OPTICAL COHERENCE TOMOGRAPHY–MEASURED PIGMENT EPITHELIAL DETACHMENT HEIGHT AS A PREDICTOR FOR RETINAL PIGMENT EPITHELIAL TEARS ASSOCIATED WITH INTRAVITREAL BEVACIZUMAB INJECTIONS

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Purpose: The purpose was to study preinjection optical coherence tomography–related factors in age-related macular degeneration eyes with retinal pigment epithelial detachment (PED) that may predispose retinal pigment epithelial (RPE) tears associated with intravitreal bevacizumab injections.

Methods: This multicenter retrospective case series involving 9 retina specialists and 7 centers investigated Stratus optical coherence tomography (Carl Zeiss Meditec, Dublin, CA) parameters in eyes with vascularized PED (vPED) from February 2006 to February 2007. Of the 1,280 eyes in 1,255 patients receiving 2,890 intravitreal injections, there were 125 eyes with vPED. For every vPED eye that developed an RPE tear (Group 1), 3 or more vPED eyes without RPE tears (Group 2) were randomly selected in each study center during the same time period for comparison. The primary outcome measure was PED height (μm), and the secondary measures included volume index (vPED height $\times$ surface area), total macular volume, subretinal fluid, cystoid macular edema, center-point thickness, central 1 mm, and pre- and postinjection best-corrected Snellen visual acuities.

Results: Twenty-one vPED eyes in 21 patients among 125 vPED eyes (16.8% of all vPED eyes) developed RPE tears. The 21 Group 1 eyes were compared with the 78 randomly selected Group 2 eyes. The vPED height was significantly higher for Group 1 eyes in comparison to Group 2 eyes (mean: 648.9 $\pm$ 245.0 vs. 338.1 $\pm$ 201.6 μm, $P < 0.001$). The same was true for the following: volume index ($P = 0.001$), subretinal fluid ($P = 0.002$), and total macular volume ($P = 0.04$). The mean preinjection and post-RPE tear best-corrected visual acuity were 0.92 logMAR (20/166) and 0.84 logMAR (20/137), respectively ($P = 0.25$). Multivariate analysis showed PED height to be the only significant risk factor associated with RPE tears in Group 1 eyes [odds ratio = 0.995 (95% confidence interval: 0.992–0.997), $P < 0.001$].

Conclusion: Elevated preinjection vPED height is the single most significant predictor for RPE tears after bevacizumab injections for vPED eyes. A vPED height >400 μm is associated with a significant risk for such a complication.

RETINA 30:203–211, 2010

Retinal pigment epithelial (RPE) tears are known to develop primarily in eyes with a retinal pigment epithelial detachment (PED) associated with age-related macular degeneration on a spontaneous basis[1–7] or after various treatments,[8–34] including conventional laser,[8,9] photodynamic therapy,[10–15] corticosteroid in-

jections,[15,16] pegaptanib injections,[17–19] ranibizumab injections,[20–22,34] and bevacizumab injections.[23–34] It has been speculated that the enhanced mechanical contraction of the choroidal neovascular membrane (CNV) induced by each of the therapeutic modalities mentioned above may predispose these eyes in addition to their natural history for RPE tears.[17–19,23–34] A number of baseline factors have been identified by natural history and recent studies for increasing the risk for RPE tears in these eyes,[4,6,7,33–37] whether on a spontaneous basis or after various therapeutic interventions, respectively. These include increased lesion size (i.e., greatest linear diameter or surface area) and increased subretinal fluid (SRF).[33–37] Although there have been many reports in the literature on RPE tears after antivascular endothelial growth factor (anti-VEGF) therapy in recent years,[17–36] only two recently published reports involved optical coherence tomography (OCT) studies on RPE tears associated with anti-VEGF therapy.[35,36] Leitritz et al[35] and Chiang et al[36] suggested an increased PED height to be a risk factor for an RPE tear. We investigated various preinjection OCT-measured parameters that may be correlated with RPE tears after bevacizumab injections. To the best of our knowledge, our study consisted of the largest case series on OCT-measured risk factors for this complication. We asked the following question: can we predict which eyes with vascularized PED (vPED) are at an increased risk for RPE tears associated with bevacizumab injections based on OCT criteria?

