Factors influencing ellipsoid zone tear in pathologic myopia choroidal neovascularization

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Abstract

This study explored factors influencing ellipsoid zone (EZ) tear in pathologic myopia choroidal neovascularization (PM-CNV) and its relationship with visual acuity mainly using optical coherence tomography (OCT). We divided 21 (22 eyes) PM-CNV patients, who were divided into non-tear (n=10) and tear (n=12) groups by whether the EZ was torn or not. Measured central macular thickness (CMT), PM-CNV lesion hyperreflectivity (HF) height and area, and myoid ellipsoid zone (MEZ)) thickness on OCT. Analyzing relationships between these factors and EZ tearing. We found EZ tear group had thicker CMT (P = 0.006), higher HF height (P = 0.001), larger HF area (P = 0.001), bigger PM-CNV area (P = 0.028), greater HF/CNV area ratio (P = 0.038), thinner MEZ (P = 0.000), worse best corrected visual acuity (BCVA) (P = 0.000). After treatment with conbercept only 4/12 eyes showed recovery of EZ integrity in tear group, with even worse BCVA. OCT provides a new bioindicator as monitoring risk factor of EZ tear for PM-CNV. PM-CNV with higher and larger HF, bigger HF area relative to the PM-CNV area have greater risk for EZ tear and poorer visual acuity. Better visual acuity will be achieved when PM-CNV was treated before EZ tear.

Introduction

This study explored factors influencing ellipsoid zone (EZ) tear in pathologic myopia choroidal neovascularization (PM-CNV) and its relationship with visual acuity mainly using optical coherence tomography (OCT). We divided 21 (22 eyes) PM-CNV patients, who were divided into non-tear (n = 10) and tear (n = 12) groups by whether the EZ was torn or not. Measured central macular thickness (CMT), PM-CNV lesion hyperreflectivity (HF) height and area, and myoid ellipsoid zone (MEZ)) thickness on OCT. Analyzing relationships between these factors and EZ tearing. We found EZ tear group had thicker CMT (*P* = 0.006), higher HF height (*P* = 0.001), larger HF area (*P* = 0.001), bigger PM-CNV area (*P* = 0.028), greater HF/CNV area ratio (*P* = 0.038), thinner MEZ (*P* = 0.000), worse best corrected visual acuity (BCVA) (*P* = 0.000). After treatment with conbercept only 4/12 eyes showed recovery of EZ integrity in tear group, with even worse BCVA. OCT provides a new bioindicator as monitoring risk factor of EZ tear for PM-CNV. PM-CNV with higher and larger HF, bigger HF area relative to the PM-CNV area have greater risk for EZ tear and poorer visual acuity. Better visual acuity will be achieved when PM-CNV was treated before EZ tear.

Pathologic myopia (PM) is the leading cause of blindness in the global population of young and middle-aged people, especially in Asian countries.[1] Choroidal neovascularization (CNV) is a common complication of PM, which often leads to rapid loss of central visual acuity and has a serious impact on the quality of life for patients.[2] The global incidence of PM-CNV has been reported to be from 5.2–11.3% and it accounts for 62% of all CNV cases in people < 50 years.[3,4] Therefore, the health burden of PM-CNV is urgently addressed.

Altered structure and function of the ellipsoid zone (EZ), which contains the photoreceptors, was considered to be the main cause of the patients' visual impairment has been reported in previous

studies.[5–12] For instance, Ye[5] demonstrated that myoid and ellipsoid zone (MEZ) thickness are suitable bioindicators of PM and its thinning was significantly associated with worsening visual acuity. Alteration of cone cell density can also be an important indicator of macular photosensitivity with high myopia.[6] The degree of EZ damaged was also an important factor in visual recovery after anti-vascular endothelial growth factor (VEGF).[10] Figueiredo found that measurement at the EZ hyporeflectivity region using en face optical coherence tomography (OCT) not only allowed assessment of photoreceptor integrity, but also visualization and quantification of the EZ recovery.[7] As the prevalence of PM-CNV is low in comparison to diabetic macular edema (DME) and exudative age-related macular degeneration (ex-AMD), previous studies about EZ have been focused on DME and ex-AMD.[9–12] However, relatively rare study of the impact of EZ integrity disruption with regard to visual acuity in patients with PM-CNV.

