PIGMENT EPITHELIAL TEARS ASSOCIATED WITH ANTI-VEGF THERAPY

Incidence, Long-term Visual Outcome, and Relationship with Pigment Epithelial Detachment in Age-related Macular Degeneration

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Purpose: To evaluate the prevalence of retinal pigment epithelium (RPE) tears associated with anti-VEGF therapy and its relation with retinal pigment epithelial detachment (PED).

Methods: A total of 226 patients with exudative age-related macular degeneration treated with intravitreal anti-VEGF were included retrospectively in the study. The presence of RPE tears; the effect of the presence, height, and duration of PED on the rate of RPE tears; and change in visual acuity during follow-up were recorded.

Results: Among 226 study patients, 28 (12.3%) had RPE tears. The RPE tear rate was significantly higher in patients with vascularized PED (vPED) than in those without PED (19.7% vs. 2.1%; $P < 0.001$). The change in visual acuity after the formation of RPE tear was not statistically significant (on logMAR scale: 0.92 ± 0.49 initially, 0.89 ± 0.41 after the RPE tear, 0.96 ± 0.45 at the last follow-up; $P = 0.613$). Pigment epithelial detachment height >580 μm (odds ratio = 69.4; 95% confidence interval = 16.7–288.1) and PED duration ≤ 4.5 months (odds ratio = 166.7; 95% confidence interval = 15.2–1000) were found to be significant risk factors for RPE tear formation.

Conclusion: The RPE tears are not infrequent among eyes treated with intravitreal anti-VEGFs. The presence, increased height, and shorter duration of vPED are potential risk factors for RPE tears associated with anti-VEGF therapy.

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Tears in the retinal pigment epithelium (RPE) is a recognized complication of neovascular age-related macular degeneration and occur most commonly in patients with retinal pigment epithelial detachment (PED).[1] Several recent publications have reported RPE tears associated with the use of intravitreal vascular endothelial growth factor (VEGF) antagonists, such as bevacizumab[2–6] and ranibizumab.[7–12]

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Few comparative analyses have attempted to identify factors indicative of a high risk of RPE tears before anti-VEGF therapy. Chan et al[3] found that the mean PED size before bevacizumab as determined by fluorescein angiography was larger for eyes with RPE tears than those without tears, and Chiang et al[13] determined that a large PED basal diameter and vertical height are correlated with an increased risk of developing an RPE tear after anti-VEGF therapy.

This retrospective study examined the prevalence of RPE tears associated with anti-VEGF therapy (intravitreal ranibizumab and bevacizumab) in eyes with and without PED; evaluated the long-term visual results; and whether presence, duration, and height of PED provide an estimate of the risk of RPE tears.

Materials and Methods

Study Design and Patients

The reports of the patients with a diagnosis of neovascular age-related macular degeneration who were at least 50 years old and treated with intravitreal anti-VEGFs (ranibizumab or bevacizumab) between December 2007 and January 2012 at Gazi University School of Medicine, Ophthalmology Department, Retina Clinic, were reviewed retrospectively for the occurrence of RPE tears. The study was approved by the Local Ethics Committee of Gazi University (LUT 07/47-34). Patients with visually significant cataract or corneal disease, advanced glaucomatous damage, other retinal vascular diseases, and a previous vitrectomy or trabeculectomy surgery in the eye with AMD were excluded from the study. The patients who missed the visits for more than 3 months were also excluded from the study. In general, patients were treated with anti-VEGF injections for 3 months followed by retreatment as determined by the clinical examination, optical coherence tomography (OCT), and/or fluorescein angiography. Baseline OCT (before treatment and at every visit) (Stratus OCT, Carl Zeiss Meditec, Dublin, CA), and fluorescein angiography (before treatment and when needed in subsequent indeterminate cases) were also performed. Choroidal neovascularization lesions and associated components were classified according to the recommendations of the Macular Photocoagulation Study Group.[14]

