcome. However, restriction of the photography to a few standard digital systems and camera models and review and confirmation of the results by the primary author likely limited the confounding effects of such variables.

In conclusion, to our knowledge, this is the largest case series on RPE tears after intravitreal bevacizumab injection for neovascular AMD. This study found that the overall risk for RPE tears after intravitreal bevacizumab injection is relatively low. However, at least 17.1% of eyes with a PED may develop RPE tears after intravitreal bevacizumab injection in contrast to the 10% incidence of RPE tears reported by natural history studies. Therefore, clinicians must be vigilant for this complication when utilizing intravitreal bevacizumab injection for treatment of neovascular AMD in eyes with a PED, although the harmful effects of this complication may be limited because additional bevacizumab therapy after RPE tears may preserve vision and delay further vision loss. More studies are warranted to validate the findings of this study and further investigate the risk profile of RPE tears associated with antiangiogenesis therapy.

Key words: bevacizumab (Avastin), choroidal neovascularization, neovascular age-related macular degeneration, retinal pigment epithelium detachment, retinal pigment epithelium rips, retinal pigment epithelium tears.

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