In the current study, we used OCT to identify changes to retinal sublayer structure and morphology. Determining the effect of EZ tear on visual acuity in PM-CNV and its recovery condition after anti-VEGF treatment by studying the factors influencing EZ tear among PM-CNV patients. This study may be useful in deepening our understanding of the mechanisms by which the EZ affects BCVA and may provide guidance for the clinical treatment and prevention of PM-CNV.

Results

Analyze populations: This study included a total of 21 (22 eyes) patients with PM-CNV, of which 9 (9 eyes) were type 1, 11 (11 eyes) were type 2 and 1 was mixed, with type 1 in the left eye and type 2 in the right eye. The morphology of PM-CNV was observed on OCTA images with “ring” (Fig. 1, a) and “sea-fan” (Fig. 2, a). OCT images showed that the EZ was not tear in any of the type 1 eyes (Fig. 1, b, c) and that the EZ was tear in all of the type 2 eyes (Fig. 2, b, c).

Baseline demographics and clinical characteristics were summarized in Table 1. EZ non-tear 10 eyes, Pearson correlation analysis was used to analyze the correlations between factors within the EZ non-tear group BCVA and CNV area (P = 0.026), HF height and HF area (P = 0.000), HF height and HF/CNV area ratio (P = 0.000) were significantly correlated. There were no correlations between the other factors within the group. Correlations between factors within the EZ tear group were analyzed using Pearson correlations for the 12 eyes of the EZ tear, with age correlating with CNV area (P = 0.019), BCVA with CMT (P = 0.019), HF height with CMT (P = 0.022), HF height with HF area (P = 0.018), and HF/CNV area ratio with CNV area (P = 0.032) were significantly correlated. No correlations were found between the other factors within the group.

Comparison between two groups: Differences between the non-tear and tear EZ groups by one-way ANOVA (Table 1). There were no differences in age between the EZ non-tear and EZ tear groups ((P = 0.734). BCVA in the non-tear and tear EZ groups were 0.45 ± 0.12, 1.15 ± 0.35 (P = 0.000), CMT were 244.60 ± 35.75 μm, 310.92 ± 59.55 μm (P = 0.006), CNV area was 0.102 ± 0.101 mm^2, 0.260 ± 0.188 mm^2 (P = 0.028), HF height were 26.70 ± 41.87 μm, 182.42 ± 122.66 μm (P = 0.001), HF area were 0.008 ± 0.013 mm^2, 0.141 ± 0.113 mm^2 (P = 0.001), HF/CNV area ratio was 0.20 ± 0.32, 1 ± 1.1 (P = 0.038),

MEZ of 28.40 ± 0.52 μm, 21.08 ± 2.02 μm (P = 0.001) respectively. All with statistical significance at P<0.05.

Analysis after anti-VEGF treatment: The clinical characteristics of both groups after treatment with conbercept in accordance with the pro re nata (PRN) protocol were as shown in Table 2. After treatment there was a statistically significant difference between the two groups for BCVA (P = 0.006), Δ BCVA (P = 0.026), CNV area (P = 0.023), HF height (P = 0.002), HF area (P = 0.003), HF/CNV area ratio (P = 0.005) and MEZ thickness (P = 0.004), respectively. In the non-tear group, after treatment with conbercept, reduced PM-CNV can be observed on OCTA images (Fig. 1, d). HF decreased in 3/10 eyes after treatment (Fig. 1, e, f) and was not statistically significant before and after treatment in all clinical parameters except BCVA (P = 0.014), CMT (P = 0.014), and CNV area (P = 0.007). In the EZ tear group, after treatment with conbercept, the change in morphology, size, and location of PM-CNV was observed on OCTA images (Fig. 2, d). HF disappeared in 2/12 eyes and EZ recovered in 4/12 eyes after treatment (Fig. 2, e, f). All clinical features were statistically significant except for the HF/CNV area ratio (P = 0.638), MEZ thickness (P = 0.157) which was not statistically significant. There was no significant change in MEZ thickness before and after treatment in either group

Discussion

In the present study, the key role of photoreceptors in visual impairment with PM-CNV was determined by using OCT to observe microstructural changes in the fundus and predict factors of EZ tear. The significant relationship between photoreceptor morphology and density degradation and BCVA deterioration has been extensively documented in previous studies. [6,13,14] Therefore, early intervention and protection of the EZ will be important to maintain visual function in PM-CNV.