Methods

This study involved nine retina specialists in seven centers in the East Coast, MidWest, and West Coast of the United States, as well as in Germany. Retrospective reviews were performed on all eyes that received intravitreal bevacizumab injections between January 2006 and January 2007. The total number of bevacizumab injections and the total number of eyes receiving the bevacizumab injections within the study period were tabulated from the billing records. The primary outcome for this study included PED height (μm) obtained by Stratus OCT (Carl Zeiss Meditec, Dublin, CA). The secondary outcomes included volume index (defined as vPED height multiplied by vPED surface area in mm^3), total macular volume (mm^3), centerpoint thickness (μm), central 1 mm (μm), amount of SRF (defined as none, mild, moderate, and marked), amount of cystoid macular edema (defined as none, mild, moderate, and marked), and preinjection and post-RPE tear best-corrected Snellen visual acuities converted to logarithm_{10} of the reciprocal of Snellen visual acuity (logMAR). At baseline, OCT, fundus photography (FP), and fluorescein angiography (FA) were performed on all eyes. The follow-up intervals after bevacizumab injections varied from 1 week to 4 weeks throughout the study period. Optical coherence tomography was performed for each visit, and FP and FA were performed at 1-month to 2-month intervals.

All vPED eyes were identified according to standard FA and OCT criteria with the following fundus features[3,15,37–41]: 1) an orange-yellow oval or a bean-shaped elevation of the RPE with a smooth, convex surface corresponding to the PED and focal irregularity within a portion of the PED or adjacent to the margin of the PED frequently in the form of a notch corresponding to the focus of CNV,[3] or 2) a fibrovascular PED with underlying occult CNV.[37] Radial chorioretinal folds associated with the PED in some cases also indicated the presence of CNV underlying the PED (e.g., Case 2).[38] The characteristic OCT findings of the vPED included a distinct elevation of the highly hyperreflective RPE layer with mild backscattering of the underlying choroidal layer in the portion of the PED without any CNV.[37] To avoid inaccurate diagnosis and measurements, subfoveal lesions with hemorrhage occupying $>50\%$ of the lesions were excluded from the study. For vPED eyes that developed RPE tears, FA showed hypofluorescence of the elevated RPE flap and intense hyperfluorescence of the bare choroid, and OCT showed interruption of the hyperreflective RPE layer with elevation or scrolling of the torn RPE flap.[40,41] Frequently, increased depth of signals corresponding to the bare choroid underlying the torn RPE was seen on OCT.[15,41]

All eyes in the study received an injection of either 1.25 mg in 0.05 mL or 2.50 mg in 0.1 mL bevacizumab according to the individual investigator's preference. Each investigator was consistent in using the

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Presented in part as a poster at the American Academy of Ophthalmology annual meeting in Atlanta, Georgia, November 8 and 9, 2008; as a paper at the Retina Society annual meeting in Scottsdale, Arizona, September 29, 2008; and as a paper at the American Society of Retina Specialists annual meeting in Maui, Hawaii, October 12, 2008.

The authors have no financial or proprietary interests in any contents of this paper.

This study involved the off-label use of a medication approved by the Food and Drug Administration.

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same dose of bevacizumab for all eyes in the same center throughout the entire study period. The total number of eyes receiving 1.25 mg and those receiving 2.50 mg of bevacizumab injections was tabulated.

To be included in the data analyses for this study, pre- and post-OCT, FP, and FA findings must have been available for review. Those lacking information on all three modalities were excluded from the analyses. Other criteria for exclusion from analyses included history of the following concomitant conditions: retinal breaks, retinal detachment, substantial cataracts ($\geq$3+ cortical, nuclear sclerotic, or posterior subcapsular cataract), substantial glaucoma ($>$0.7 cup-to-disk ratio and on $>$2 hypotensive medications), presumed ocular histoplasmosis syndrome, optic neuropathy or neuritis, various retinal vascular occlusions, and any other conditions that may influence the vision outcome other than neovascular age-related macular degeneration associated with a vascularized PED.

