Swept-Source Optical Coherence Tomography Correlations Between Retina and Choroid Before and After Vitrectomy for Epiretinal Membranes

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• PURPOSE: To describe retinal and choroidal morphology before and after surgery for epiretinal membranes (ERM) in swept-source OCT (SS-OCT). Additionally, to evaluate factors responsible for visibility of the suprachoroidal layer (SCL) and suprachoroidal space (SCS).

• DESIGN: Prospective consecutive case series.

• METHODS: Twenty-nine eyes of 29 patients with symptomatic, idiopathic ERM were included. Pars plana vitrectomy with ERM removal and ILM peeling was performed. We examined patients with SS-OCT twice preoperatively (9–12 months and 1 week before surgery), then postoperatively at 1 week and 6 and 12 months.

• RESULTS: Twelve months after surgery visual acuity improved to 20/50 (0.48 logMAR), statistically significantly higher as compared to 1 week preoperatively ($P < .001$). Preoperative loss of visual acuity was commonly associated with progression of deformation of the plexiform layers, as central retinal thickness (CRT) did not decrease in this period, nor did photoreceptor defects increase. Choroidal thickness decreased 6 months after surgery ($P = .02$) and remained stable until 12 months postoperatively ($P = .2$). The outer choroidoscleral boundary was irregular in 16 eyes preoperatively but only in 4 eyes 12 months post surgery. SCS and SCL were visible in 15 eyes.

• CONCLUSION: During the natural course of idiopathic ERM, deformation of the outer plexiform layer progresses and is associated with decreased visual acuity. Eyes with an initially irregular outer choroidoscleral boundary (CSB) recover visual acuity faster after vitrectomy with ILM peeling for ERM. Three factors are independently associated with the visibility of the SCS: disarrangement of plexiform layers, CRT, and multiple adhesion points between retina and ERM. (Am J Ophthalmol 2016;165: 100–107. © 2016 by Elsevier Inc. All rights reserved.)

EARLIER STUDIES PUT UNDER DEBATE THE PREDICTIVE value of various morphologic details of the retina, concluding that retinal thickness and photoreceptor layer and external limiting membrane integrity are the most important in estimating the outcome of idiopathic epiretinal membrane (ERM) surgery.[1–4] However, a recent meta-analysis revealed that many discrepancies exist between studies, and the need for a good predictive model still remains.[5]

Swept-source optical coherence tomography (SS-OCT) is an emerging technology that offers simultaneous, high-resolution, wide-field cross-sectional imaging of the vitreous, retina, and choroid. In a recent study we confirmed that in addition to the retina being altered in idiopathic ERM, the choroid is affected as well. We confirmed that choroidal thickness was decreased 3 months after surgery.[6] Further study is required to determine whether this decrease is long lasting.

Furthermore, we have previously noted several novel findings of the choroidal architecture, such as the suprachoroidal layer, suprachoroidal space, and possible irregularities of the outer choroidoscleral boundary.[7] The meaning of those findings was not exclusively studied.

The suprachoroidal layer consists of 2 bands, an inner hyperreflective band and an outer hyporeflective band. The hyporeflective band of the suprachoroidal layer probably corresponds to the suprachoroidal space. The suprachoroidal space was historically observed only in choroidal effusion syndrome. Recently, this layer was reported to be more frequently visible in hyperopia.[8] Furthermore, we confirmed this layer to be more often visible in macular diseases than in healthy eyes.[7] In patients with ERM without metamorphopsia and without vision complaints, we did not observe this layer in any of 20 analyzed eyes.[7] In another retrospective study of 21 eyes, examined before and after vitrectomy for idiopathic ERM, we noted this layer in 4 cases.[6] It was also observed that the suprachoroidal layer is even more often visible in eyes with full-thickness macular holes and vitreomacular traction syndrome.[9] The factors correlating with the visibility of this layer are still not precisely understood. With the advent of new technology enabling the introduction of drugs to the suprachoroidal space, the role of the visualization of the suprachoroidal layer and suprachoroidal space might be of growing importance.[10,11]

The aim of this prospective analysis was to estimate if there are factors associated with the visibility of the suprachoroidal layer in eyes with idiopathic ERM. An additional

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intention was to describe long-term changes in retinal and choroidal morphology, visualized with SS-OCT, before and after vitrectomy for idiopathic ERM.