While the pathological changes with PM-CNV progress slowly and vision gradually loses over 10 years without treatment.[15] However, since the PM eye axis gradually lengthens, the EZ in the outer layer of the retina become thinner and the BCVA worse.[5] Therefore, the present study had the advantage of retrospectively studying the effect of EZ tear with PM-CNV patients on their vision, to predict the factors contributing to EZ tear and to be able to provide a biological indicator to monitor whether the EZ was torn or not. This study showed that higher HF and larger area, bigger HF/CNV area ratio, greater CNV area and thinner MEZ increased the risk of EZ tear, as well as type 2 PM-CNV patients had all EZ tear, whereas type 1 had almost continuous and intact EZ. There was no correlation between age and the factors within groups and between groups. It suggests that EZ tear may be related to the disease duration, type and size of PM-CNV. Therefore, it is helpful to identify the above risk factors before starting treatment for PM-CNV to warn patients and provide prognostic information.

In previous studies, EZ tear was not only significantly associated with BCVA, but also predicted visual acuity recovery after anti-VEGF treatment.[16] Similar findings were found in the present study. It was found

that the BCVA in the EZ tear group was about 1/2 of normal BCVA in the non-tear group, and after anti-VEGF treatment the BCVA in the EZ tear group was only 0.65±0.22 lower than the 0.45±0.12 in the non-tear group before anti-VEGF treatment. Indicating that the EZ tear severely affected the BCVA of the PM-CNV, leading to even worse visual function. However, Milani[17] expressed the opposite view, who found that an increase in BCVA was observed even in the absence of EZ at baseline and final follow-up, hence he believed that the integrity of the EZ may not be the major factor for BCVA, and that it was the integrity of the external limiting membrane and EZ of the bleeding and lesion attachment that may be the main factor influencing BCVA. His findings were similar to those of the 10/12 eyes in tear group of present study, where the EZ integrity was not recovered but the BCVA was increased after anti-VEGF treatment. Thus, we hypothesize that it is possible that the cone cells are not destroyed after EZ tear and are distributed above the lesion to maintain normal visual function, but this hypothesis will need to be confirmed in the future by large-scale and long-term studies.

Integrity of regional photoreceptors was a powerful predictor of whole retinal vision function.[18] The photoreceptor cone cells are predominantly located in the fovea, with a gradual decrease in the periphery.[19] Likewise, PM-CNV also occurs mostly below the macular fovea, or in the parafovea.[20] In this study, the EZ was torn and disappeared in the tear group, and the BCVA deteriorated severely, which was not consistent with Milani's[17] study either. Therefore, we speculated that the EZ tear may have led to changes in the density and arrangement rules of the cone cells as well leading to severe functional deterioration. Previous studies have also found that the density of the cone cells was also an important factor in visual dysfunction, and were able to confirm our conjecture, however they examined high myopia.[6] The density and arrangement patterns of PM-CNV cone cells need to be studied in an efficient way in the future.

Among the photoreceptor morphological parameters, MEZ thickness was one of the most important predictors of photosensitivity, especially in the inner region.[6] In this study MEZ thickness also played a role in the impact of EZ tear. The MEZ zone contains the mitochondria, dictyosome, endoplasmic reticulum and can produce ATP, light of protease and chemicals necessary to maintain photosensitivity.[21,22] Previous studies have found a significant thinning of the MEZ in PM with a high correlation with BCVA deterioration. This could also suggest that thinner MEZ is an important factor in the deterioration of PM-CNV visual acuity.