Statistical analyses were compared between those vPED eyes that developed RPE tears (Group 1) and randomly selected vPED eyes that did not develop postinjection RPE tears from each center during the same time period (Group 2). For Group 2 eyes, those with a follow-up time of $<$3 months were excluded from analyses to ensure the passage of sufficient time without the development of RPE tears among those eyes. To enhance the statistical validity of the comparison, three or more vPED eyes without postinjection RPE tears were randomly selected for every vPED eye that developed a postinjection RPE tear in each center that participated in the study during the same time period. There were a total of 78 eyes in Group 2. The preinjection OCT-related parameters that were compared between the 2 groups included the primary and secondary outcome measures as stated earlier: vPED height, volume index, total macular volume, center-point thickness, central 1-mm subfield, and the amount of SRF and cystoid macular edema. Other baseline parameters that were contrasted to investigate the comparability of the 2 groups included age, sex, race, right eye versus left eye, and 1.25 mg versus 2.5 mg of bevacizumab injections. To acquire accurate measurements of the vPED heights, we used the Proportional Process Report 4.0.1 software (Carl Zeiss Meditec, Dublin, CA) for Stratus OCT to obtain undistorted images of the vPED (Figure 1A). Each measurement was performed on the bottom image generated by this software that showed an undistorted view of the vPED within a rectangular box with a total height of 63 mm, corresponding to a 2,000-μm scan across the fundus (Figure 1B). Dividing 2,000 μm by 63 mm equals 31.75 μm/mm. Multiplying this conversion factor to the vPED height in millimeter yields the vPED height in micrometers (μm). To obtain consistent and reliable results, the same investigator (C.K.C.) performed all the measurements of the preinjection vPED height for the Stratus OCT on all the patients in the same fashion. One of the six scanned images that showed the most robust appearance of the vPED was chosen for generating the undistorted view of the vPED through the Proportional Report 4.0.1 software. A line perpendicular to the base of the vPED was drawn from the base of the vPED to its highest point (apex) for measuring the vPED height in a consistent manner for all patients in both groups. The Stratus OCT images used for measurements were also consistently limited to 30 days before bevacizumab injections for all eyes in both groups.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 15.0 software (SPSS Inc., Chicago, IL). Descriptive statistics were used to summarize the characteristics of the sample. The independent *t* test was used to compare the continuous variables (age, vPED height, volume index, total macular volume, center-point thickness, and central 1-mm subfield) between Group 1 and Group 2 eyes. The Pearson chi-square test of independence was used to compare the categorical variables between Group 1 and Group 2 eyes. A Mann–Whitney U test was also used to compare the differences in SRF and cystoid macular edema between Group 1 and Group 2 eyes. A paired *t* test was used to compare the vision outcome before bevacizumab injection with vision outcome after the development of RPE tears. To determine the significant predictors of the risk for RPE tears, a binary logistic regression was used. $P < 0.05$ was considered statistically significant.

The approval for this study was obtained from the Institutional Review Board of Desert Regional Medical Center in Palm Springs, CA. Strict criteria were followed to ensure compliance with the Health Insurance Portability and Accountability Act to shield the identity and protect the privacy of all study participants.

Results

There was a combined total of 2,890 bevacizumab injections in 1,280 eyes of 1,255 patients for all 7 centers. There were 25 eyes that underwent bilateral injections. Pre- and postinjection OCT, FA, and FP data were available for 1,010 of these 1,280 eyes. Among these 1,010 eyes were 125 vPED eyes. There were 21 vPED eyes in 21 patients who developed RPE tears (Group 1), consistent with a prevalence of 2.1% of all analyzed eyes and 16.8% of vPED eyes. Of the 21 patients, 12 were men and 9 were women. There were 11 right eyes and 10 left eyes. The mean time interval from the bevacizumab injection to the development of an RPE tear was 30.4 ±