The patients' hospital files were reviewed for the demographic data of the patient, best-corrected visual acuity (BCVA), lesion characteristics including type of the neovascular age-related macular degeneration, presence and duration of vPED, formation of RPE tears, dimensions of the PED including the height in OCT before and after anti-VEGF treatment, and the number of anti-VEGF injections. Best-corrected visual acuity was determined with ETDRS chart and was converted to logMAR for statistical analysis. Change in BCVA, OCT measurements, and the period between the last injection and RPE tear formation were also noted in those cases with RPE tear formation. The rate of RPE tears in all eyes and in eyes with vPED were determined. The height of vPED before and after anti-VEGF injection; the correlation between the presence, height, and duration of PED and development of RPE tears; the anatomical and functional results after RPE tear formation and the need for anti-VEGF injections during the post-RPE tear follow-up were analyzed. Also, RPE tears were graded from one to four based on the greatest length in the vector direction of the tear and involvement of the fovea (using fluorescein angiography analysis, a measurement of greatest linear diameter [millimeter] was obtained and was graded from one to four).[15] Grade 1 tears were defined as 200 mm. Grade 2 tears were between 200 mm and 1-disk diameter. Grade 3 tears were 1-disk diameter. Grade 4 tears were defined as Grade 3 tears that involved the center of the fovea.[15] The grade of RPE tear and relation with visual outcomes was determined. All patients were imaged with the same Stratus OCT machine (Carl Zeiss Meditec), and all vPED measurements were performed by the same investigator (S. Doguizi). We used the Proportional Process Report 4.0.1 software (Carl Zeiss Meditec) for Stratus OCT.[16] Vascularized PED height on OCT was recorded using the retinal thickness analysis protocol and built-in manual caliper measurement tool, from the same retinal location for every visit.[16] vPED duration was defined as the duration between the first appearance of vPED and formation of RPE tear. Patients with PED at the first visit were excluded from the analysis because the exact duration of PED could not be determined in those cases. We also excluded the patients whose follow-up interval time exceeded more than 3 months to determine the vPED duration quite accurately.

Statistical Analysis

Repeated-measure analysis of variance was used to analyze the changes in visual acuity in patients with RPE tears. The predictive value of PED height and duration for the development of RPE tears was evaluated using receiver operating characteristic (ROC) analysis, and the area under the curve (AUC) was calculated. The increase in risk among categorical variables and the odds ratio with 95% confidence interval (CI) was calculated when applicable.

Statistical analyses were performed using Excel for Windows (version 2003, Microsoft, Redmond, WA) and the Statistical Package for the Social Sciences for Windows (version 15.0, SPSS, Chicago, IL). The statistical level of significance was set to $P < 0.017$ when the Bonferroni correction was used, and $P < 0.05$ otherwise.

Results

The study included 226 eyes of 197 patients who met the inclusion criteria. The mean age of the patients was 72.1 ± 7.5, with 97 (49.2%) being male and 100 (50.8%) being female. There was preponderantly classic choroidal neovascularization in 44 (19.5%) eyes, with occult choroidal neovascularization with minimal or no classic component in 182 eyes (80.5%). An RPE

tear occurred during the course of anti-VEGF treatment in 28 eyes (12.3%). Most eyes with RPE tears (26 eyes, 92.8%) had associated vPED. All RPE tears developed in patients with preexisting vPEDs except for two cases in which an RPE tear occurred after treatment of a classic choroidal neovascularization. The total number of eyes with associated vPED was 132, and the rate of RPE tear in eyes with associated vPED was 19.7% (26/132). The mean follow-up time for all patients was 28.23 ± 11.23 months, and the mean follow-up interval duration was 1.9 ± 0.8 months.

RPE tears occurred after ranibizumab in 14 of 137 eyes (10.2%) and after bevacizumab injection in 14 of 89 eyes (15.7%) (P = 0.32). The RPE tear was detected within a month after an anti-VEGF injection in all the patients; most of which occurred after the first anti-VEGF injection (26 eyes, 92.8%).

