RETINAL PIGMENT EPITHELIAL TEARS IN THE ERA OF INTRAVITREAL PHARMACOTHERAPY: RISK FACTORS, PATHOGENESIS, PROGNOSIS AND TREATMENT (AN AMERICAN OPHTHALMOLOGICAL SOCIETY THESIS)

By David Sarraf MD, Anthony Joseph MD, and Ehsan Rahimy MD

ABSTRACT

Purpose: To describe the risk factors, pathogenesis, and prognosis of retinal pigment epithelial (RPE) tears and to demonstrate our hypothesis that continued anti–vascular endothelial growth factor (VEGF) therapy after an RPE tear has occurred correlates with improved long-term visual and anatomical outcomes.

Methods: We searched a database of 10,089 patients and retrospectively identified a large case series of 56 eyes with neovascular age-related macular degeneration (AMD) complicated by an RPE tear over an 8-year period. Baseline visual acuity (VA) was tabulated and analysis of the RPE tear was performed with multimodal imaging. Follow-up VA, progression of the tear, and severity of fibrosis were evaluated, and each was correlated with number of anti-VEGF injections.

Results: Average follow-up for the 56 eyes was 42 months, and mean logMAR VA at baseline was 0.88 (Snellen VA 20/150) with minimal decline over 3 years. LogMAR VA plotted against number of anti-VEGF injections demonstrated that more frequent and cumulative injections correlated with better VA ($P<.0001$). A greater number of anti-VEGF injections was associated with minimal progression of the RPE tear, reduced fibrosis, and lower risk of a large, end-stage exudative disciform scar.

Conclusions: Fifteen to 20% of vascularized pigment epithelial detachments (PEDs) may develop RPE tears after anti-VEGF therapy due to progressive contraction of the type 1 choroidal neovascular membrane in a PED at risk. Continued monitoring of RPE tears for exudative changes warranting anti-VEGF therapy may stabilize VA, improve anatomical outcomes, reduce fibrosis, and decrease the risk of developing a large blinding end-stage exudative disciform scar.

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INTRODUCTION

Retinal pigment epithelial (RPE) tears can complicate various chorioretinal disorders, including traumatic chorioretinopathy,[1-3] high myopia,[4,5] angioid streaks,[6] choroidal tumors,[7-9] light chain deposition disease,[10] central serous chorioretinopathy,[11-13] and polypoidal choroidal vasculopathy (PCV).[14-16] Musashi and colleagues[14] reported on the incidence of low-grade RPE tears that they referred to as "microrips" and noted that these developed in 11 (7.1%) of 156 eyes with PCV, whereas Pauleikhoff and associates[15] observed RPE tears in 2 (14.3%) of 14 eyes with PCV. Severe cases of central serous chorioretinopathy associated with systemic steroid therapy and/or the presence of fibrin have also been associated with RPE tears[5,12,13]; rarely, a patient with central serous chorioretinopathy or PCV may even develop a giant RPE tear extending to the periphery (Figure 1).[5] The common denominator in many of these various disorders complicated by an RPE tear is an underlying pigment epithelial detachment (PED).

The most common association of RPE tear by far is the neovascular form of age-related macular degeneration (AMD). Hoskin and colleagues[17] were the first to identify RPE tears in patients with PED and neovascular AMD, and they described the clinical and angiographic findings, which included a window defect corresponding to the area of RPE loss and blockage in the region of the retracted RPE. Interestingly, the fundus autofluorescence findings are the reverse with hypoautofluorescence in the region of lost RPE and hyperautofluorescence corresponding to the retracted RPE.[18] Optical coherence tomography (OCT) typically demonstrates a zone of RPE dehiscence and an adjacent tented-up PED with a retracted and irregular RPE monolayer (Figure 2).[19-21]

While RPE tears are most common in the neovascular form of AMD, they develop almost always in association with a vascularized PED. During the natural history of PEDs in AMD, the spontaneous tear rate has been found to be approximately 10% to 12%.[15,17,22-26] Pauleikhoff and coworkers[15] specifically noted an RPE tear rate of 12.5% (9 of 72 eyes) in their natural history study of patients with vascularized PED and AMD. Tears of the RPE can also develop after various laser therapies for PED, including argon laser photocoagulation[27-29] and photodynamic therapy.[30-34]

In the era of intravitreal pharmacotherapy, there has been an explosion of reports of RPE tears developing after intravitreal anti–vascular endothelial growth factor (VEGF) therapy, usually shortly after the first, second, or third injection. Our group was one of the first to describe this complication in 6 neovascular AMD eyes with vascularized PED after intravitreal pegaptanib injection.[35] There have been a large number of subsequent reports describing this complication after intravitreal bevacizumab,[26,36-48] ranibizumab[49-58] and aflibercept[59,60] therapy, almost always in eyes with vascularized PED and neovascular AMD. In a comprehensive literature review, Chang and Sarraf[5] found that almost all cases of RPE tear identified after pegaptanib, bevacizumab, or ranibizumab therapy were associated with a baseline vascularized PED, and most recently Doguizi and Ozdek[61] noted that 26 of 28 eyes that developed RPE tear after anti-VEGF therapy harbored a vascularized PED at baseline.

We have determined an RPE tear rate of approximately 14% to 17% in eyes with vascularized PED receiving intravitreal anti-VEGF therapy in two separate studies, one retrospective[62] and one prospective.[58] Another group has confirmed a similar tear rate of

From the Jules Stein Eye Institute, David Geffen School of Medicine at UCLA, Los Angeles, California (Dr Sarraf, Dr Joseph, Dr Rahimy); Kaiser Permanente, Department of Ophthalmology, Woodland Hills, California (Dr Sarraf); Greater Los Angeles Veterans Affairs Healthcare Center, Los Angeles, California (Dr Sarraf); and Mid Atlantic Retina, The Retina Service of Wills Eye Hospital, Thomas Jefferson University, Philadelphia, Pennsylvania (Dr Rahimy).

17%,[26] and more recently Doguizi and Ozdek[61] have shown an even higher RPE tear rate of 20% in eyes with vascularized PED and neovascular AMD. In this latter study, 26 of 28 RPE tears occurred within 1 month of the first injection. This finding has been corroborated by previous studies, as Chang and Sarraf[5] noted in their review that the average number of injections before the development of an RPE tear was 1.3 and median time between last injection and diagnosis of the RPE tear was 4 weeks. This temporal association of tears with intravitreal anti-VEGF injection, along with the aforementioned high rates of occurrence, indicates that anti-VEGF therapy may increase or at least accelerate the rate of this complication.

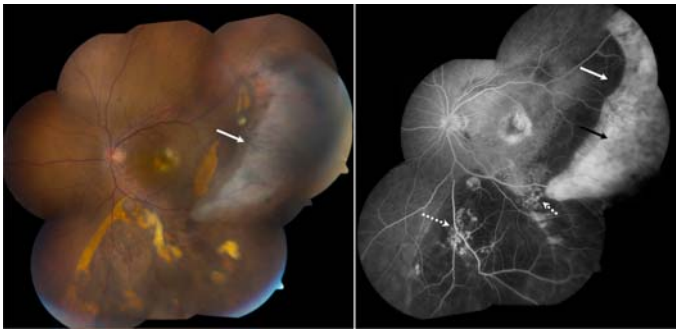

FIGURE 1

Color fundus photograph and fluorescein angiogram of a giant retinal pigment epithelial (RPE) tear in an elderly Asian man with polypoidal choroidal vasculopathy. Left, Color fundus photograph montage of the left eye showing a giant RPE tear extending to the temporal periphery of the left eye (arrow). Fibrous ingrowth is appreciated, especially within the inferior portion of the tear. A fibrotic disciform scar is present centrally in the macula, and there are multiple patches of resolving subretinal hemorrhage in the temporal macula and in the inferior midperiphery. Right, Fluorescein angiogram montage of the left eye showing a large hyperfluorescent window defect (black arrow) corresponding to the giant RPE tear and an adjacent hypofluorescent blocking defect (white arrow) corresponding to the retracted RPE. There is staining of the disciform scar centrally and diffuse blockage from the subretinal hemorrhage in the inferior midperiphery. Numerous hyperfluorescent polyps (broken arrows) with associated feeder vessels are visualized along the inferotemporal arcade and in the inferior midperiphery.