METHODS

THIS IS A PROSPECTIVE CONSECUTIVE CASE SERIES OF 29 EYES of 29 patients with idiopathic ERM operated on in the year 2013. Inclusion criteria were symptomatic ERM scheduled for vitrectomy. We excluded eyes with membranes secondary to other pathologies such as retinal detachment, laser photocoagulation, or vascular occlusion and also excluded patients with previous ocular surgery (except noncomplicated cataract surgery performed at least 12 months before the beginning of the study), coexisting age-related macular degeneration, nicotine abuse, diabetes or glaucoma, or refractive errors above +2 and −2 diopter before cataract surgery. We obtained institutional ethics committee approval (Centrum Zdrowia Matki Polki, Lodz, Poland) and the study complied with the Declaration of Helsinki. Patients were recruited from the authors' outpatient department and signed informed consent for the study.

In all eyes we measured visual acuity (Snellen charts) and performed a complete ophthalmic examination and SS-OCT (DRI-Atlantis; Topcon, Tokyo, Japan) before surgery at 2 time points: 9–12 months and then 1 week before vitrectomy. Postoperatively, we examined the patients at 1 week, 6 months, and 12 months. In all cases, we performed a single line scan with a resolution of 1 μm, with a length of 12 mm. Focal central retinal thickness was measured manually as the distance between the internal limiting membrane (ILM) and the retinal pigment epithelium (RPE). Choroidal thickness was measured manually (by Z.M. and K.O.) on black-and-white images, between the line representing RPE (the outermost hyperreflective retinal layer) and the outer choroidoscleral boundary (the outer hyperreflective line of the choroid). The software included a caliper for manual measurements. Irregularities of the inner and outer plexiform layers were categorized as either striae or waves[12] (Figure 1). The extent of adhesion between ERM and the retina surface was categorized as either multiple adhesion points to the retina (Figure 1, Top; Figure 2, Center top) or flat adhesion without evident anteroposterior traction[13] (Figure 1, Top; Figure 3). Additionally, we analyzed the visibility of the suprachoroidal space (Figure 3), the regularity of the outer choroidoscleral boundary[3] (regular vs irregular) (Figure 4), defects of the photoreceptors, and central hyperreflective deposits (Figure 1, Bottom, star). We used SigmaStat (Systat, London, UK) for Windows for statistical analysis.

• **SURGICAL TECHNIQUE:** Two experienced surgeons (J.N., Z.M.) performed all of the operations. Core vitrectomy and Membrane Blue Dual staining (0.06% solution for 1 minute) were performed. ERM peeling within the vascular arcades followed. Then, a second staining was performed for 30 seconds. If present, the second layer of the ERM was then peeled. If not, the ILM was grasped with ILM forceps and peeled off in a circular fashion (Supplemental Video, available at AJO.com). In cases of multilayered membranes, staining was applied until the ILM was peeled. No tamponade was used in any case.

RESULTS

TWENTY-NINE PATIENTS (23 WOMEN AND 6 MEN) WITH A mean age of 68 years were included in this study. Four eyes were pseudophakic at the beginning of the study; 6 other eyes had phacoemulsification performed in the first year after vitrectomy.

• **VISUAL ACUITY:** There was a statistically significant decrease in the preoperative mean visual acuity from 20/63 to 20/160 (from 0.48 to 0.85 logMAR; 0.42 to 0.17 Snellen) ($P < .001$) during the 9–12 months preoperative observation period. There was a statistically significant improvement in the mean visual acuity from 20/125 (0.81 logMAR; 0.2 Snellen) 1 week after surgery ($P = .69$) to 20/63 (0.54 logMAR; 0.34 Snellen) 6 months later ($P < .001$) and 20/63 (0.48 logMAR; 0.41 Snellen) 12 months after vitrectomy ($P < .001$). Final visual acuity improved statistically significantly from the values obtained 1 week before surgery ($P = .01$) but did not differ from visual acuity noted 9–12 months preoperatively. There was a trend toward correlation between final visual acuity and central retinal thickness 1 week preoperatively, but without strong statistical significance ($P = .08$) (Table 1).