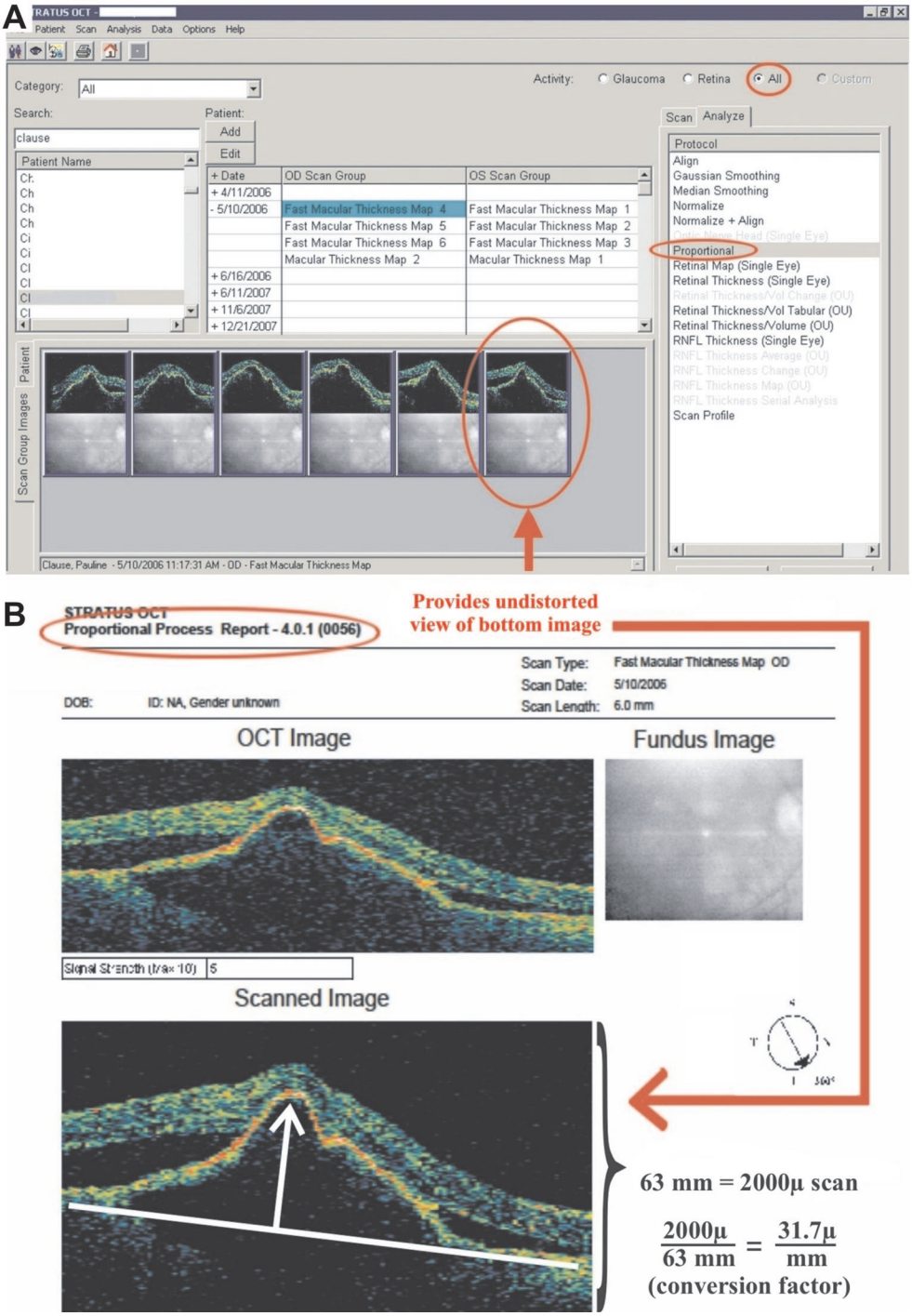

Fig. 1. **A,** Stratus OCT Proportional Process Report 4.0.1 was used to obtain unprocessed images of the vPED for accurate measurements of the vPED heights. **B,** The bottom rectangular-block image shows an undistorted view of the vPED with a total height of 63 mm corresponding to a 2,000-μm scan across the fundus. Thus, the conversion factor for changing the vPED height in mm to μm is 31.75 μm/mm (2,000 μm divided by 63 mm).

22.7 days, with a range of 4 days to 91 days. The mean follow-up time for these eyes was 144.9 ± 74.5 days, with a range of 42 days to 350 days. There were 78 vPED eyes in Group 2 (vPED eyes without RPE tears).

Univariate Analyses

The following baseline characteristics for Group 1 and Group 2 eyes were found to be comparable.