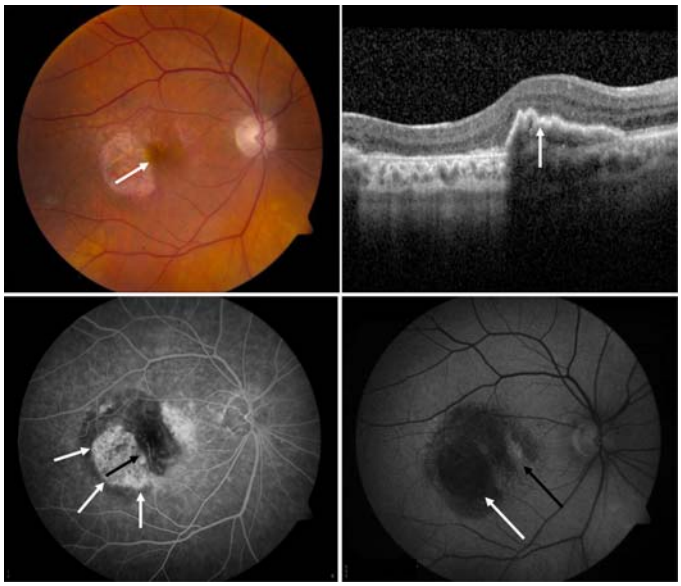

FIGURE 2

Multimodal imaging of a retinal pigment epithelial (RPE) tear in an elderly man with neovascular age-related macular degeneration. Upper left, Color fundus photograph of an RPE tear temporal to the fovea of the right eye (arrow). Bottom left, Fluorescein angiogram delineating the margins of the tear (white arrows) that is hyperfluorescent due to transmission; adjacent retracted RPE is hypofluorescent due to blockage (black arrow). Bottom right, Corresponding fundus autofluorescence showing hypoautofluorescence of the tear (white arrow) due to loss of the RPE and hyperautofluorescence of the retracted RPE (black arrow) due to increased density of RPE fluorophores, ie, lipofuscin. Upper right, Spectral-domain optical coherence tomography registered through the RPE tear showing dehiscence and loss of the RPE corresponding to the tear and an adjacent peaked pigment epithelial detachment with a retracted and irregularly scrolled RPE monolayer (arrow).

There is great interest in the clinical community for guidelines regarding management of patients once they have developed this potentially devastating complication.[61,63,64] To date, the number of RPE tears studied and/or the length of follow-up has been limited. In their long-term study of RPE tears, Asao and colleagues[63] noted an average length of follow-up of 27 months (13 to 44 months) but included only 10 eyes with RPE tears in their analysis. In more robust studies, Gutfleisch and coauthors[65] evaluated 37 eyes with RPE tears that were followed for a mean period of 88 weeks or 22 months (SD, 51 weeks), and Coco and colleagues[64] evaluated 21 eyes with RPE tears followed for an average length of 25 months and as long as 48 months. Most recently, Doguizi and Ozdek[61] studied 28 eyes with RPE tears that were assessed over an average length of follow-up of 20 months (SD, 14 months). To the best of our knowledge, our study will evaluate the clinical characteristics and treatment outcomes of the largest number of RPE tears collected (56 eyes) with the longest follow-up (average follow-up of 42 months and ranging from 5 to 96 months) ever reported of eyes with RPE tears receiving continued anti-VEGF therapy. We hypothesize that continued anti-VEGF therapy after an RPE tear occurs correlates with improved visual and anatomical outcomes.

MATERIALS AND METHODS

Investigational review board (IRB) approval was obtained for this retrospective chart review through the Kaiser IRB committee, and the research study adhered to the tenets of the Declaration of Helsinki and was conducted in accordance with regulations set forth by the Health Insurance Portability and Accountability Act (HIPPA).

We searched the Kaiser Woodland Hills database consisting of 10,089 patients and reviewed all AMD patients with a diagnosis of RPE tear that developed spontaneously or after anti-VEGF therapy. We identified 83 AMD patients (and 96 eyes) with a diagnosis of RPE tear over an 8-year period between January 2005 and July 2013. The lead author (D.S.) reviewed the fundus photographic and fluorescein angiographic (FA) images for each of these 96 eyes. Clinical charts were consulted and historical and examination data were tabulated for each of the 83 patients. Those cases without high-quality imaging and without a definite RPE tear upon consultation of color and angiographic images were excluded, as were those cases with inadequate follow-up (<5 months). Forty eyes were eliminated because of insufficient follow-up or inadequate imaging, historical, or clinical documentation. Excluded cases were similar to those included in the study in terms of baseline demographics and lesion type. In total, 56 eyes with RPE tears from 49 AMD patients were included in the study.

For each of the 56 eyes, Snellen visual acuity (VA) at baseline, at 1-, 2-,and 3-year intervals, and at last follow-up was collected and tabulated. Each patient's clinical chart was also reviewed for history of anti-VEGF injections preceding and following RPE tear. Standard Snellen VA was converted to logarithm of the minimum angle of resolution (logMAR) for purposes of statistical analysis, which included comparison of VA among the different grades of tears and among different injection schedules using the Kruskal-Wallis test for comparison. A *P* value of <.05 was considered to be statistically significant.

Baseline analysis of the RPE tear was also performed, including grading of the tear and documentation of the presence of hemorrhage and fluid as demonstrated with color fundus photography, FA, and OCT analysis. At 1-year follow-up, grading of the tear was repeated and the development of fibrosis was assessed; any evidence of progression of the tear was noted and this analysis was repeated at the patient's last follow-up in which color photography, FA, and OCT was available. The number of annual anti-VEGF injections and the specific type of anti-VEGF injections administered were also recorded, tabulated, and correlated with progression of the RPE tear.

Tears of the RPE were graded according to the classification scheme first described by Sarraf and colleagues (Figure 3).[22] Briefly, RPE tears were graded from 1 to 4 based on the greatest length in the vector direction of the tear and involvement of the fovea. Grade 1 tears were defined as <200 µm. Grade 2 tears were between 200 µm and 1 disc diameter (DD). Grade 3 tears were >1 DD. Grade 4 tears were defined as grade 3 tears that involved the center of the fovea. Additionally, each patient's clinical images were closely analyzed to determine the underlying lesion, associated fibrosis, associated hemorrhage, and location at presentation.

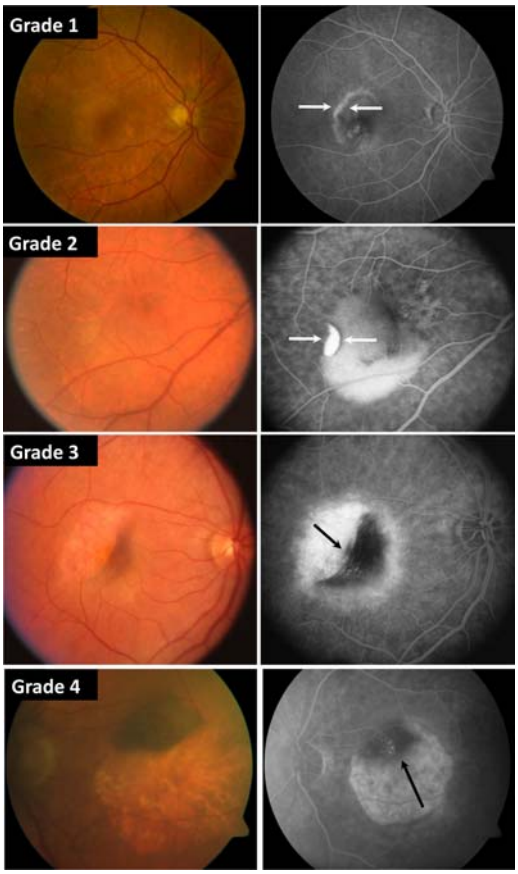

FIGURE 3

Color fundus photograph and corresponding fluorescein angiogram of grade 1 through 4 retinal pigment epithelial (RPE) tears in eyes with neovascular age-related macular degeneration. Color photo (upper left) and fluorescein angiogram (upper right) of grade 1 RPE tear (white arrows) measuring less than 200 µm in the vector direction of the tear. Color photo (upper middle left) and fluorescein angiogram (upper middle right) of grade 2 RPE tear (white arrows) measuring between 200 µm and 1 disc diameter (DD) in the vector direction of the tear. Color photo (lower middle left) and fluorescein angiogram (lower middle right) of grade 3 RPE tear (black arrow) measuring greater than 1 DD in the vector direction of the tear, but not crossing fixation. Color photo (lower left) and fluorescein angiogram (lower right) of grade 4 RPE tear (black arrow) measuring greater than 1 DD in the vector direction of the tear, and crossing fixation.

RESULTS

Fifty-six eyes from 49 patients (25 male, 24 female) with RPE tears secondary to neovascular AMD were identified and their charts retrospectively reviewed for relevant clinical information, including Snellen VA and history of anti-VEGF injections. All 56 eyes had baseline fundus photography and FA to confirm the presence of an RPE tear. Baseline patient demographics, mean logMar VA, and mean follow-up as well as baseline PED and tear characteristics including tear grade are presented in Table 1.