• **DETAILS OF RETINAL MORPHOLOGY:** Central retinal thickness did not increase significantly during the preoperative period ($P = .4$) (Table 1). Photoreceptor defects did not increase in any case, nor did the hyperreflective deposits under the fovea. We observed that the outer plexiform layer and the inner plexiform layer are disarranged in all cases of ERM. However, the stage of disarrangement differed. At the initial visit we observed irregularities in the form of hyperreflective striae at the outer border of the inner plexiform layer and outer plexiform layer in all eyes (Figure 1, Top).[9] In 12 eyes, besides visible striae, at some spots the disarrangement was more pronounced and wavy. Thus we called this form of disarrangement "hyperreflective waves" at the outer border of the inner plexiform layer and outer plexiform layer (Figure 1, Bottom). Central retinal thickness and mean retinal thickness were significantly higher ($P = .007$, $P = .008$, respectively), and visual acuity was significantly lower ($P = .049$), in eyes with these hyperreflective waves when compared to eyes with hyperreflective striae only. The irregularities of the plexiform

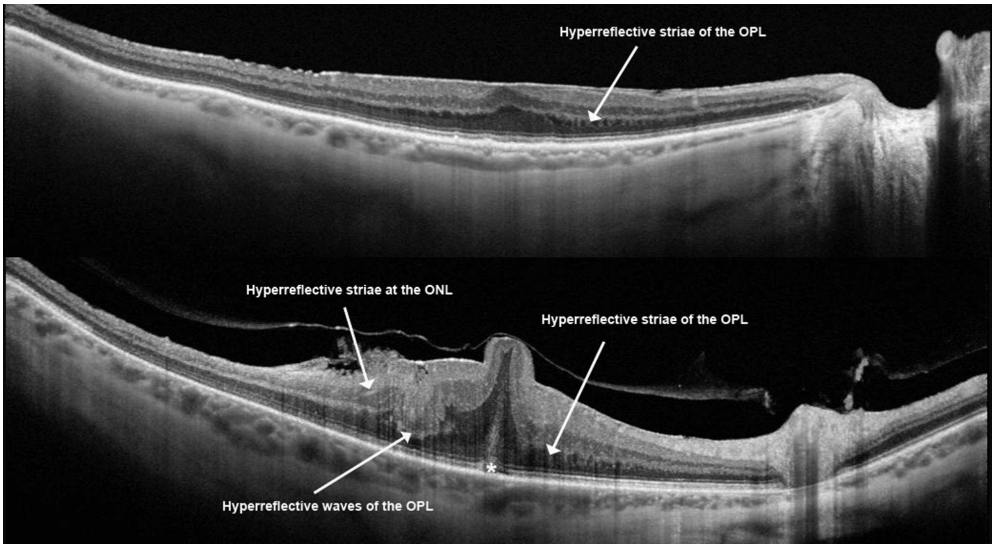

FIGURE 1. Hyperreflective striae (A) vs hyperreflective waves (B) of the outer plexiform layer in swept-source optical coherence tomography (SS-OCT) in idiopathic epiretinal membranes. (A-Top) SS-OCT of an 82-year-old man with idiopathic epiretinal membrane. Visual acuity was 0.52 logMAR (0.3 Snellen) before surgery and central retinal thickness was 388 μm. Hyperreflective striae are visible (arrows). These striae have similar reflectivity to outer and inner plexiform layers, but seem to infiltrate the nuclear layers. ONL = outer nuclear layer; OPL = outer plexiform layer. (B-Bottom) SS-OCT of a 41-year-old man with idiopathic epiretinal membrane. Visual acuity was 1 logMAR (0.1 Snellen) before surgery and central retinal thickness was 841 μm. Nasal to the fovea, hyperreflective striae are visible (arrows). These striae have similar reflectivity to plexiform layers, but seem to infiltrate the nuclear layers. Additionally, temporal to the fovea, the plexiform layers have a wavy, irregular contour. The white star indicates a subretinal hyperreflective deposit.

layers always increased during the preoperative follow-up and 7 eyes with hyperreflective striae developed additional hyperreflective waves (Figure 3, upper box) developed additional hyperreflective waves (Figure 3, lower left box). After surgery, those irregularities of the outer plexiform layer tended to normalize, and the outer plexiform layer was completely regular in most eyes 12 months after surgery (Table 2).