This study has some limitations. To begin with, the effect of different refraction and axial length on MEZ thickness and EZ tear in PM-CNV patients was not studied. Secondly, because of the limitations of the OCTA technique itself, OCTA displays the blood flow signal by detecting the red blood cell flow rate. when the red blood cell flow rate was too slow or too fast, OCTA was unable to detect the blood flow signal (neovascularization) and the image appeared as a non-perfused or non-vascular area.[23] This may lead to errors during our CNV area calculations, resulting in errors in the HF/CNV area ratio. Thirdly, all measurements of HF height, HF area, CNV area and MEZ thickness in this study were made manually and it was difficult to guarantee the accuracy of this data. Finally, the present study was a retrospective study

with a small sample size. Follow-up was short and irregular, and it was not possible to study the long-term visual effects of EZ for PM-CNV patients.

In conclusion, PM-CNV with higher HF, larger HF area, and greater HF area relative to CNV area are highly likely to have a relatively high risk of EZ tear. It is beneficial for both the clinician and the patient to assess these risk factors prior to treatment for PM-CNV progression. Patients with non-tear EZ will have better visual quality.

Methods

Study population: This study examined a retrospective case series of 21 patients (22 eyes) with PM-CNV treated at the Central Hospital Affiliated to Shandong First Medical University from February 2020 to April 2022. Inclusion and exclusion criteria were determined with reference from the literature.[1, 20, 24, 25] Inclusion criteria: (1) Refractive error <-6.00 D and axis length >26.50 mm. (2) The presence of scleral staphyloma, choroidal atrophy, and CNV was defined as PM according to the international criteria for PM (Meta-PM). (3) Treatment with a single conbercept according to PRN scheme. Exclusion criteria: (1) Refractive media clouding that interfered with fundus examination. (2) Presence of systemic diseases such as diabetes and hypertension. (3) Exclusion of CNV secondary to other diseases, such as exudative age-related macular degeneration (ex-AMD), inflammatory CNV, chronic central serous chorioretinopathy CNV, etc. (4) Previous history of other ocular diseases such as trauma, glaucoma, epiretinal membrane, etc. (5) Previous anti-VEGF, retinal photocoagulation, photodynamic therapy, etc. All populations included in the study were grouped according to whether the EZ was torn or not. There were two groups: non-tear and tear EZ.

The study was approved by the Ethics Committee of the Central Hospital Affiliated to Shandong First Medical University. All study adhered to the principles of the Declaration of Helsinki. The study was explained to all subjects about the nature of the study and the possible risks and benefits. Written informed consent was signed by all participating study subjects.

Patient assessment & treatment: Retrieve patient characteristics from the case-based system, including age, gender, follow-up time, medical history and history with previous ocular disease treatment. All patients underwent a comprehensive baseline and follow-up ophthalmology examination. These included best corrected visual acuity (BCVA) (standard logarithmic visual acuity scale), refraction, intraocular pressure, slit lamp, indirect fundoscopy, OCT and OCTA examinations. Transforming BCVA to logarithm of the minimum angle of resolution (logMAR) visual acuity before the analysis of the data.

PM-CNV was defined by OCT and/or OCTA images. All patients were acquired with Zeiss Cirrus HD-5000 device with central 840 nm wavelength. The OCT was performed by an experienced ophthalmologist, and the Macular Cube 512x128 mode was used for OCT to obtain OCT structural pictures of the macula, and the Angio 3×3mm^2 and 6×6 mm^2 mode was used for OCTA to obtain fovea 3×3 mm^2 and 6×6 mm^2 OCTA, and the best image (signal intensity ≥ 7/10) was retained. A hyperreflective (HF) lesion seen on an

OCT horizontal B-scan image through the fovea located under the retinal pigment epithelium (RPE) with the RPE layer intact would be defined as type 1 PM-CNV, and otherwise as type 2. (Fluorescein fundus angiography was not used to diagnose PM-CNV for better follow-up of patients).

All patients who were diagnosed with PM-CNV received single conbercept treatment based on the PRN plan. Conbercept (Chengdu Kanghong Biotechnology Co., Ltd., Sichuan, China) is a distinct VEGF fusion protein which blocks all isoforms of VEGF-A, VEGF-B, VEGF-C, and placenta growth factor (PGF), and it has a long half-life in the vitreous.[26] The disappearance of PM-CNV on OCT and/or OCTA was observed at follow-up without the need for revisiting anti-VEGF therapy.