TABLE 1. DEMOGRAPHICS, VISUAL ACUITY, AND PED AND TEAR CHARACTERISTICS IN PATIENTS WITH RPE TEARS ASSOCIATED WITH AMD

Number of patients	49
Male	25 (51%)
Female	24 (49%)
Bilateral exudative AMD	30 (61%)
Bilateral RPE tear	7 (14%)
Total number of tears	56
Mean age at tear	79 (60-91; SD=7.9)
Mean follow-up (mo)	42 (5-96; SD=22.9)
Spontaneous	9 (16%)
Postinjection	47 (84%)
Hemorrhage	17 (30%)
Mean VA pre-tear	0.81 (N=48, SD=0.61) – 20/125
Mean VA post-tear	0.88 (N=53, SD=0.66) – 20/150
Mean pre-tear injections	4 (N=53, SD=3.9)
Mean 1-year injections	5 (N=47, SD=3.8)
Mean final injections	14 (N=54, SD=13.4)
Initial lesion	
Fibrovascular PED	47 (84%)
Classic CNVM	2 (4%)
Scar	1 (2%)
Mixed classic and scar	4 (7%)
Mixed classic and PED	2 (4%)
Tear grade	
Grade 1	1 (2%)
Grade 2	26 (46%)
Grade 3	17 (30%)
Grade 4	12 (21%)
Initial fibrosis	
None	42 (75%)
<50%	5 (9%)
>50%	8 (14%)
NA	1 (2%)

AMD, age-related macular degeneration; CNVM, choroidal neovascular membrane; NA, not available; PED, pigment epithelial detachment; RPE, retinal pigment epithelium; VA, visual acuity; VEGF, vascular endothelial growth factor.

Mean logMAR VA prior to the development of the RPE tear was 0.81 (Snellen equivalent 20/125). Baseline mean VA upon development of the RPE tear was reduced to 0.88 (20/150). The great majority of eyes (88%) demonstrated a fibrovascular PED prior to the development of an RPE tear, whereas only 2 eyes (4%) were found to harbor a purely classic choroidal neovascular membrane (CNV). RPE tears developed after at least one intravitreal injection of either pegaptanib, bevacizumab, or ranibizumab in 47 of the 56 eyes, and 9 tears developed spontaneously without prior anti-VEGF therapy. There was a roughly equal number of eyes that developed RPE tears after bevacizumab (n=19 eyes) and ranibizumab (n= 26 eyes) therapy and no indication of a greater risk of tear development with either drug. The median number of anti-VEGF injections prior to the development of an RPE tear was 3. Approximately half of the tears that developed were either grade 3 or 4 in severity, and nearly all the remaining tears were grade 2

(Table 1). Thirty patients (61%) had documented neovascular AMD in both eyes, and 7 patients (14%) eventually developed RPE tears in both eyes over the course of their follow-up.

Average length of follow-up was 42 months, with a range of 5 to 96 months. The baseline mean logMAR VA of 0.88 was relatively stable over the first year with mean logMAR VA of 0.96 at 1 year and was minimally declined over the next 2 years to a mean logMAR VA of 1.08 at 3 years (Figure 4).

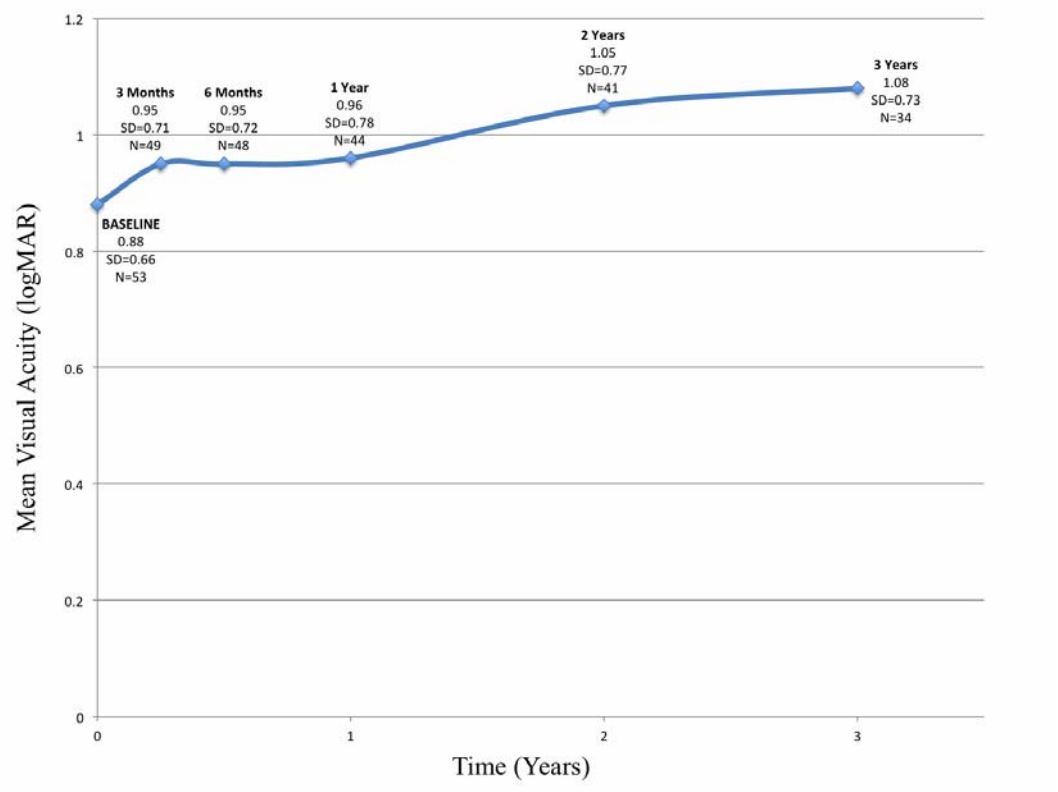

FIGURE 4

Mean logMAR visual acuity plotted against time of follow-up in eyes with baseline retinal pigment epithelial (RPE) tears and neovascular age-related macular degeneration. After an initial decline, the mean visual acuity appears relatively stable in the first year following an RPE tear, with a very slight decline in subsequent years. Note that given the variable onset and follow-up of eyes in this study, there are fewer patients at longer follow-up intervals.

To determine if the baseline grade severity and duration of the RPE tear had a significant effect on visual outcome, we performed the following analyses. Comparison of logMAR VA of eyes with grade 2 vs grade 4 tears demonstrated decreased acuity in the latter group at 6 months (0.84=20/125 vs 1.20=20/300; *P*=.05) and at 1 year (0.92=20/150 vs 1.31=20/400; *P*=.17); results were statistically significant at the 6-month interval. Similarly, comparison of VA of eyes with grade 3 vs grade 4 tears again demonstrated decreased acuity in the grade 4 group at 6 months (0.95=20/200 vs 1.20=20/300; *P*=.19) and at 1 year (0.86=20/150 vs 1.31=20/400; *P*=.11), although these results were not significant. When including only eyes with at least 2 years of follow-up (n=39), there was no significant difference in VA with grade 2 vs grade 4 tears (1.33=20/400 vs 1.50=20/600; *P*=.56), nor was there any significant difference with grade 3 vs grade 4 tears (1.20=20/300 vs 1.50=20/600; *P*=.46) at final follow-up, although this interval was variable. The same was true for eyes with at least 3 years of follow-up (Table 2).

In a separate analysis to determine if continued intravitreal anti-VEGF therapy improved visual outcomes, we compared eyes that received at least 2 intravitreal injections of an anti-VEGF agent within 6 months of the observation of the RPE tear (n=34) vs those that did not (n=16) and found better VA on average at 6 months (0.80=20/125 vs 1.31=20/400; *P*=.14), 12 months (0.82=20/125 vs 1.31=20/400 *P*=.13), and at final follow-up (1.13=20/250 vs 1.77=counting fingers (CF); *P*=.06) in the group that received at least 2 injections, although the results were not statistically significant. The final follow-up was variable with a mean of approximately 40 months for both groups. Similarly, we compared eyes that received at least 4 injections within 12 months of observation of RPE tear (n=28) vs those that did not (n=19) and found better average acuity at 12 months (0.80=20/125 vs 1.26=20/400 *P*=.13) and at final follow-up (1.07=20/250 vs 1.71=CF; *P*=.04) in those eyes that received at least 4 injections; these results were statistically significant for final follow-up which was approximately 41 months on average. Similar results were seen if the minimum number of injections was increased to 3 within 6 months and 6 within 12 months with statistical significance at final follow-up for both comparisons (Table 3).