Long-term VA in Patients With RPE Tear

The mean BCVA of the eyes with RPE tears (on logMAR scale) was 0.92 ± 0.49 at the beginning, 0.89 ± 0.41 after the formation of RPE tear, and 0.96 ± 0.45 at the last follow-up visit. The difference in BCVA after the formation of RPE tear was not significant during mean follow-up period of 20.6 ± 14.4 months (F = 0.261; P = 0.613; Figure 1). The mean number of anti-VEGF injections was 4.07 ± 2.9 during this follow-up period.

Fourteen percent (n = 4) of eyes had Grade 1 tears (diameter smaller than 200 mm), 32.1% (n = 9) had Grade 2 tears (diameter between 200 mm and 1-disk diameter), 32.1% (n = 9) had Grade 3 tears (diameter greater than 1-disk diameter), and 21.4% (n = 6) had Grade 4 tears (Grade 3 tears that involved the foveal center). Final visual acuity was worse for the larger RPE tears (Grades 3 and 4) when compared with the smaller tears (Grades 1 and 2) (1.1 logMAR vs. 0.82 logMAR P = 0.098). Eyes with Grade 4 tears had the worst final BCVA (Grade 4 tears: 1.24 logMAR; Grade 3 tears: 0.96 logMAR; Grade 2 tears: 0.90 logMAR; Grade 1 tears: 0.74 logMAR).

The Relationship Between RPE Tears and PED

The RPE tears developed in 26 of 132 patients (19.7%) with vPED and 2 of 94 patients (2.1%) without PED (Table 1). The RPE tear rate was significantly higher in patients with vPED than in those without PED (χ^2 = 15.613; $P < 0.001$). On the assumption that other predictors (e.g., age, gender) were kept constant, the risk of RPE tears was higher in patients with vPED than those without PED (odds ratio = 11.3; 95% CI = 2.6–48.8).

The median height of vPED was 850 μm (interquartile range = 248; range = 230–1300) in eyes with an RPE tear before RPE tear formation and 320 μm (interquartile range = 196; range = 0–850) in eyes without an RPE tear (Z = 5.635; $P < 0.001$). The difference was statistically significant, which means that vPED height is a significant predictor of RPE tears.

To determine the cutoff vPED height for developing an RPE tear, an ROC curve was drawn, which has shown that vPED height effectively predicted RPE tear formation. On the assumption that other predictor variables were kept constant, PED height predicts RPE tear risk with 85% sensitivity and 92% specificity. The cutoff PED height for developing an RPE tear was 580 μm, and the predictivity of the ROC model was

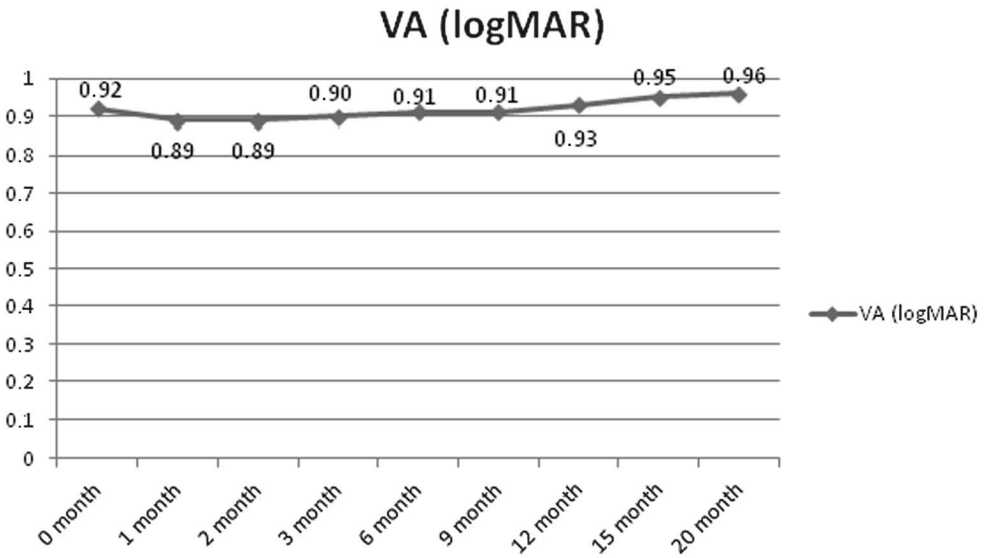

Fig. 1. Mean visual acuity score in eyes with retinal pigment epithelium tears. Retinal pigment epithelium tear occurred after the first injection at month 1 in 26 of 28 eyes.