In 11 eyes we observed multiple adhesion points between the retina and the ERM (Figure 2, Top); in the remaining 15 eyes ERM was flat, covering the retinal surface (Figure 1, Top; Figure 3, Top, Bottom). Postoperatively, we observed more frequently hyperreflective dots in the outer nuclear layer (Figure 2, Bottom) in eyes with multiple adhesion points. These had similar reflectivity to the outer plexiform layer ($P = .01$) (Table 2).

• **DETAILS OF CHOROIDAL MORPHOLOGY:** The suprachoroidal layer and suprachoroidal space were visible in 15 eyes (Figures 2 and 3). Multiple regression analysis revealed that there were 3 independent factors associated with the visibility of the suprachoroidal layer. Firstly, this layer is more often visible in eyes with ERM in which the outer plexiform layer forms waves on its outer surface (Figure 2, Top), when compared to eyes with solely hyperreflective striae at the outer surface of the outer plexiform layer (Figure 1, Top) ($P = .02$). Secondly, it is associated with multiple adhesion points to the retina ($P = .001$) (Figure 2, Top); and thirdly, it correlates with central retinal thickness before surgery ($P = .006$). The suprachoroidal layer and suprachoroidal space remained visible in the same eyes during the entire follow-up period.

An irregular choroidoscleral boundary was observed in 16 eyes before surgery (Figure 4, Right). These patients had higher postoperative visual acuity ($P = .03$) at month 6, but this correlation diminished by the end of the follow-up period ($P = .3$). The outer choroidoscleral boundary remained irregular in 16 eyes 1 week after surgery, reducing to 10 eyes 6 months after surgery and 4 eyes during the final examination, 12 months after surgery.

Choroidal thickness remained unchanged during the preoperative period, but a statistically significant decrease was noted at postoperative sixth month ($P = .02$), and this remained stable until 12 months postoperatively ($P = .2$). Choroidal thickness correlated with age ($P = .007$).

DISCUSSION

THE CHOROIDOSCLERAL BOUNDARY MAY BE PRECISELY delineated with SS-OCT. Data suggest that patients with an irregular outer choroidoscleral boundary (55% of our cases) recovered visual function more rapidly after surgery