TABLE 2. VISUAL ACUITY OUTCOME VS BASELINE GRADE OF RETINAL PIGMENT EPITHELIAL TEAR IN EYES WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

CATEGORY	3 MONTHS	6 MONTHS	12 MONTHS	FINAL
All	Mean logMAR visual acuity (standard deviation) - Snellen equivalent			
Grade 2	0.79 (0.59) - 20/125	0.84 (0.66) - 20/125	0.92 (0.76) - 20/150	1.34 (0.97) - 20/400
Grade 3	0.89 (0.86) - 20/150	0.95 (0.87) – 20/200	0.86 (0.84) - 20/150	1.19 (1.07) - 20/300
Grade 4	1.36 (0.64) - 20/400	1.20 (0.63) - 20/300	1.31 (0.71) - 20/400	1.55 (0.97) - 20/600
Grade 2 vs 4 *P* value		***.05***	.17	.37
Grade 3 vs 4 *P* value		.19	.11	.27
Follow up ≥24 months				
Grade 2	0.72 (0.59) - 20/100	0.77 (0.65) - 20/125	0.81 (0.62) - 20/125	1.33 (0.97) - 20/400
Grade 3	0.72 (0.61) - 20/100	0.79 (0.58) - 20/125	0.74 (0.61) - 20/100	1.20 (1.04) - 20/300
Grade 4	1.27 (0.70) - 20/400	1.21 (0.64) - 20/300	1.20 (0.71) - 20/300	1.50 (1.05) - 20/600
Grade 2 vs 4 *P* value		***.05***	.20	.56
Grade 3 vs 4 *P* value		.14	.15	.46
Follow up ≥36 months				
Grade 2	0.78 (0.65) - 20/125	0.75 (0.65) - 20/125	0.76 (0.65) - 20/125	1.28 (1.04) - 20/400
Grade 3	0.79 (0.60) - 20/125	0.86 (0.57) - 20/150	0.81 (0.60) - 20/125	1.29 (1.03) - 20/400
Grade 4	1.18 (0.76) - 20/300	1.17 (0.78) - 20/300	1.18 (0.79) - 20/300	1.55 (1.17) - 20/600
Grade 2 vs 4 *P* value		.11	.28	.51
Grade 3 vs 4 *P* value		.46	.34	.68

We also plotted final logMAR VA vs final number of anti-VEGF injections and found that more cumulative injections correlated with better VA (Spearman correlation coefficient = -0.67; $P<.0001$), although we must take into account variable follow-up intervals (Figure 5). To control for variable follow-up intervals, we also plotted final logMAR VA vs annual injection frequency and found that more frequent injections correlated with better VA (Spearman correlation coefficient = -0.66; $P<.0001$) (Figure 6).

Finally, we evaluated follow-up imaging of the tears to examine the relationship between fibrosis and frequency of anti-VEGF injection and to evaluate the relationship between progression of the tear grade and frequency of anti-VEGF injection. Of note, 4 eyes that failed to receive continued anti-VEGF therapy after development of an RPE tear demonstrated a large end-stage exudative disciform scar with final imaging. The likelihood of this adverse outcome decreased with increased annual injection frequency (OR=0.016; 95% CI=<0.001 to 7.68; $P=.19$), although the result was not statistically significant. When comparing at least one injection per year vs no injection to assess for this outcome, we see similar findings with statistical significance (OR=0.095; 95% CI=0.010 to 0.87; $P=.04$). When including eyes with >50% fibrosis in the analyses, the results became significant for both scenarios (Table 4). We also examined change in fibrosis between baseline and final imaging and found progression in 19 eyes. Again, the likelihood of this outcome decreased with increased annual injection frequency (OR=0.80; 95% CI=0.65 to 0.99; $P=.04$). Finally, we examined the progression of tear grade, which occurred definitively in 4 eyes, but the likelihood of this result did not appear to be related to injection frequency (Table 4).

TABLE 3. COMPARISON OF VISUAL ACUITY OUTCOME VS NUMBER OF ANTI-VEGF INJECTIONS IN EYES WITH BASELINE RETINAL PIGMENT EPITHELIAL TEARS ASSOCIATED WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

	3 MONTHS	6 MONTHS	12 MONTHS	FINAL
Injections at 6 months	Mean logMAR visual acuity (standard deviation) - Snellen equivalent			
<2 (n=16)	1.38 (0.93) - 20/400	1.31 (0.93) - 20/400	1.31 (0.92) - 20/400	1.77 (1.11) - CF
≥2 (n=34)	0.79 (0.57) - 20/125	0.80 (0.57) - 20/125	0.82 (0.68) - 20/125	1.13 (0.85) - 20/250
P value		.14	.13	.06
<3 (n=19)	1.30 (0.92) - 20/400	1.26 (0.90) - 20/400	1.26 (0.89) - 20/400	1.71 (1.07) - 20/600
≥3 (n=31)	0.77 (0.54) - 20/125	0.77 (0.55) - 20/125	0.80 (0.67) - 20/125	1.11 (0.85) - 20/250
P value		.14	.13	***.05***
Injections at 12 months				
<4 (n=19)	1.30 (0.92) - 20/400	1.26 (0.90) - 20/400	1.26 (0.89) - 20/400	1.71 (1.07) – CF
≥4 (n=28)	0.68 (0.45) - 20/100	0.75 (0.56) - 20/125	0.80 (0.67) - 20/125	1.07 (0.88) - 20/250
P value			.13	***.04***
<6 (n=28)	1.12 (0.81) - 20/250	1.12 (0.81) - 20/250	1.13 (0.88) - 20/250	1.62 (1.04) - 20/600
≥6 (n=19)	0.62 (0.45) - 20/80	0.70 (0.57) - 20/100	0.74 (0.58) - 20/100	0.90 (0.77) - 20/150
P value			.15	***.02***

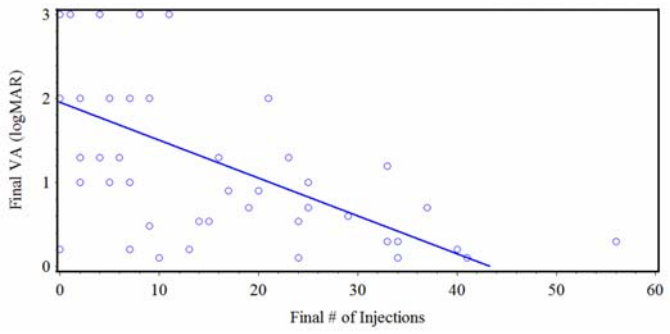

FIGURE 5

Scatter diagram of final logMAR visual acuity of eyes with baseline retinal pigment epithelial tears associated with neovascular age-related macular degeneration plotted against the total number of anti-VEGF injections over the course of all available follow-up. The line of best fit demonstrates that more cumulative injections correlated with better visual acuity (Spearman correlation coefficient = -0.67; *P*<.0001), although one must take into account variable follow-up intervals.

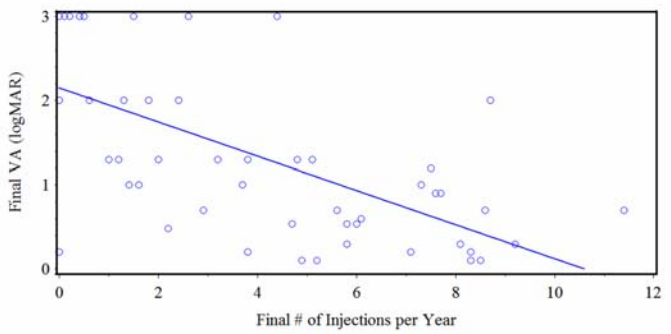

FIGURE 6

Scatter diagram of final logMAR visual acuity of eyes with baseline retinal pigment epithelial tears associated with neovascular age-related macular degeneration plotted against the annual frequency of anti-VEGF injections over the course of all available follow-up. The line of best fit demonstrates that more frequent annual injections correlated with better visual acuity (Spearman correlation coefficient = -0.66; *P*<.0001).

TABLE 4. ANATOMICAL OUTCOME OF RETINAL PIGMENT EPITHELIAL TEAR CORRELATED WITH NUMBER OF ANTI-VEGF INJECTIONS IN EYES WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

Tears with imaging	52
Mean follow-up (months)	29.2 (4 - 96; SD 21.3)
Mean logMAR VA	1.21 (0 - 3; SD 0.97)
Final tear grade	
Grade 1	1 (2%)
Grade 2	19 (37%)
Grade 3	17 (33%)
Grade 4	9 (17%)
Ungradable*	6 (12%)
Final fibrosis	
None	21 (40%)
<50%	16 (31%)
>50%	10 (19%)
End-stage disciform	4 (8%)
Ungradable*	1 (2%)
Progression of tear	4 of 45 (9%)
Per number of injections/year	OR 0.94 (*P=.73)*
Progression of fibrosis	19 of 50 (38%)
Per number of injections/year	OR 0.80 (***P=.04)***
Large end-stage disciform scar	4 of 50 (8%)
Per number of injections/year	OR 0.02 (*P=.19)*
≥1 injection/year	OR 0.10 (***P=.04)***
Final fibrosis >50%†	14 of 50 (28%)
Per number of injections/year	OR 0.76 (***P=.03)***
≥1 injection/year	OR 0.05 (***P=.01)***

OR, odds ratio; SD, standard deviation; VA, visual acuity.
*Ungradable due to hemorrhage or scar.
†Includes large end-stage exudative disciform scar.