Measurements

The central macular thickness (CMT) was obtained by the analysis function that comes with the software. PM-CNV and HF area, HF height, MEZ thickness manually depicted on the software ImageJ version1.581j8 (Wayne Rasband National Institutes of Health, USA) and the software automatically calculates the final values, setting the same reference value each time during the measurement (Distance in pixele:429, Known distance:3, Pixel aspect ratio:1.0, Unit of length: mm). HF height was the distance between the highest point of the HF and the bruch membrane. MEZ thickness was the MZ to EZ in the foveal area of 3 mm (Fig. 3).

Statistical analysis: Statistical calculations were performed using the Statistical Package for the Social Sciences (version 26.0, IBM SPSS). The continuous data for the base were expressed by means ± standard deviations. The Shapiro-Wilk test was performed on all variables to determine whether they conformed to a normal distribution. Pearson correlations were used to analyze correlations between variables within groups. Analysis of factors influencing EZ tear by one-way ANOVA comparing the differences between the two groups. Wilcoxon signed rank test was used to compare clinical parameters of patients before and after treatment with conbercept anti-VEGF. The statistical significance was $P < 0.05$.

Declarations

Author contributions

R. J., Z. W. designed this study. R. J., D. C., X. L. collected and measured data. R. J., Z. W., D. C., X. L. analyzed data. R. J., Z. W. wrote this article. All authors discussed the results and commented on the manuscript.

Data availability statement

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author.

Competing Interests

No competing interests are declared by the author.

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Tables

Table 1. Baseline Demographic and Clinical Characteristics of the PM-CNV Study Population. *PM* pathologic myopia; *CNV* choroidal neovascularization; *EZ* Ellipsoid Zone; *BCVA* best corrected visual acuity; *LogMAR* logarithm of the minimum angle of resolution; *CMT* central macular thickness; *HF* hyperreflective; *MEZ* Myoid and Ellipsoid Zone. *P* with statistical significance is shown in boldface

Characteristics	EZ non-tear Group (Type 1)	EZ tear Group (Type 2)	*P*
Age, y	44.60 ± 16.20	47.08 ± 17.35	0.734
Sex, n			
Male	2/10	2/12	
Female	8/10	10/12	
BCVA, (LogMAR)	0.45 ± 0.12	1.15 ± 0.35	**0.000**
CMT, (μm)	244.60 ± 35.75	310.92 ± 59.55	**0.006**
CNV area, (mm^2)	0.102 ± 0.101	0.260 ± 0.188	**0.028**
HF height, (μm)	26.70 ± 41.87	182.42 ± 122.66	**0.001**
HF area, (mm^2)	0.008 ± 0.013	0.141± 0.113	**0.001**
HF/ CNV area ratio	0.20 ± 0.32	1 ± 1.1	**0.038**
MEZ thickness, (μm)	28.40 ± 0.52	21.08 ± 2.02	**0.000**

Table 2. Comparison of Clinical Characteristics after anti-VEGF Treatment with PM-CNV. *PM* pathologic myopia; *CNV* choroidal neovascularization; *EZ* Ellipsoid Zone; *BCVA* best corrected visual acuity; *LogMAR* logarithm of the minimum angle of resolution; *CMT* central macular thickness; *HF* hyperreflective; *MEZ* Myoid and Ellipsoid Zone. P_1 = non-tear versus tear group after treatment; P_2 = non-tear group before and after treatment; P_3 = tear group before and after treatment. *P* with statistical significance is shown in boldface.