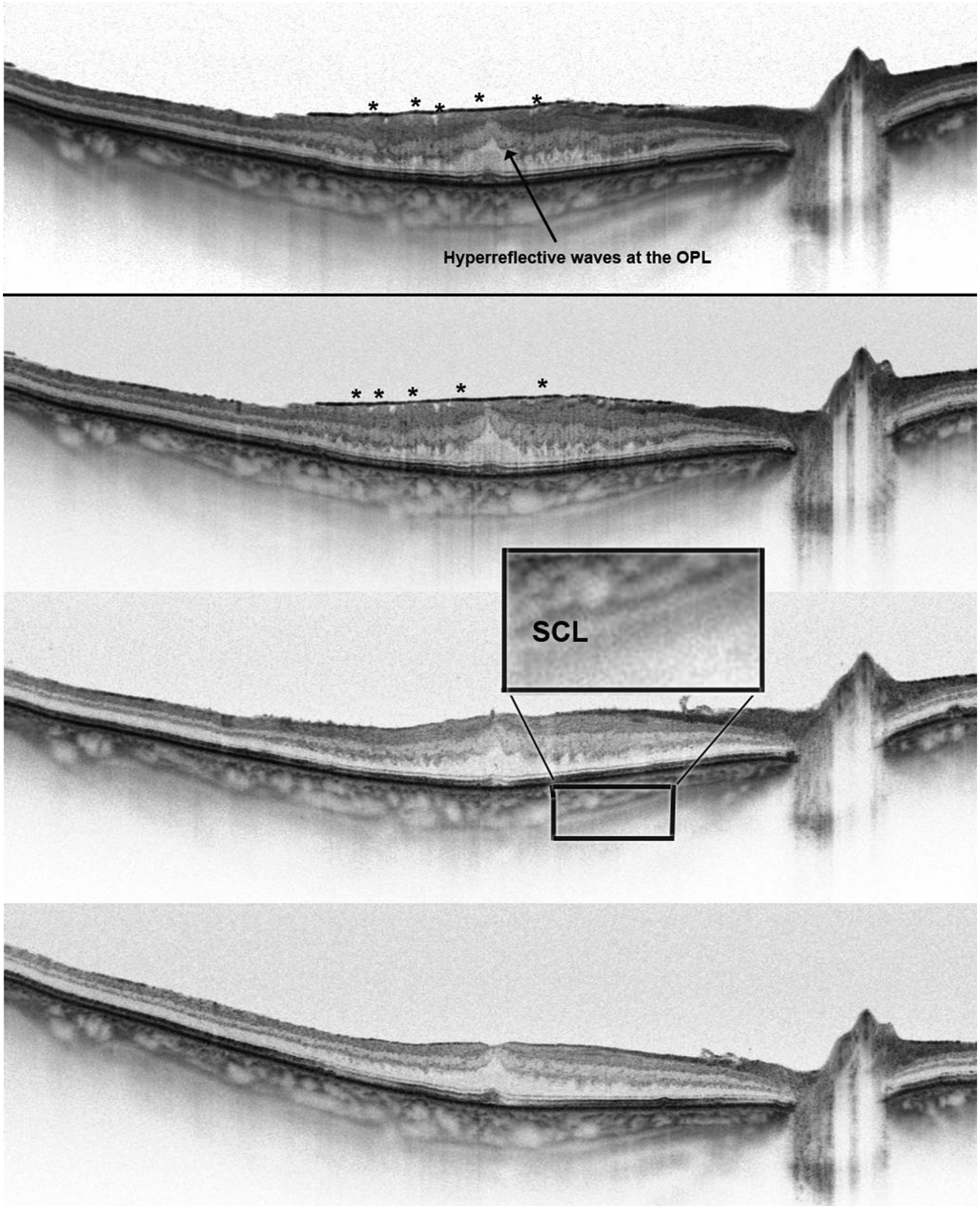

FIGURE 2. Swept-source optical coherence tomography of idiopathic epiretinal membrane with multiple adhesion points to the retina (black stars). The suprachoroidal layer is visible. (Upper) Twelve months before surgery. (Center top) One week before surgery. (Center bottom) One week after surgery. (Lower) Twelve months after surgery. OPL = outer plexiform layer; SCL = suprachoroidal layer.

for idiopathic ERM when compared to those with a regular outer choroidoscleral boundary. The suprachoroidal layer (also called lamina fusca or lamina suprachoroidea) may be visualized more often in eyes with more advanced disease and possibly longer-lasting tangential traction (increased retinal thickness, more disarranged plexiform layers, and multiple adhesion points between retina and vitreous). Moreover, choroidal thickness decrease was noted shortly after vitrectomy for idiopathic ERM. This decrease was stable during the first 12 months after surgery.

Both SS-OCT and enhanced depth imaging OCT enable the visualization of the suprachoroidal space and suprachoroidal layer in healthy eyes and in several macular conditions. The suprachoroidal layer consists of 5–10 layers of pigmented cells interspersed with multiple layers of flattened processes of fibroblastic cells.[14] The suprachoroidal layer is visible as 2 bands at the choroidoscleral boundary (an upper hyperreflective line and a lower hyporeflective line). We estimated that the lower hyperreflective line corresponds to the suprachoroidal space, which until recently had only