CASE DESCRIPTIONS

Case 1

A 75-year-old woman had a vascularized PED due to neovascular AMD. She developed a grade 3 RPE tear shortly after the second intravitreal pegaptanib injection in her right eye, with subsequent decline of VA to 20/400 (Figure 7). The patient deferred further anti-VEGF therapy, and at the 6-year follow-up visit was noted to harbor a large end-stage exudative disciform scar with hand motions (HM) vision. The left eye subsequently transitioned to the neovascular form of AMD with a vascularized PED that evolved to geographic atrophy after many years of continued anti-VEGF therapy, with most recent VA of 20/70 in the left eye.

Case 2

An 82-year-old woman had a vascularized PED complicated by a grade 3 RPE tear after her second intravitreal ranibizumab injection in the right eye that reduced the VA to the 20/100 level (Figure 8). The patient was monitored closely for many years with clinical examination and sequential multimodal imaging, including spectral domain (SD)-OCT evaluation, and intravitreal anti-VEGF therapy was consistently administered when there were any signs of leakage and/or exudation. After 6 years of continued clinical monitoring and over 40 anti-VEGF injections of either bevacizumab or ranibizumab therapy in the right eye, the RPE tear showed minimal progression with concentric extension, and negligible fibrosis had developed, and vision was improved to 20/40 in the affected eye.

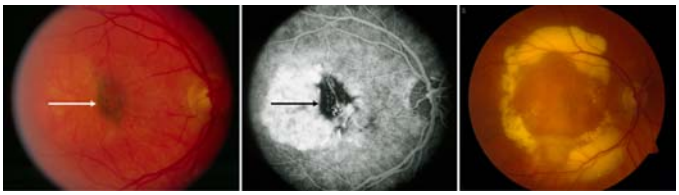

FIGURE 7

Case 1. Progression of a baseline grade 3 retinal pigment epithelial (RPE) tear to a large end-stage, exudative, disciform scar, without anti-VEGF treatment, in the right eye of an elderly white woman with neovascular age-related macular degeneration. Color fundus photograph (left) and fluorescein angiogram (middle) of a baseline grade 3 RPE tear of the temporal fovea of the right eye (arrows) that developed after second intravitreal pegaptanib injection. The patient declined further anti-VEGF therapy, and 6 years later, color fundus photograph (right) demonstrates a large blinding end-stage exudative disciform scar.

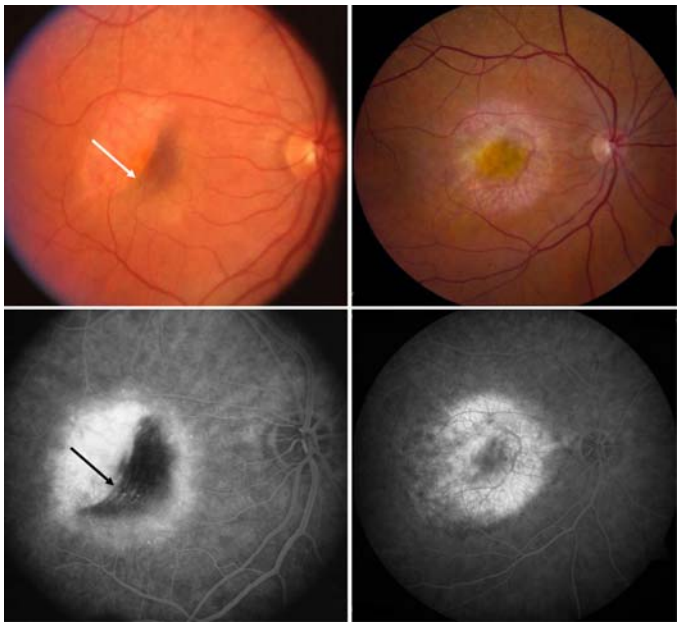

FIGURE 8

Case 2. Color fundus photograph and fluorescein angiogram of a grade 3 retinal pigment epithelial (RPE) tear at baseline with minimal progression at 6-year follow-up in the right eye of an elderly woman with neovascular age-related macular degeneration receiving continued anti-VEGF therapy. Color fundus photograph (upper left) and fluorescein angiogram (lower left) showing baseline grade 3 RPE tear in temporal macula of the right eye (arrows) that developed after second intravitreal ranibizumab injection. After 6 years of continued anti-VEGF therapy, color fundus (upper right) and fluorescein angiogram (lower right) images demonstrate minimal progression of the tear nasally and negligible development of fibrotic scarring. Visual acuity was maintained at the 20/40 level in this eye.

Case 3

An 89-year-old man developed a severe macular hemorrhage associated with a vascularized PED affecting the right eye with VA of CF in the affected eye. After 3 intravitreal ranibizumab injections in the right eye, the heme had resolved, and the vision improved to 20/40; however, a grade 3 RPE tear was noted in the temporal macula (Figure 9).

After 4 years of continued monitoring with clinical examination and multimodal imaging, including SD-OCT analysis, and the administration of over 20 intravitreal anti-VEGF injections, including bevacizumab, ranibizumab, and aflibercept, the RPE tear showed minimal progression with extension nasally, there was no evidence of fibrosis or disciform scar formation, and the VA had stabilized to 20/70. The patient subsequently developed a vascularized PED in the left eye, and after the second intravitreal bevacizumab injection, developed a grade 2 RPE tear at the inferotemporal edge of the PED with stabilization of VA to the 20/40 level. The patient was closely monitored and continued anti-VEGF injections were administered in the left eye per SD-OCT guidance, but he was then lost to follow-up for 3 to 4 months during which time he developed a severe macular hemorrhage in the left eye, with reduction of VA to the CF level. Serial anti-VEGF therapy was then resumed, the hemorrhage eventually resolved, and a second grade 2 RPE tear was now noted in the nasal macula. His VA eventually stabilized at the 20/70 level in the left eye at his most recent evaluation, approximately 2 years after the development of the original RPE tear, with no evidence of significant disciform fibrosis after over 20 anti-VEGF injections in this left eye (Figure 9).

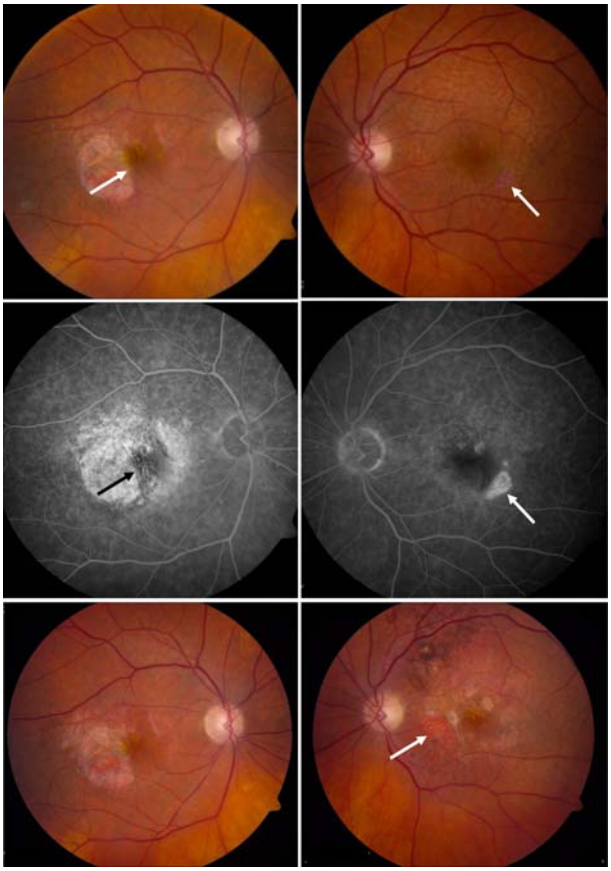

FIGURE 9

Case 3. Color fundus photograph and fluorescein angiogram of a baseline grade 3 retinal pigment epithelial (RPE) tear of the right eye and baseline grade 2 RPE tear of the left eye with minimal progression of the tears several years later after continued anti-VEGF therapy for the treatment of neovascular age-related macular degeneration in each eye. Color fundus photograph and fluorescein angiogram demonstrating grade 3 RPE tear of the right eye (upper left, middle left, respectively) and grade 2 RPE tear of the left eye (upper right, middle right, respectively). Color fundus photographs of the right (lower left) and left (lower right) eyes 4 years after the original tear in the right eye and 2 years after the original tear in the left eye, demonstrating minimal progression of the RPE tears after continued anti-VEGF therapy, although a new RPE tear is present in the nasal macula of the left eye (arrow). Note the complete absence of fibrotic scarring explaining the favorable VA of 20/70 in each eye.