Table 1. Retinal Pigment Epithelium Tear Rates According to the Presence, Height, and Duration of PED

		RPE tear (+) (n) (%)	RPE tear (–) (n) (%)	*P**
PED presence	PED (+)	26 (19.7)	106 (80.3)	<0.001
	PED (–)	2 (2.1)	92 (97.9)	
PED height	≤580 μm	3 (3.0)	98 (97.0)	<0.001
	>580 μm	17 (68.0)	8 (32.0)	
PED duration	≤4.5 months	10 (90.9)	1 (9.1)	<0.001
	>4.5 months	3 (5.9)	48 (94.1)	

*Fisher's exact test.
PED, pigment epithelial detachment; RPE, retinal pigment epithelium.

significant (AUC = 0.897; 95% CI = 0.803–0.992; $P < 0.001$; Figure 2).

Using the cutoff vPED height, two groups (PED height >580 vs. ≤580 μm) can be described, between which the RPE tear rates differed significantly ($\chi^2 = 63.463$; $P < 0.001$; Table 1). On the assumption that other predictors were kept constant, vPED height >580 μm is a significant risk factor for the formation of RPE tear (odds ratio = 69.4; 95% CI = 16.7–288.1).

In addition to vPED height, the effect of vPED duration on formation of RPE tears was also evaluated in this study. A certain vPED duration could be established in 72 of the 132 eyes with PED (72/132), and these eyes were included for analysis of the duration. Of the 72 eyes with a known duration of vPED, 28 developed vPED in the fellow eye; 46 developed vPED in the same eye; and 18 (25%) of eyes with known PED duration developed RPE tear during anti-VEGF treatment.

Sixty of 132 eyes were excluded from the analysis because they had already vPED in the first visit because a certain vPED duration could not be determined for these eyes. The rate of RPE tear during the follow-up in eyes with unknown vPED duration (or preexcluded vPED) was 13.3% (8/60) eyes, which was significantly less than the rate of RPE tear 25% (18/72) in eyes with a known vPED duration ($P = 0.04$). The median vPED duration was 4.5 (interquartile range = 3; range = 2–12) months in eyes with an anti-VEGF–related RPE tear and 8 (interquartile range = 3; range = 4–24) months in patients without an RPE tear. The vPED duration was significantly lower in patients with an RPE tear than that those without an RPE tear ($Z = 3.951$; $P < 0.001$).

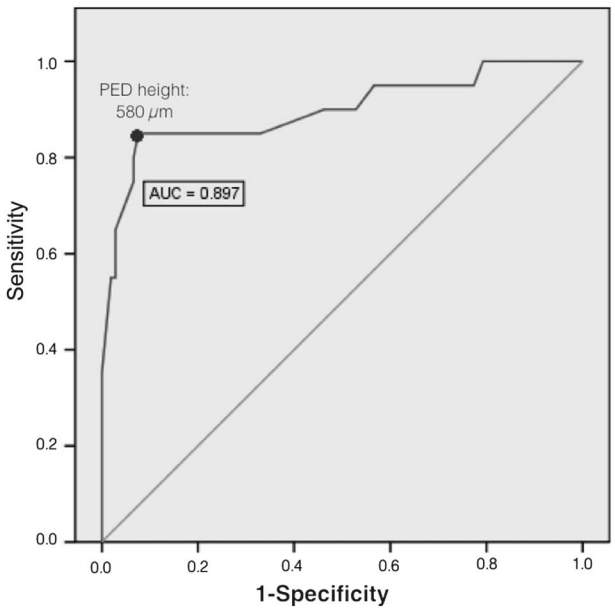

Fig. 2. Receiver operating characteristic curve for the predictive value of PED height for tears (AUC = 0.897; $P < 0.001$).