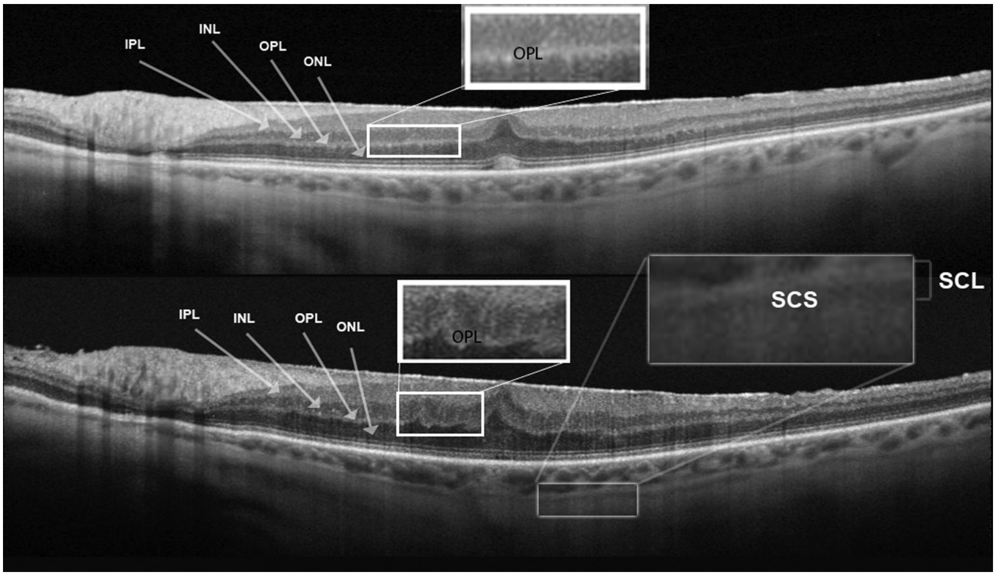

FIGURE 3. Preoperative follow-up of a 67-year-old woman with idiopathic epiretinal membrane with flat adhesion to the retinal surface. (Top) Swept-source optical coherence tomography 12 months before surgery. Visual acuity was 0.15 logMAR (0.7 Snellen). Striae at the outer border of the outer plexiform layer are visible (box). (Bottom) Swept-source optical coherence tomography 1 week before surgery. Visual acuity decreased to 0.82 logMAR (0.15 Snellen). No photoreceptor defects are observed. Striae at the outer border of the outer plexiform layer progressed and formed waves. Irregularities of the inner plexiform layer are seen (box). The enlarged box presents suprachoroidal layer (SCL) and suprachoroidal space (SCS). OPL = outer plexiform layer; ONL = outer nuclear layer; IPL = inner plexiform layer; INL = inner nuclear layer.

been observed in eyes with effusion syndrome.[7] The factors associated with the visibility of the suprachoroidal layer and suprachoroidal space are not completely understood. It was suggested that the suprachoroidal layer is observed more often in hyperopia.[8] Our recent study confirmed that traction exerted by the posterior hyaloid may also contribute to the visibility of the suprachoroidal layer.[9]

We found 3 independent factors associated with the visibility of the suprachoroidal layer and suprachoroidal space. Multivariate analysis confirmed that the suprachoroidal layer and suprachoroidal space are more frequently visible in eyes with multiple adhesion points between the retina and ERM (Figure 2), in eyes with increased central retinal thickness, and in those with a wavy (more irregular) outer border of the plexiform layers (Figure 1, Bottom). Based on these findings, we assume that the visibility of the suprachoroidal space and suprachoroidal layer in SS-OCT may correspond to prolonged tangential traction to the macula caused by more advanced ERM. However, during the course of the study, the suprachoroidal space did not appear as a new finding in any of the cases we studied, nor did it disappear from any eyes in which it was present at the beginning of the study. This might suggest that some additional factors play a role in the visibility of the suprachoroidal space, or that the observation period was too short.

The role of imaging suprachoroidal space may be of importance, especially since suprachoroidal drug delivery is becoming more widely explored. Theoretically, it is the preferred site for drug delivery to the retina and choroid as it enables diffusion of the drug to the choroid and noninterference with optical pathways. Experimental studies confirmed that during suprachoroidal drug delivery, injected substances reach higher concentrations than when other routes are used.[15] This is probably because natural kinetic barriers such as the sclera or ILM are omitted. Suprachoroidal injections, in contrast to intravitreal injections, do not cause immune reactions; thus this injection site might enable us to avoid serious complications after intravitreal injection, such as endophthalmitis.[16] There are data that the clearance of drugs from the suprachoroidal space is fast; thus new methods for the sustained release of drugs in this space are being explored.[17,18]

The choroidoscleral boundary may either be regular and follow the natural oval shape of the globe, as in most healthy eyes, or be irregular. We have observed irregular choroidoscleral boundary in ERM and also in earlier studies of other vitreoretinal interface diseases, but we did not evaluate the finding.[6,7,9] Here, we observed that visual acuity recovers faster in eyes with a preoperatively irregular choroidoscleral boundary. We assume that an irregular outer choroidoscleral boundary might be a result of focal dilation of particular choroidal vessels. Arteries dilate in hypoxic conditions. It must be considered that the natural environment inside the eye has 5% oxygen, vs 21% in the air that surrounds us.[19] When tissue is exposed to either increased or decreased oxygen levels