DISCUSSION

Tears of the RPE are a well-known complication of vascularized PED and may occur spontaneously or after various therapies for neovascular AMD. In the era of intravitreal pharmacotherapy, there has been a revival of interest in this subject as there has been a plethora of reports of RPE tears developing after each of the various intravitreal anti-VEGF agents, including pegaptanib,[35,66,67] bevacizumab,[26,36-48] ranibizumab,[49-58] and aflibercept[59,60] therapy.

We have developed an interest in this topic as our group was one of the first to document the association of RPE tears with anti-VEGF therapy when we described 6 cases that developed after intravitreal pegaptanib injection.[35] Each eye demonstrated a vascularized PED due to neovascular AMD, and all 6 tears developed after the first (4 eyes) or second (2 eyes) pegaptanib injection and 3 eyes had severe vision loss to the CF level.[35]

Subsequently there have been numerous reports documenting this same complication in eyes after bevacizumab,[26,36-48] ranibizumab,[49-58] and aflibercept[59,60] therapy. There has been much debate about whether the development of RPE tears after intravitreal injection may be attributed to the natural history of vascularized PED in AMD or may be attributed to the injection technique or the drug. While certain investigators have suggested that the intravitreal injection procedure may cause vitreomacular traction or rapid shifts in intraocular pressure resulting in an RPE tear,[25,46] these external forces do not seem to be logical or likely etiologies, given the disparate circumstances in which RPE tears occur. The forces inherent within a PED are certainly the most likely factor leading to the development of an RPE tear, and the question of whether the pharmacological effect of the anti-VEGF agent is exacerbating this complication is critical to answer.

Natural history studies of PED are replete in the literature, and the rate of development of an RPE tear has been noted to be in the range of 10% to 12%.[15,17,22-26] We have identified an RPE tear rate of approximately 15% in eyes with vascularized PED and AMD in separate retrospective[62] and prospective[58] studies. This tear rate has been confirmed by Chan and colleagues,[26] whereas Doguizi and Ozdek[61] noted an even higher tear rate of 20%, indicating that anti-VEGF therapy may be causative. Moreover, the temporal association of the development of an RPE tear with the administration of the anti-VEGF agent is undeniable. Typically, these tears develop within a short period following the first, second, or third injection.[5,61]

Given the possibility that intravitreal anti-VEGF injection therapy may be causing or accelerating the development of RPE tears, it is important to identify the characteristics of the PED that may increase the risk of this complication. Retrospectively, we studied 60 eyes with vascularized PED and neovascular AMD, of which 10 developed RPE tears after various intravitreal anti-VEGF therapies, including pegaptanib, bevacizumab, and ranibizumab injections.[62] We compared the baseline imaging characteristics of the PEDs in

the eyes that developed tears vs the eyes that did not develop tears and found that the baseline greatest linear diameter of the PED as measured by FA analysis and the baseline height of the PED as measured by OCT evaluation were statistically significant risk factors for the development of an RPE tear.[62] The presence of a hyperfluorescent "ring" sign around the border of the PED with FA analysis was an additional risk factor at baseline and was suggestive of a developing seam, or fault line, in the PED indicating that the RPE tear may be in evolution prior to the administration of the intravitreal anti-VEGF agent (Figure 10).

We confirmed these outcomes in a prospective study of vascularized PEDs treated with ranibizumab therapy.[58] Eyes with PED and neovascular AMD were randomized to standard-dose intravitreal ranibizumab therapy (0.5 mg) vs high-dose (2.0 mg) therapy, and all eyes were followed for 1 year on a monthly basis. Altogether, 5 of 37 eyes were complicated by RPE tears, of which 4 developed in the high-dose arm. Baseline PED diameter of 5 mm and PED height of 600 µm were considered statistically significant risk factors for the development of RPE tears (Figure 11). The baseline height of the PED was highly statistically significant, and while the risk for RPE tears was approximately 15% in the entire cohort, it increased to 30% in eyes with baseline PEDs that were 600 µm in height or greater.[58] Interestingly, this threshold height of 600 µm was also noted to be important in a more recent study in which a specific PED height of 580 µm or greater was found to be a highly statistically significant predictor and risk factor for the development of an RPE tear.[61]

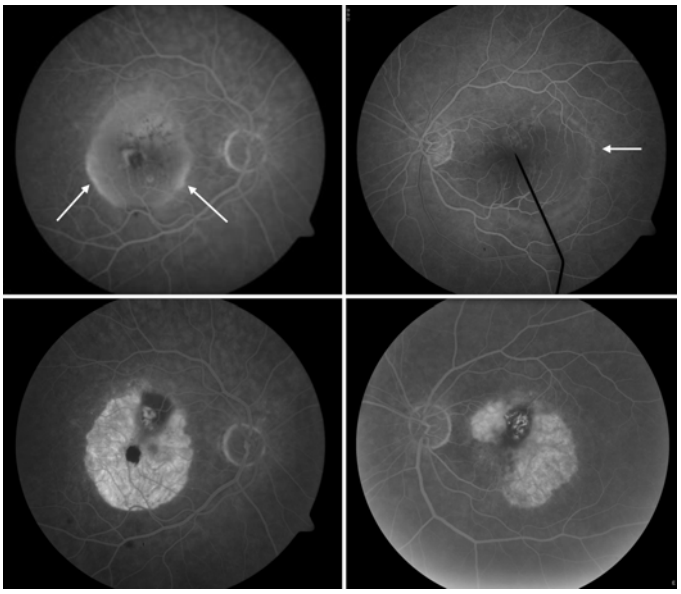

FIGURE 10

Baseline and follow-up fluorescein angiogram of bilateral large vascularized pigment epithelial detachment (PED) with hyperfluorescent "ring" signs at baseline and progression to bilateral grade 4 retinal pigment epithelial (RPE) tears shortly after the first ranibizumab injection for the treatment of neovascular age-related macular degeneration in each eye. Baseline fluorescein angiogram of the right (upper left) and left (upper right) eyes shows a large vascularized PED with a hyperfluorescent "ring" sign (arrows) in each eye. Follow-up fluorescein angiogram of the right (lower left) and left (lower right) eyes after the first ranibizumab injection in each eye demonstrates bilateral large grade 4 RPE tears.

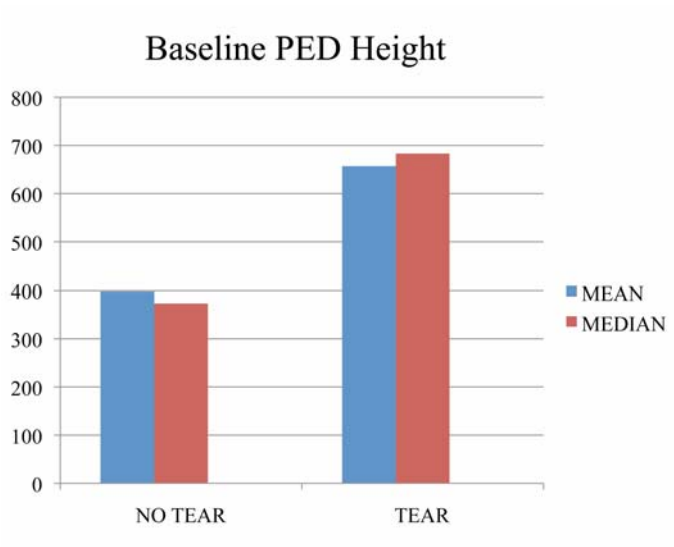

FIGURE 11

Results of a prospective study[58] that demonstrated that optical coherence tomography (OCT)–measured mean and median baseline pigment epithelial detachment (PED) height in the group that did not progress to retinal pigment epithelial (RPE) tear was significantly lower than the baseline PED height in group that did progress to RPE tear. Note that the average baseline PED height is 400 µm in the group without RPE tears but it is over 600 µm in the RPE tear group. This was statistically significant (*P*=.02).