To determine the cutoff vPED duration for developing an RPE tear, the ROC curve was drawn, which has shown that vPED duration predicted the formation of RPE tears. On the assumption that other predictors were kept constant, vPED duration predicts RPE tear risk with 77% sensitivity and 98% specificity. The cutoff vPED duration for developing RPE tear was 4.5 months, and the predictivity of the ROC model was significant (AUC = 0.855; 95% CI = 0.703–1.000; $P < 0.001$; Figure 3).

Using the cutoff vPED duration, two groups (PED duration >4.5 vs. ≤4.5 months) can be described, between which the RPE tear rates differed significantly ($P < 0.001$; Table 1). On the assumption that other predictors were kept constant, vPED duration ≤4.5 months is a significant risk factor for RPE tears (odds ratio = 166.7; 95% CI = 15.2–1000).

Discussion

RPE tears can complicate the natural history of vPEDs associated with neovascular AMD (range, 10–12%).[1,17,18] Recent evidence indicates that anti-VEGF therapy might increase or accelerate the rate of this complication. Retinal pigment epithelium tears have been reported with all kinds of anti-VEGF treatments: intravitreal bevacizumab, pegaptanib, and ranibizumab.[8,12,19,20–25] Patients with occult choroidal neovascularization and a vPED are assumed to have a higher

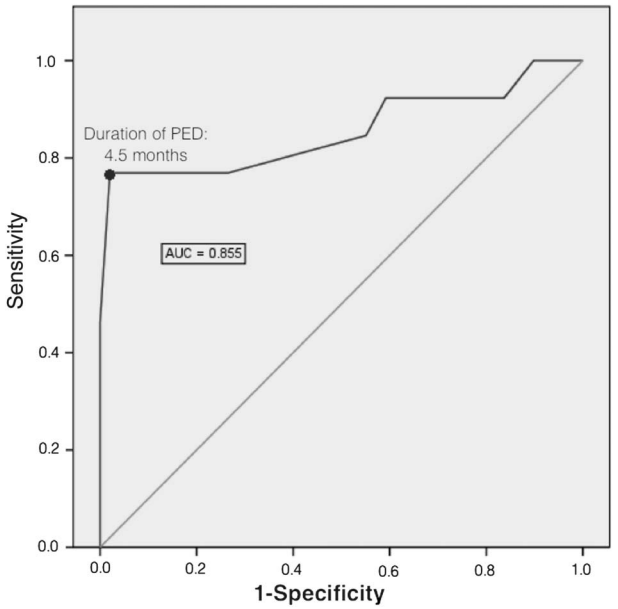

Fig. 3. Receiver operating characteristic curve for the predictive value of PED duration for tears (AUC = 0.855; $P < 0.001$).

risk of RPE tears. Retinal pigment epithelium tears develop during anti-VEGF therapy for lesions associated with PED in exudative AMD in 12% to 27% of treated eyes.[3,12,13,20] In a retrospective case series of 1280 eyes treated with intravitreal bevacizumab, which included a group of 125 eyes with vascularized PEDs, the rate of development of RPE tears was reported to be 16.8%.[16] In a prospective case series of 420 patients with neovascular AMD who underwent at least one bevacizumab injection over a 1-year period, 74 patients were identified with pretreatment serous retinal PED, of which 13 (18%) developed an RPE tear after treatment.[26]

An important predictor for RPE tear development may be the dimensions of the vPEDs. Chiang et al[13] reported that there were highly significant differences in the median PED size on fluorescein angiography (greatest linear diameter 3.2 vs. 1.8 mm, respectively; $P \leq 0.001$) and the median maximum PED height on OCT (394 vs. 149 μm, respectively; $P \leq 0.001$) between the tear and non-tear groups.