Age, Sex, Race, Right Eye Versus Left Eye, and 1.25-mg Versus 2.5-mg Dose. An independent *t* test found no significant differences in age between the 2 groups (78.9 ± 7.4 vs. 78.4 ± 8.6; $P = 0.80$). Pearson chi-square analyses showed no significant differences between the 2 groups for sex and right eye versus left eye ($P = 0.15$ and $P = 0.85$, respectively; Table 1). White race was found in 99% of all patients in each of

Table 1. Univariate Analysis on Significant Risk Factors for RPE Tears

Parameters	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	*P*
PED height	648.9 ± 245.0 μm	338.3 ± 201.6 μm	<0.001*
Volume index	9.3 ± 6.3 mm^3	3.5 ± 4.0 mm^3	0.001*
Total macular volume	8.0 ± 1.8 mm^3	7.4 ± 1.2 mm^3	0.04*
Subretinal fluid	NA	NA	0.002†

*P values were obtained with independent *t* test.
†*P* value was obtained with chi-square analysis.
NA, not applicable; SD, 1 standard deviation.

the 2 groups. For Group 1 eyes, 8 eyes received 2.5-mg and 13 eyes received 1.25-mg bevacizumab injections. For Group 2 eyes, 24 received 2.5-mg and 54 received 1.25-mg bevacizumab injections. Chi-square analysis showed a lack of significant differences between the 2 doses for RPE tears in comparing the 2 groups ($P = 0.58$, Fisher exact test). There were significant differences between the 2 groups for the following OCT-related parameters (Table 1).

Vascularized Pigment Epithelial Detachment Height. Significantly greater mean vPED height was found in Group 1 in comparison to Group 2 eyes (648.9 ± 245.0 μm vs. 338.1 ± 201.6 μm; $P < 0.001$, *t* test).

Volume Index. There was higher mean volume index for Group 1 eyes compared with Group 2 eyes (9.3 ± 6.3 vs. 3.5 ± 4.0 mm^3; $P = 0.001$, *t* test; mean vPED sizes [surface areas] of Group 1 and Group 2 were 13.7 ± 6.9 vs. 9.8 ± 7.5 mm^2; $P = 0.03$, *t* test, respectively).

Total Macular Volume. There was significantly greater mean total macular volume in Group 1 in comparison to Group 2 eyes (8.0 ± 1.8 vs. 7.4 ± 1.2 mm^3; $P = 0.04$, *t* test).

Subretinal Fluid. Chi-square analysis showed significantly more SRF in Group 1 in comparison to Group 2 eyes ($P = 0.002$). The results from the Mann–Whitney U analysis showed increased SRF for Group 1 eyes over Group 2 eyes, although not significant ($P = 0.07$).

There were no significant differences between the two groups for the following OCT-related parameters.

Center-Point Thickness and Central 1-mm Subfield. Analysis with paired *t* test showed no significant differences between the 2 groups on both the mean center-point thickness and mean central 1-mm subfield (294.8 ± 125.8 vs. 267.7 ± 89.3 μm, $P = 0.26$; and 311.9 ± 103.1 vs. 279.2 ± 78.1 μm, $P = 0.12$, respectively).

Cystoid Macular Edema. Mann–Whitney analysis showed a lack of significant difference between the 2 groups for cystoid macular edema ($P = 0.32$). There was a lack of statistical difference in the preinjection