Characteristics	EZ non-tear Group (Type 1)	EZ tear Group (Type 2)	P_1	P_2	P_3
BCVA, (LogMAR)	0.33 ± 0.08	0.65 ± 0.22	**0.006**	**0.014**	**0.002**
ΔBCVA, (LogMAR)	0.12 ± 0.09	0.5 ± 0.3	**0.026**		
CMT, (μm)	222 ± 18.16	262.83 ± 31.96	0.31	**0.007**	**0.002**
CNV area, (mm^2)	0.026 ± 0.029	0.131 ± 0.118	**0.023**	0.068	**0.002**
HF height, (μm)	0	82.42 ± 63.13	**0.002**	0.068	**0.002**
HF area, (mm^2)	0	0.066 ± 0.076	**0.003**	0.068	**0.002**
HF/ CNV area ratio	0	0.68 ± 0.78	**0.005**	0.068	0.638
MEZ thickness, (μm)	28.40 ± 0.52	20.92 ± 1.98	**0.004**	1	0.157

Figures

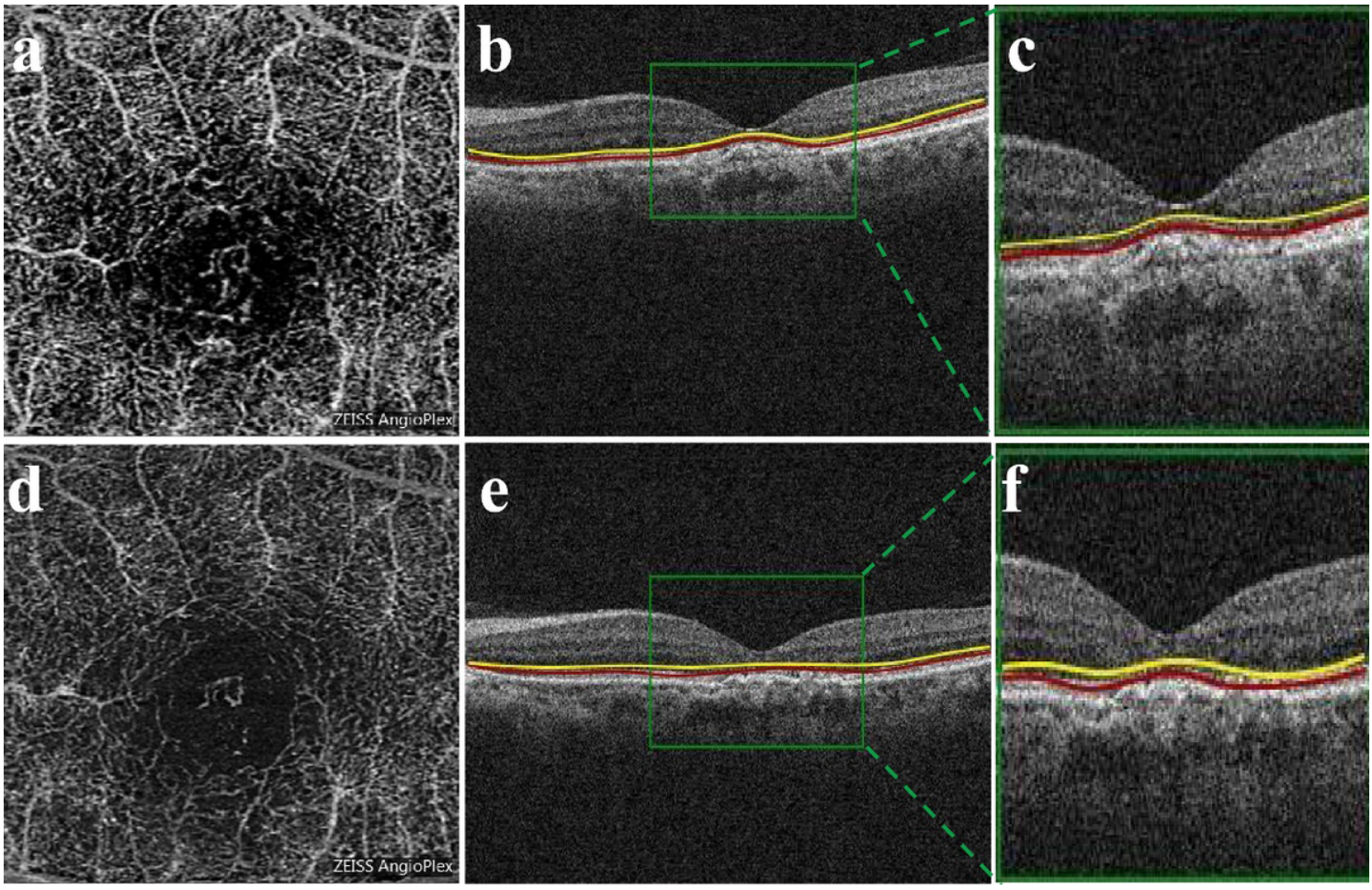

Figure 1

optical coherence tomography angiography of EZ with non-tear: “ring" neovascularization was visible in fovea before treatment (a) and after treatment (d). The EZ was intact on the optical coherence tomography, and the PM-CNV lesion was located under the RPE layer before treatment (b, c,) and after treatment decreased. (e, f).