In our study, the rate of RPE tears in eyes with vPED was 19.7% (26/132), and we identified OCT analysis of maximum height as a predictor of RPE tear after anti-VEGF therapy (Z = 5.635; $P < 0.001$). We also determined that 580 μm was the cutoff point of PED height for the risk of an RPE tear using an ROC curve. Similarly Sarraf et al[27] described a height of 550 μm high-risk factors for the subsequent development of an RPE tear, and Leitritz et al[28] described increasing probability of RPE tears particularly beyond the height of 400 μm. These studies demonstrate the importance of OCT analysis in the management of patients with vPED in the setting of AMD.

The causes of RPE tears are still uncertain. Histopathological studies have shown that new vessels insinuate themselves into Bruch's membrane and might separate the RPE and basement membrane from the subjacent outer portion of the membrane.[29] Gass[30] described the tangential contraction of subretinal neovascularization as the leading cause of RPE tears. As another etiology, Chuang and Bird[31] postulated that high choroidal hydrostatic pressure and reduced permeability of Bruch's membrane induce tear formation. An abrupt increase in the amount of sub-RPE fluid could stretch the RPE, leading to a "blow-out" tear.[32] Alternatively, a thinned detached RPE over a chronic PED might also cause RPE tear formation.[18] Spaide et al[33] also postulated that contracture of the proliferation under the surface of a PED could cause a tear in the overlying RPE monolayer after anti-VEGF therapy. This contracture would also cause the RPE to retract and scroll.

As we learn from the literature, RPE tears mostly develop within 1 to 2 months of the beginning of anti-VEGF therapy.[13,34] In this study, we also investigated a possible relationship between the duration of PED and RPE tear formation. To the best of our knowledge, this is the first study demonstrating an inverse relationship between the duration of PED and RPE tear formation (Z = 3.951; $P < 0.001$) in the literature. The PED had been present for a much shorter period in the eyes that developed an RPE tear. A short duration of PED means that the neovascular process is fresh, with immature vessels. Because the immature vessels are more susceptible to anti-VEGFs, the response to anti-VEGF therapy may be more dramatic and may include fibrovascular contraction of the choroidal neovascularization and interruption of the tight junctions maintained by VEGF.[35] This might induce RPE tear formation.

In some previously published studies, the visual prognosis of RPE tears was not so guarded, which concurs with our findings.[14,16,26,27,36,37] We found that VA can be maintained, with no deterioration in the VA with continued anti-VEGF therapy after the formation of RPE tear within a mean follow-up period of 20.6 ± 14.4 months (F = 0.261; $P = 0.613$). The mean number of anti-VEGF injections was 4.07 ± 2.9 during this follow-up period. Similar to our results, Coco et al[36] reported that RPE tears treated with antiangiogenic drugs experienced a functional benefit. Conversely, another study reported that 30 patients with RPE tears showed progressive visual loss during 22 months follow-up.[37] In another study Sarraf et al[15] reported that the grading of RPE tears according to greatest

linear diameter may have prognostic value in predicting visual acuity with or without continued anti-VEGF therapy. Lower grade tears have better visual acuity and response to anti-VEGF therapy. Similarly, in our study, final visual acuity was worse for the larger RPE tears (Grades 3 and 4) when compared with the smaller tears (Grades 1 and 2) (1.1 logMAR vs. 0.82 logMAR $P = 0.098$), and the worst final visual acuity was determined in eyes had Grade 4 tears with continued anti-VEGF therapy. This difference was not statistically significant because of a small sample size.

The limitations of this study include its retrospective nature; and because of the low rate of occurrence of RPE tear across the study analyzed, statistical comparisons of VA outcomes between different grades and the difference the RPE tear rates of patients who received ranibizumab and bevacizumab are limited and may not provide meaningful inference.

In conclusion, vPED is more likely to lead to development of an acute RPE tear. In our study, the 19.7% incidence of RPE tear in eyes with vPED undergoing anti-VEGF therapy was similar to reported data. Patients seem to maintain good VA in most cases, especially with low grades and continued anti-VEGF treatment. Pigment epithelial detachment height and the shorter duration of PED are potential risk factors for developing RPE tear.

Key words: retinal pigment epithelium tears, vascular endothelial growth factor, ranibizumab, bevacizumab, retinal pigment epithelial detachment, macular degeneration.

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