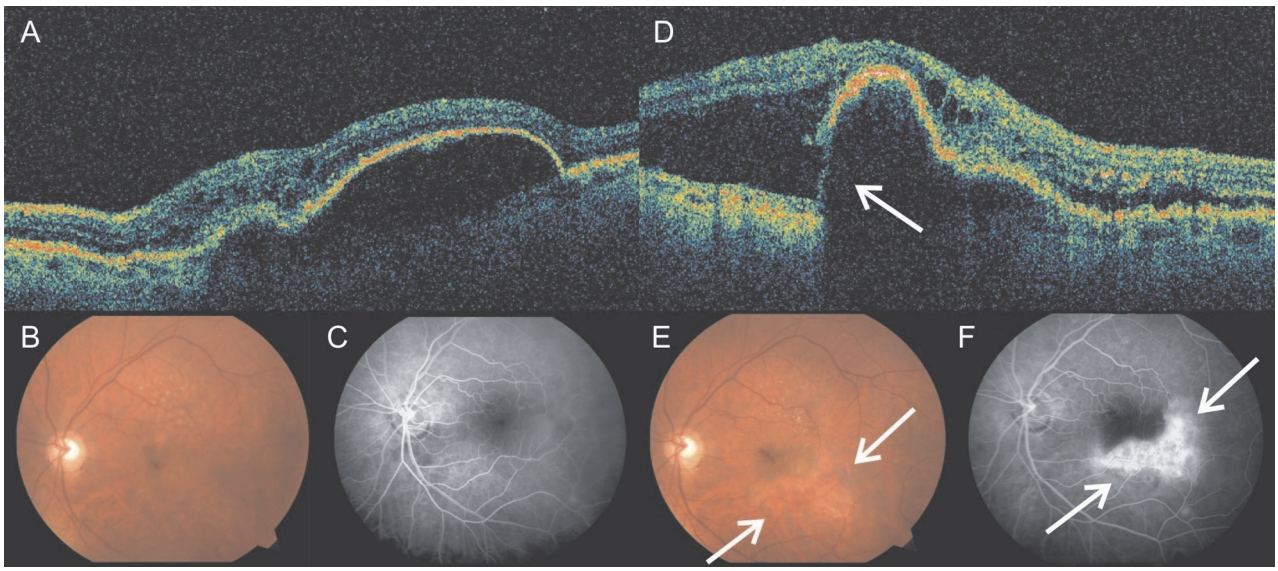

Fig. 2. Case 1: an 84-year-old man's left eye showed a vPED on (**A**) OCT, (**B**) FP, and (**C**) FA. The presenting vPED height was 412.7 μm, and there was moderate SRF adjacent to the vPED. **D,** OCT, (**E**) FP, and (**F**) FA showed that an inferotemporal RPE tear developed 45 days after the second bevacizumab injection. The preinjection BCVA was 20/200, and the posttear BCVA was 20/400.

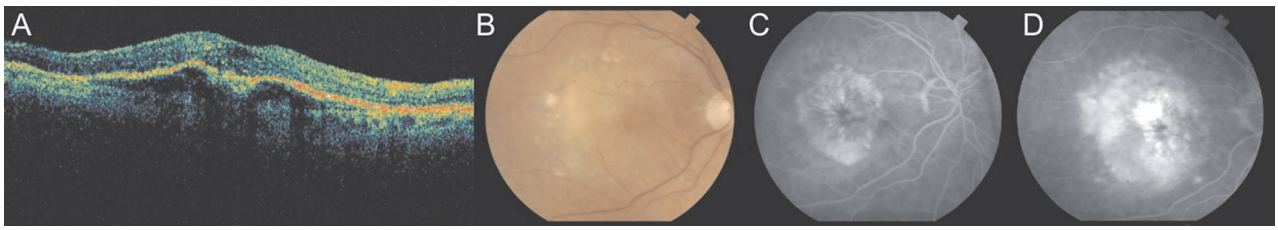

Fig. 3. Case 3: an 86-year-old woman presented with a subfoveal vPED in the right eye with a large vPED size of 12.6 mm^2 but a vPED height of only 260.3 μm shown on (**A**) OCT, (**B**) FP, and (**C**) FA images. **D,** Follow-up FA showed no RPE tears 7 months after multiple bevacizumab injections. This case illustrates that PED height supersedes PED surface area in determining the risk for RPE tears associated with bevacizumab injections.

and post-RPE tear best-corrected Snellen visual acuity outcome for the 21 vPED eyes that developed RPE tears (0.92 ± 0.41 logMAR or 20/166 vs. 0.84 ± 0.46 logMAR or 20/137, respectively; paired *t* test, $P = 0.25$).

Multivariate Analysis

The results obtained using logistic regression showed that vPED height was the only independent significant factor predicting the risk of RPE tears (odds ratio = 0.995; 95% confidence interval: 0.992–0.997; $P < 0.001$).

Representative Case Reports

Increased Risk For Retinal Pigment Epithelium Tears. Case 1 was an 84-year-old man who showed a PED height of 412.7 μm associated with a vascularized PED in the left eye (Figure 2, A–C). An inferotemporal RPE tear developed 45 days after the second bevacizumab injection in the left eye (Figure 2, D–F). There was moderate SRF adjacent to the PED. The preinjection best-corrected visual acuity (BCVA) was 20/200, and the posttear BCVA was 20/400.

Case 2 was a 92-year-old woman who presented with a marked PED height of 1,019 μm in the right eye with a vascularized PED. There was substantial SRF adjacent to the PED. There were multiple radial chorioretinal folds within and surrounding the PED. A superior RPE tear developed at 43 days after the third bevacizumab injection. The preinjection BCVA was 20/400, and the posttear BCVA was 20/400.