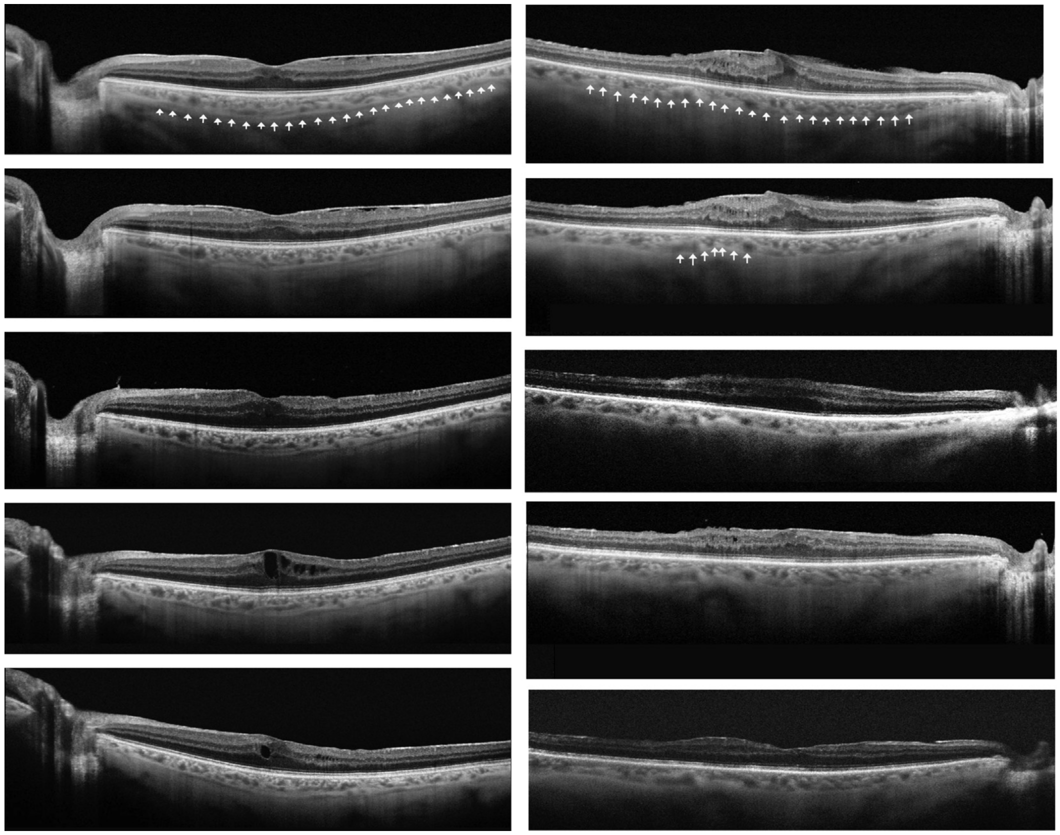

FIGURE 4. **Swept-source optical coherence tomography in idiopathic epiretinal membranes in 2 eyes: (Right column) eye with an irregular choroidoscleral boundary; and (Left column) eye with a regular outer choroidoscleral boundary. (Upper images) Twelve months before surgery; (Center top images) 1 week before surgery; (Center images) 1 week after surgery; (Center bottom images) 6 months after surgery; (Bottom images) 12 months after surgery.**

TABLE 1. Visual Acuity and Retinal and Choroidal Thickness Changes Before and After Vitrectomy for Idiopathic Epiretinal Membranes

	Visual Acuity (Snellen)	Visual Acuity (logMAR)	Central Retinal Thickness (μm)	Maximum Retinal Thickness (μm)	Central Choroidal Thickness (μm)
6–12 months before surgery	0.42	0.48	475	514	221
1 week before surgery	0.17	0.85	468	522	222.7
1 week after surgery	0.2	0.81	434	502	218
6 months after surgery	0.34	0.54	376	442	213
12 months after surgery	0.41	0.48	357	430	209

from those it is used to, neural stress and the destruction of neural tissue may occur.[20] It has also earlier been speculated that hypoxia may have a role in idiopathic ERM formation.[21–23] Excising the vitreous, which consumes oxygen, means that ocular tissues are exposed to a more highly oxygenated environment. As vessels constrict in increased tension of oxygen, the decrease of choroidal thickness maintained 1 year after vitrectomy in our group is not surprising. On the other hand, in another study we did not notice changes in choroidal thickness after macular hole surgery.[9] The exact relationship between these findings requires further study. The fact that visual acuity recovered faster in patients with preoperative irregular choroidoscleral boundary might suggest that the varying lumen of choroidal vessels may contribute to the self-healing capacities of the eye. Twelve months after surgery, this correlation was not further statistically significant, but the choroidoscleral boundary had normalized in most cases by then.