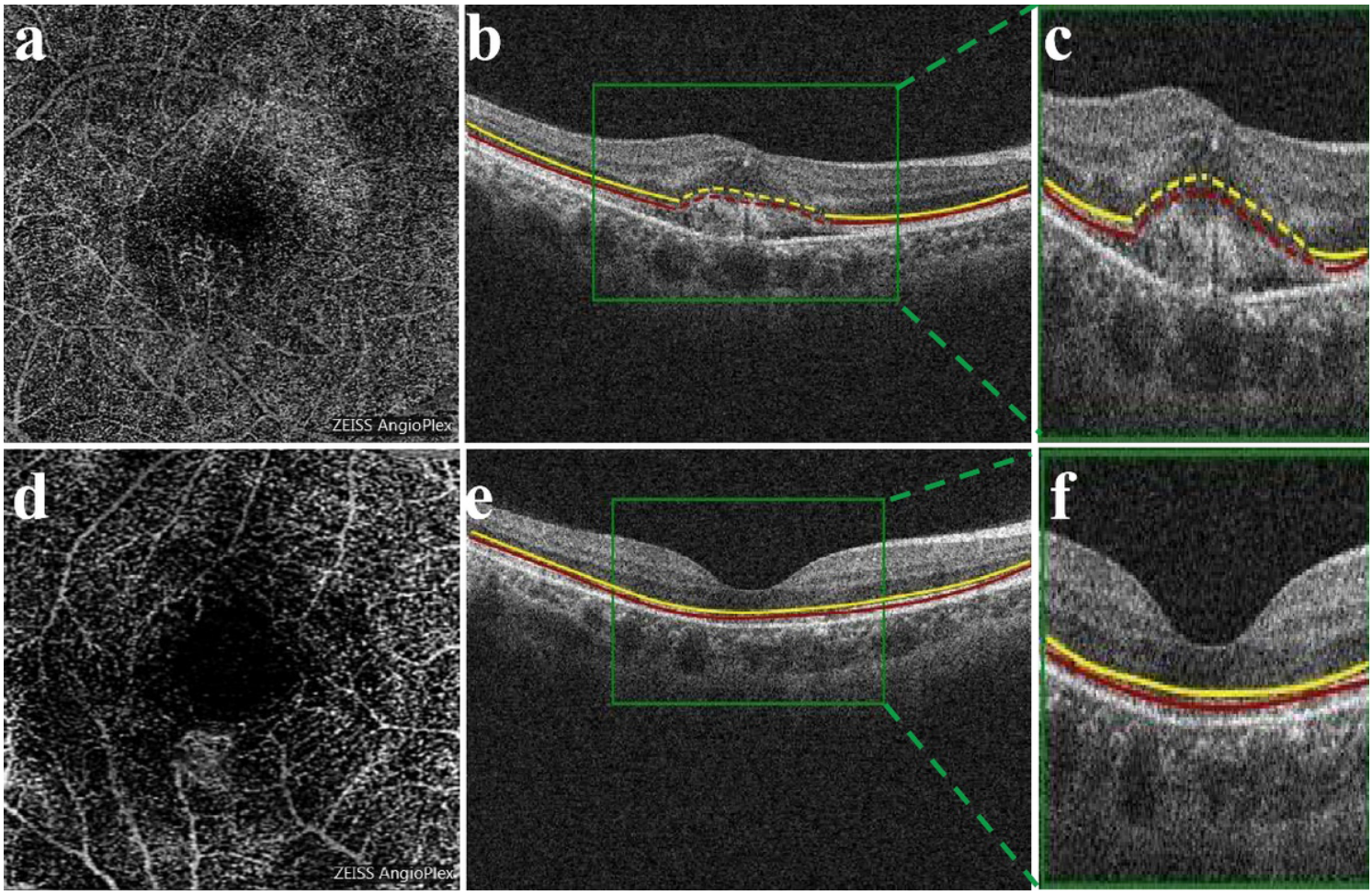

Figure 2

EZ tear optical coherence tomography angiography with “sea-fan” neovascularization visible in fovea before treatment (a). After treatment, the “clumped” neovascularization was located next to the parafovea (d). optical coherence tomography the EZ tear can be seen before treatment EZ tear and disappears (b, c) after treatment EZ integrity was restored (e, f).