Although not statistically significant, the high-dose ranibizumab arm of the aforementioned prospective study had a 4 times greater risk of RPE tear, suggesting that the drug action may be a causative factor in the development of RPE tears.[58] Anti-VEGF therapy has been associated with retinal tear formation and retinal detachment in proliferative diabetic retinopathy,[68-71] and this may very well be attributable to an angiofibrotic switch.[72-74] Kuiper and colleagues[74] found that the balance of vitreous levels of VEGF vs connective tissue growth factor (CTGF) determined the nature of neovascular fronds. Greater VEGF levels correlated with active retinal neovascular fronds, whereas greater CTGF levels correlated with predominantly fibrotic neovascular membranes. With anti-VEGF therapy in neovascular AMD, therefore, there may be an angiofibrotic switch such that CTGF levels predominate over VEGF levels, leading to a more fibrotic CNV with greater contractile properties. This may explain the association of RPE tears with anti-VEGF therapy in eyes with neovascular AMD.

We attempted to identify this precise mechanism of action for the development of RPE tears in an imaging study utilizing SD-

OCT.[21] Previous investigators determined that radial choroidal folds as identified with FA were a risk factor for the development of RPE tears, indicating an underlying contractile nature of the CNV leading to an RPE tear.[75,76] Using SD-OCT imaging, we identified 8 eyes with vascularized PED that demonstrated signs of contraction, such as folding and retraction of the RPE monolayer due to the underlying type 1 CNV prior to initiation of anti-VEGF therapy. Other signs of CNV contraction, such as a peaked PED and buckling of the underlying Bruch's membrane causing a hyporeflective cleft, were also identified with SD-OCT analysis at baseline. Each eye progressed to an RPE tear shortly after intravitreal bevacizumab or ranibizumab therapy (6 of 8 eyes after the first injection) with evidence of even greater contraction demonstrated with SD-OCT evaluation of the PED and type 1 CNV that was adherent to the internal surface of the RPE monolayer, indicating that anti-VEGF therapy may exacerbate existing contractile properties of the type 1 CNV leading to an RPE tear (Figure 12).[21] These observations are supported by recent SD-OCT imaging studies demonstrating CNV complexes adherent to the inner leaflet of the PED[77-79] and histopathological analyses of excised vascularized RPE tears that similarly confirmed adherent CNV to the underlying surface of the torn RPE.[80,81]

We created a model to explain the mechanism of RPE tear development after intravitreal anti-VEGF injection.[21] We believe a PED at risk, ie, a vascularized PED greater than 600 µm in height, is highly susceptible to developing an RPE tear due to forces of increased hydrostatic pressure that build internally within the PED and direct outward. The presence of a type 1 CNV exerting contractile effect on the undersurface of the RPE monolayer of the PED is an additional risk factor that sets the stage for the evolution to an RPE tear. In the setting of intravitreal anti-VEGF therapy, there is a cumulative increase in the contractile properties of the type 1 CNV, leading to further tangential tractional force on the RPE monolayer. This, coupled with the increased hydrostatic pressure inherent in a PED at risk, may result in a sudden rupture or rip of the RPE at its weakest point, typically very near the base of the PED, leading to an RPE tear (Figure 13).[82,83] Various investigators have employed physical principles to explain the location of RPE tears very near the base of the PED, and they note that the cumulative forces leading to a rip are greatest near the base and least at the center of the PED.[82,83]

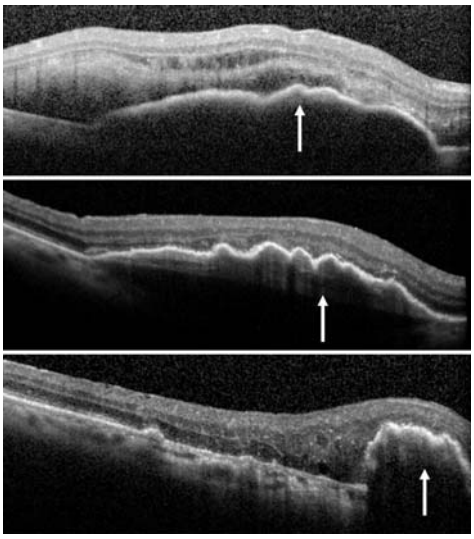

FIGURE 12

Spectral-domain optical coherence tomography (SD-OCT) panel showing progression of type 1 choroidal neovascular membrane (CNV) contraction associated with vascularized pigment epithelial detachment (PED) after intravitreal anti-VEGF therapy, leading to a retinal pigment epithelial (RPE) tear. Top, Baseline SD-OCT of a large vascularized PED with subretinal and intraretinal fluid demonstrating irregular folds (arrow) due to contraction of type 1 CNV along the internal RPE monolayer. Middle, Subsequent SD-OCT of the vascularized PED after first intravitreal bevacizumab injection showing organization and contraction of type 1 CNV along the internal margin of the RPE monolayer causing increasing folds and irregularity of the PED (arrow). Bottom, Follow-up SD-OCT after second intravitreal bevacizumab injection, demonstrating a large RPE tear adjacent to a retracted PED (arrow). Note the irregular folds of the PED associated with the type 1 CNV.

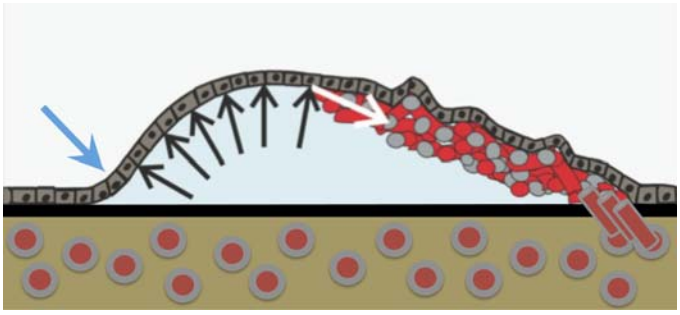

FIGURE 13

Cartoon model depicting the hydrostatic and contractile forces necessary to create a retinal pigment epithelial (RPE) tear within a vascularized pigment epithelial detachment (PED) after anti-VEGF therapy for neovascular age-related macular degeneration. Note that the type 1 choroidal neovascular membrane (CNV) along the internal surface of the RPE monolayer creates significant tangential traction (white arrow), while the large fluid-filled PED has a substantial hydrostatic force directing outward (black arrows). With further contraction of the type 1 CNV after anti-VEGF injection, a rupture occurs at the weakest point of the PED located near its base (blue arrow). (Illustration courtesy of Richard Spaide, MD. Adapted from Nagiel et al.[21])

With chronicity, PEDs with type 1 CNV may develop a unique multilayered appearance that includes a characteristic fusiform-shaped lamellar scar notable in the sub-PED compartment.[77,79,84-86] Rahimy and colleagues[86] described this SD-OCT presentation in 38 eyes that had received an average of 28 anti-VEGF injections administered over a mean 37 months and noted excellent median VA of 20/50. It is hypothesized that this multilayered fibrovascular scar may develop as a result of the effect of unopposed CTGF from long-term anti-VEGF therapy leading to an angiofibrotic switch.[86] Contractile properties of this banded, fusiform-shaped scar are present, including a hyporeflective cleft, indicating buckling of the underlying Bruch's structure. The presence of a complex fibrovascular scar occupying the sub-PED space may reduce the hydrostatic forces within the chronic multilayered PED, potentially stabilizing the internal compartment of the PED, and thereby decreasing the risk of a catastrophic high-grade tear.[86] This is supported by the findings of Doguizi and Ozdek,[61] who noted that the mean duration of PED complicated by an RPE tear was 4.5 months and that acute vascularized PEDs of 4.5 months duration or less was a highly statistically significant predictor and risk factor for the progression to RPE tear.

The visual and anatomical prognosis of an RPE tear will be determined by its size and location. We previously developed a grading system of RPE tears to shed light on the visual and anatomical outcome of RPE tears.[22] In that study, we obtained linear measurements of the RPE tear in the vector direction of the tear in 21 eyes of 20 patients. Tears were divided into 4 grades: grade 1 (<200 μm), grade 2 (200 μm to 1 DD), grade 3 (>1 DD but not crossing fixation) and grade 4 (>1 DD but crossing fixation) (Figure 3). Lower-grade tears had a better visual and anatomical prognosis with or without continued anti-VEGF therapy, whereas grade 4 tears had an adverse anatomical and visual outcome with or without continued anti-VEGF therapy. A major limitation of this study, however, was the relative short length of follow-up (average of 1.4 years) and the small number of eyes studied with RPE tears.[22]

Interestingly, in this previous study,[22] larger grade 4 tears were not more significantly associated with hemorrhage than the lower-grade tears. Whereas there may be a greater propensity to induce contraction leading to an RPE tear with anti-VEGF therapy, there is a lower propensity for bleeding that may be related to the additional antipermeable properties of anti-VEGF agents.[87-90] This is in direct contrast to another study that we performed in which we found that of 20 eyes with severe macular hemorrhage (average, 3.3 DD) and no prior anti-VEGF therapy, 7 (35%) eyes harbored or developed underlying RPE tears, indicating that hemorrhage may be more likely to accompany a spontaneous RPE tear that develops without the administration of an anti-VEGF agent.[91] On average, hemorrhage resolved after 4 anti-VEGF injections in this study with an average increase of VA from 20/710 to 20/100 despite the high proportion (35%) of eyes with underlying RPE tears.[91] Despite these studies, the traditional consensus has been that there is little to offer the patient once an RPE tear develops, given that the visual and anatomical prognosis is considered to be very poor and given that no therapies (new or old) have been proven to be definitively beneficial.[17,23,40,65,92] Our data contradicts this principle and indicates that continued clinical monitoring of newly developed RPE tears and sustained antiVEGF therapy according to anatomical indication may reduce adverse outcomes and improve prognosis.