Pilli and associates were the first to report on hyperreflective striae within retinal layers in OCT. They reported that those striae appear more often in eyes with decreased visual acuity and that those striae disappear after surgery.[12] Our study confirms these findings. We additionally observed that hyperreflective striae tend to progress if ERM is not treated and develop to hyperreflective waves of particular retinal layers. In our study, visual acuity was significantly

TABLE 2. Retinal and Choroidal Morphology Before and After Vitrectomy for Idiopathic Epiretinal Membrane

	6–12 Months Before Surgery	1 Week Before Surgery	1 Week After Surgery	6 Months After Surgery	12 Months After Surgery
Hyperreflective striae at the outer plexiform layer	100%	100%	100%	16/29	0/29
Hyperreflective dots in outer nuclear layer	0	0	8/29	6/29	3/29
Wavy outer plexiform layer	12/29	19/29	0/29	0/29	0/29
Visible suprachoroidal layer and space	15/29	15/29	15/29	15/29	15/29
Irregular choroidoscleral boundary	8/29	16/29	16/29	10/29	4/29
Multiple adhesion points between retina and epiretinal membrane	11/29	11/29	-	-	-
Photoreceptor defects	3/29	3/29	3/29	2/29	2/29
Highly reflective foveal region	4/29	4/29	-	-	-

lower in eyes with more severe plexiform layer disarrangement (waves at the plexiform layers when compared to striae). The irregularities disappear up to 12 months after surgery. Uji and associates also observed irregularities of particular retinal layers and referred to this as reduced "parallelism." They reported that parallelism is more homogenous than retinal thickness in healthy eyes and correlates with metamorphopsia better than retinal thickness in eyes with idiopathic ERM.[24]

Oxygenation is a critical factor in various sight-destroying diseases such as cataract, glaucoma, age-related macular degeneration, and diabetes. The human retina is supplied with oxygen by both choroidal and retinal vasculature. In the fovea, which is localized in the middle of the avascular zone, only the choroid supplies the retina with oxygen and nutrients. The 3 main oxygen-consuming departments in the retina are photoreceptor inner segments, outer plexiform layer, and the deeper region of the inner plexiform layer.[25,26] The outer plexiform layer consists of processes of bipolar and horizontal cells invaginated between the terminals of photoreceptors. Oxygen diffuses from the choroid to the outer plexiform layer.[27] During the natural course of idiopathic ERM changes in the morphology of the outer retinal layers progress, even if loss of visual acuity is slow. This may prevent complete restoration of visual acuity after surgery. We observed patients with idiopathic ERM for 6–12 months before surgery. In this period the central retinal thickness remained unchanged ($P = .4$) but visual acuity significantly decreased ($P < .001$). Thus, we suspect that other morphologic changes must be causative factors for this visual acuity loss. No new photoreceptor defects were observed during this time, but we noted an increase in the deformation of the outer plexiform layer (Figure 3). This would confirm the hypothesis from Gass that the decrease in visual acuity in ERM is mostly due to alternations in the outer retinal layers.[28] Other authors also observed that the thickness of particular retinal layers, among them outer plexiform layer, outer nuclear layer, and inner nuclear layer, are significantly higher in ERM cases than in healthy subjects.[29] Electrophysiological studies confirmed that decreased visual acuity is secondary to changes in both the inner and the outer retina.[30]

In conclusion, during the natural course of idiopathic ERM, deformation of the outer plexiform layer progresses and this is associated with decrease in visual acuity. Multivariate analysis confirmed that outer plexiform layer deformation, central retinal thickness, and multiple adhesion points between retina and ERM were all independently associated with the visibility of the suprachoroidal space. Additionally, after vitrectomy with ILM peeling for ERM, eyes with an irregular choroidoscleral boundary recover visual acuity faster than those with a regular choroidoscleral boundary.

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