Low Risk For Retinal Pigment Epithelium Tears. Case 3 was an 86-year-old woman who presented with a subfoveal vascularized PED in the right eye as shown on OCT (Figure 3, A), FP (Figure 3, B), and FA (Figure 3, C). Despite a relatively large PED size of 12.6 mm^2, the PED height was only 260.3 μm. There was minimal SRF overlying the PED. Seven months after multiple bevacizumab injections, no RPE tears developed in this eye (Figure 3, D). This case indicates that PED height supersedes PED surface area in determining the risk for RPE tears associated with bevacizumab injections.

Preservation of Vision Despite Retinal Pigment Epithelium Tear. Case 4 was a 74-year-old woman who presented with a subfoveal vascularized PED with a height of 266.7 μm as shown on OCT (Figure 4, A), FP (Figure 4, B), and FA (Figure 4, C). Despite developing an RPE tear 27 days after bevacizumab injection, the central vision was preserved because of the sparing of the central fovea from involvement with the RPE tear and the continued suppression of the CNV with more bevacizumab injections (Figure 4, C).

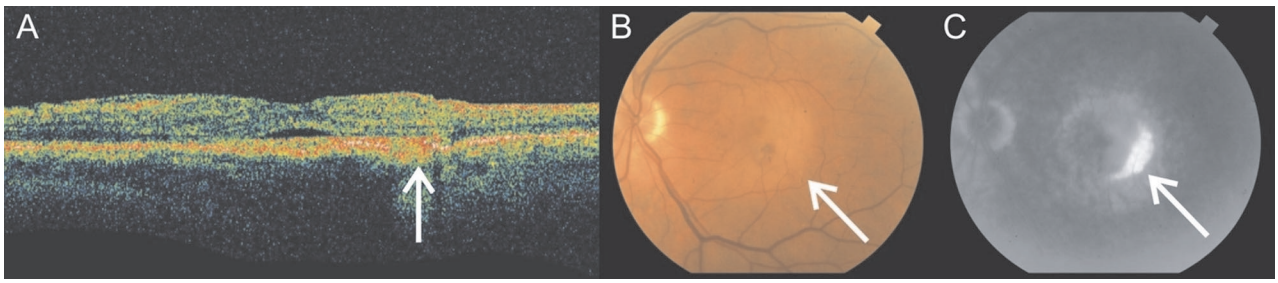

Fig. 4. Case 4: a 74-year-old woman presenting with a subfoveal vPED with only a height of 266.7 μm developed an RPE tear 27 days after bevacizumab injection as shown on (**A**) OCT, (**B**) FP, and (**C**) FA images. Nevertheless, good central vision was preserved because of the sparing of the central fovea from involvement with the RPE tear and the continued injection of bevacizumab to suppress the neovascular activity.

The preinjection BCVA was 20/200, and the posttear BCVA was 20/70.

Discussion

Univariate analyses in this study (Table 1) showed increased vPED height (mean: 648.9 ± 245.0 μm, $P < 0{,}001$) and greater amount of SRF ($P = 0.002$) in vPED eyes that developed RPE tears (Group 1) in comparison to vPED eyes without RPE tears (Group 2) after bevacizumab injections, consistent with recent reports.[35,36] Increased total macular volume (8.0 mm^3, $P = 0.04$) and volume index (vPED height multiplied by vPED surface area) associated with a tendency for postinjection RPE tears are new findings not reported previously. The lack of significant differences in specific baseline characteristics between the Group 1 and Group 2 eyes (i.e., age, sex, race, right eye vs. left eye, and doses of bevacizumab injections) enhanced the internal validity of the study for comparing the two groups to identify the risk factors relating to RPE tears associated with bevacizumab injections. The performance of the measurements of the vPED height by the same investigator (C.K.C.) in precisely the same fashion on Stratus OCT images with undistorted views generated through the Proportional Process Report 4.0.1 software on all the patients also increased the reliability of the measurements for statistical comparison between the 2 groups. To the best of our knowledge, there is a lack of commercially available computerized software with a built-in caliper system for time and spectral-domain OCT units in assessing the PED heights.

The lack of significant difference in the mean preinjection and post-RPE tear BCVAs was likely because of the continued suppression of the CNV by further bevacizumab injections after RPE tears in the study eyes and the sparing of the fovea by the RPE tears in certain eyes (e.g., Case 4; Figure 4).