Our study is the largest collection of RPE tears to be published, to our knowledge, with the longest follow-up. Gutfleisch and colleagues[65] studied 37 patients with RPE tears followed for an average of 88 weeks (SD, 51 weeks) and found that 53.2% were legally blind at 12 months and that an adverse visual outcome was most attributable to severe fibrosis and the development of a disciform scar. However, the investigators failed to mention whether these eyes had received continued anti-VEGF therapy. Asao and associates[63] studied 10 eyes with RPE tears followed for 27 months (range, 13 to 44 months) and noted an average decrease in VA but anatomical stability of at least one-half of the RPE tears at 12 months after receiving a mean of 3.3 anti-VEGF injections. Doguizi and Ozdek[61] analyzed 28 eyes with RPE tears followed for an average of 21 months (SD, 14 months) and found that mean VA minimally decreased during this period in which patients received an average of 4 anti-VEGF injections. From these results, the investigators recommended continued anti-VEGF therapy for eyes with RPE tears. Coco and associates[64] concurred with these recommendations on the basis of their comparative study of RPE tears in which one group (n=9) of tears was left untreated and the second group (n=12) was treated with an average of 5.8 intravitreal anti-VEGF injections over an average follow-up period of 25 months (range, 6 to 48 months). In this study, average VA improved in the latter treated group and it decreased in the former untreated group, indicating that continued anti-VEGF therapy may be of benefit. However, this study failed to attribute this anatomical benefit to the prevention of an atrophic or fibrotic disciform scar, which occurred equally in both groups.

In our study, we analyzed 56 eyes with RPE tears that were followed for an average length of 42 months and as long as 96 months (8 years). As with previous studies, almost all eyes (88%) in our study harbored a vascularized PED at baseline indicating that in addition to the contractile nature of the CNV which is exacerbated by anti-VEGF therapy, hydrostatic mechanisms inherent in a PED may also be important in the development of RPE tears, especially catastrophic large, severe grade 4 RPE tears. In contrast, purely classic type 2 CNV was only rarely associated with an RPE tear (2 of 56 eyes, 4%), both of which were small grade 2 RPE tears.

Mean logMAR VA at baseline for all tears was 0.88 (Snellen VA=20/150), was relatively stable at 6 months and 1 year, and showed slight decline after 2 years and longer, with a mean of 5 injections in the first year and 14 at final follow-up (Table 1). This would indicate that although we are unlikely to see improvements of VA with continued anti-VEGF therapy, we may expect to stabilize VA in the long term even with more adverse severe grade 4 RPE tears.

We aimed to compare the long-term visual outcomes of various grades of severity of RPE tears in eyes that received continued anti-VEGF therapy. Grade 2 and grade 3 RPE tears demonstrated better visual outcomes than the more adverse grade 4 tears at the 6- and 12-month intervals. However, at the 2- and 3-year intervals there appeared to be little difference in the VA outcomes between the different grades of tears, although the overall mean VA demonstrated long-term stability over several years. This lack of difference that developed with longer intervals of follow-up may be explained by long-term decay in the vision of the more favorable grade 2 and 3 RPE tears and has been noted in various other prospective trials studying neovascular AMD in general.[93-97] In these studies, the long-term decay of VA has been attributable to various causes, including fibrosis, atrophy, and loss of pharmacologic effect, or

tachyphylaxis, of the anti-VEGF drug.

We performed numerous statistical analyses to determine the effect of intravitreal injections on the visual and anatomical outcomes and found a consistent trend across all of these correlations indicating that more injections were associated with a more favorable VA outcome. While it is possible that a selection bias may be inherent in this analysis because eyes that are seeing better are more likely to receive injections, we believe that continued anti-VEGF therapy may be stabilizing vision in the long term as a result of the more optimal anatomical outcomes that we identified in this study many years after pharmacotherapy was initiated.

In this current study, there appeared to be a long-term anatomical benefit across all grades of severity of RPE tears. Continued anti-VEGF therapy for all grades of RPE tears reduced the development of fibrosis and seemed to decrease the risk of large end-stage exudative disciform scars. Eyes with RPE tears that received continued anti-VEGF therapy typically had minimal or no fibrotic scar development and often retained an anatomical morphology very similar to the baseline presentation with minimal progression of the RPE tear. Eyes with RPE tears in which anti-VEGF therapy was discontinued, however, were at risk of developing large blinding end-stage exudative disciform scars associated with CF or HM vision. This is especially important, as eyes with RPE tears showed especially high rates of bilateral neovascular AMD (61%) in our study. This has been confirmed by previous studies in which a high risk of bilateral RPE tear was noted, 35% at 3 years and 53% at 10 years in two separate studies,[92,98] although the rate of bilateral RPE tears in our study was much lower (14%). This stresses the need to optimize the anatomical outcome in the first eye with an RPE tear, critical for the patient's overall visual performance and quality of life.

Therefore, once an RPE tear develops, the retinologist should resist any temptation to discharge the patient from his or her care and should instead continue to monitor this eye closely for any signs of leakage and/or exudation indicating an active neovascular membrane as guided by clinical examination and multimodal imaging, especially SD-OCT evaluation. In the presence of fluid or heme associated with the tear, anti-VEGF therapy should be initiated and continued until resolution of these exudative findings. This will promote stability of the type 1 CNV and RPE tear, limit the development of fibrosis, and prevent the development of a large blinding end-stage exudative disciform scar. While the VA may not be optimal, the more favorable anatomical outcome will enhance the patient's eccentric and peripheral vision and may enhance the patient's quality of life, especially in the presence of neovascular AMD with or without an RPE tear in the fellow eye. Moreover, stabilization of the visual outcome will be more likely with continued anti-VEGF therapy, especially with lower-grade tears.

Recently, various investigators have recommended more invasive surgical therapies to manage RPE tears. Polito and associates[99] performed complex surgical procedures, including full macular translocation with 360 degrees retinotomy, in 6 patients with RPE tear and noted on average several lines of improvement with long follow-up intervals. However, the investigators did not note the grade of the RPE tear and, in fact, illustrated a grade 3 RPE tear in the published paper in which the tear did not cross fixation, raising questions regarding the necessity of such a complicated surgery. Maaijwee and coworkers[100] performed RPE-choroid graft translocation in 6 patients with RPE tear and found an average improvement of VA from 20/160 to 20/80 with a 6-month to 2-year follow-up. While the results in these studies seem encouraging, the therapies are extremely invasive, highly sophisticated, and fraught with potential serious complications, including retinal detachment, and have yet to be confirmed with larger controlled prospective trials. Our recommendation to monitor RPE tears for signs of leakage using multimodal imaging modalities and to administer continued anti-VEGF therapy to stabilize vision, limit fibrosis, and prevent the development of severe end-stage exudative disciform scars may be a safer, more practical option in the treatment of this challenging complication.

Limitations of this present study include the retrospective design and variable follow-up period, although a very large majority of eyes had at least 1-year follow-up, which is unprecedented. Statistical analysis was also limited by the relatively small number of eyes in each comparative group, but the overall number of RPE tears (56) is the largest study on this subject to date. The mean follow-up period of 42 months is very long and unique and includes all those patients with a record of VA and clinical examination at the final follow-up interval. However, the mean follow-up drops to 29 months, still the longest of any RPE tear study to our knowledge, if multimodal imaging is a required element for final follow-up.

While this study supports continued clinical and OCT monitoring of RPE tears for signs of exudation and leakage warranting continued anti-VEGF therapy to stabilize long-term visual and anatomical outcomes, development of strategies to prevent the occurrence of RPE tears would more effectively optimize the visual and anatomical prognosis of neovascular AMD and would more successfully prevent blindness from this devastating disease. Inhibiting molecular targets, such as CTGF, which promote fibrosis and potentially promote greater contractile activity of the neovascular membrane leading to an RPE tear, may offer hope in preventing this potentially devastating complication, which is a leading factor limiting the success of therapy for vascularized PED.

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