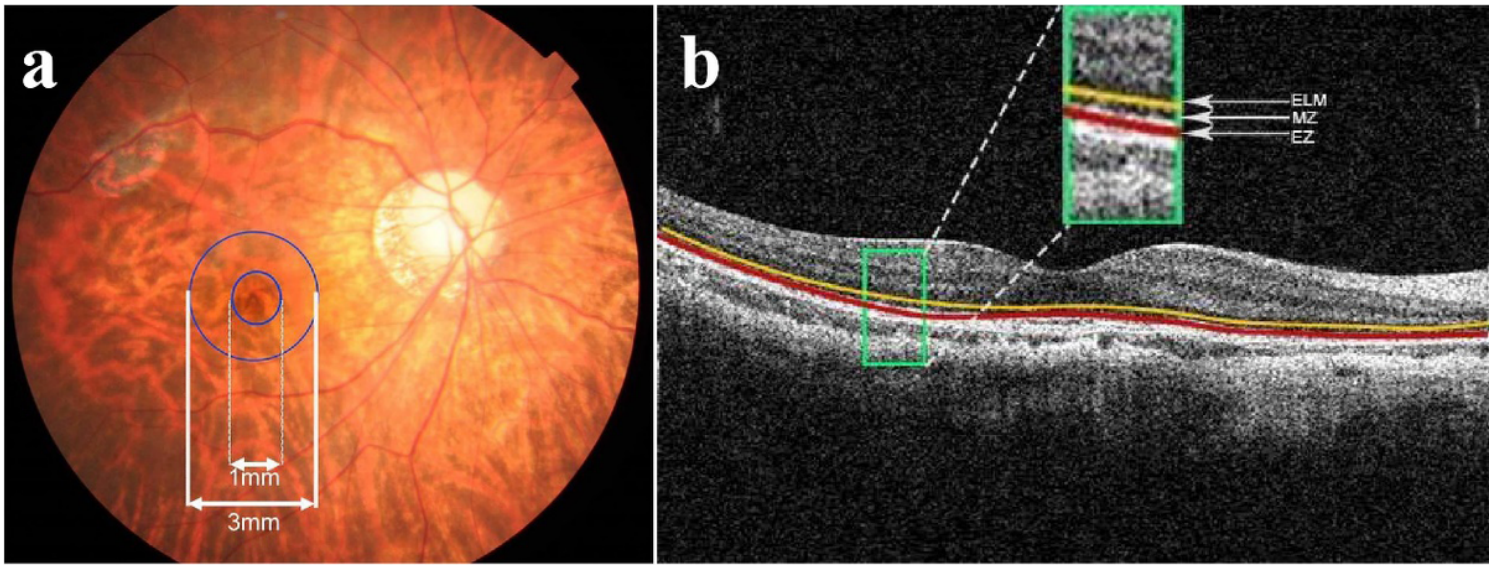

Figure 3

Macular area analyzed by optical coherence tomography. The macular area was divided into two subregions: fovea area of 1 mm in diameter, parafovea area of 1 to 3 mm (a). The borders of the fundus structures were segmented by automated algorithm. Algorithm performs segmentation and determines the lateral macular retinal sublayer (b, yellow line: external limiting membrane, red line: ellipsoidal zone).