The most important and interesting finding of this study was the identification of vPED height to be the only independent factor correlating with RPE tears. Given the mean vPED height of 648.9 ± 245.0 μm for vPED eyes with RPE tears, any vPED eye with a PED height of 400 μm or more is at risk for an RPE tear after bevacizumab injections. This finding is consistent with the report by Chiang et al,[36] who showed that a median vPED height of 398 μm was associated with RPE tears in vPED eyes in their recent study. In fact, our study suggested that any vPED eye with a vPED height ≥600 μm is at particular risk for an RPE tear after bevacizumab injections, especially in the presence of increased SRF. The reason for a relatively low odds ratio (0.995) despite a highly significant P value of <0.001 and a significantly narrow 95% confidence interval (0.992–0.997) is likely the high variability of the vPED heights (226.7–1,190.5 μm) for vPED eyes that developed RPE tears in this series. Our results are also consistent with the report by Leitritz et al,[35] who found increasing probability of RPE tears in an exponential manner with the increase in vPED height based on a linear regression model, particularly beyond the height of 400 μm. Thus, vPED height is a powerful predictor for the risk of RPE tears in vPED eyes that can be consistently obtained and replicated in the clinical setting. The results of our study also suggest that PED height supersedes PED surface area in determining the risk for RPE tears associated with bevacizumab injections (e.g., Case 3; Figure 3).

The limitations of this study included its retrospective nature and the lack of standardized visual acuity measurements. Another shortcoming was the absence of a pure control group of vPED eyes lacking any treatment for comparison. Thus, unknown confounding variables could have been present. However, to conduct a prospective study and to withhold treatment for a large number of vPED eyes to form a control group for comparison would likely be unethical, considering multiple therapies currently available for treating such eyes. Even for a retrospective study, it would be exceedingly difficult to assemble sufficient number of vPED eyes lacking any treatment to serve as a control group with baseline characteristics comparable to the vPED eyes that have undergone treatment as a result of the current popularity of anti-VEGF treatment and photodynamic therapy for managing these eyes despite the lack of consensus on the optimal method of treatment. Another controversial issue concerns any causal relationship of intravitreal bevacizumab injection to RPE tears. Some may contend the cause of RPE tears in vPED eyes to be entirely related to the natural history of the vascularized processes. However, multiple studies including our study suggest a contributing effect of intravitreal anti-VEGF therapy in addition to the spontaneous tendency for RPE tears in vPED eyes. For instance, the prevalence of RPE tears was found to be 16.8% in our study, in comparison to the lower prevalence of only 10% to 12% for RPE tears consistently reported by multiple previous natural history studies on this condition.[1,5,42] There is also indirect evidence supporting the contributing effect of anti-VEGF therapy for RPE tears in vPED eyes found in multiple recent reports of increased tendency for retinal tears and tractional retinal detachments in diabetic eyes shortly after intravitreal anti-VEGF injections to reduce optic nerve and retinal neovascularization before a vitrectomy because of enhanced contraction and shrinkage of epiretinal neovascular

tissues with fibrous proliferation.[43,44] A similar mechanism is at play for both situations. Finally, the limitation on the accuracy of the PED height measurements attributed to our indirect manual method was partially compensated by the consistent technique of PED height assessment by the same investigator on all study eyes. The future development of specific software for Spectral-domain OCT units with a caliper system superimposed on undistorted images of the PED will enhance the accuracy of PED height measurements.

In conclusion, this study showed a significant relationship to RPE tears for the following OCT parameters in vPED eyes on univariate analyses: increased vPED height, greater volume index and total macular volume, and larger amount of SRF. However, multivariate analysis showed that vPED height is the only independent significant risk factor associated with RPE tears. Any vPED eye with a vPED height of 400 μm or more may be at risk for RPE tears after bevacizumab injections, particularly in the presence of increased SRF. The measurement of vPED height provides a convenient method for the clinician to determine the relative risk of an eye with a vascularized PED for developing an RPE tear in association with bevacizumab injections. Additional studies are warranted to confirm the results of this study.

Key words: Avastin, bevacizumab, intravitreal injection, fibrovascular pigment epithelial detachment, optical coherence tomography, retinal pigment epithelial detachment, retinal pigment epithelial height, retinal pigment epithelial rip, retinal pigment epithelial tear, vascularized pigment epithelial detachment.

Acknowledgments

The authors thank Grenith Zimmerman, PhD, at the School of Allied Health Professions, Loma Linda University, Loma Linda, CA, for contributions to a portion of the statistical analyses for this study.

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