Insights Into Epiretinal Membranes: Presence of Ectopic Inner Foveal Layers and a New Optical Coherence Tomography Staging Scheme

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• PURPOSE: To describe the presence of continuous ectopic inner foveal layers associated with epiretinal membranes (ERMs) and to present a new optical coherence tomography (OCT) staging system of ERMs.

• DESIGN: Retrospective multicenter observational case series.

• METHODS: Clinical charts and spectral-domain OCT images of 194 eyes of 172 consecutive patients diagnosed with ERMs were reviewed and analyzed.

• RESULTS: The presence of continuous ectopic inner foveal layers was identified in 63 out of 194 eyes (32.5%) and this morphology was significantly associated with lower visual acuity. ERMs were divided into 4 stages. Stage 1 (43 out of 194 eyes, 22.1%) ERMs were mild and thin and a foveal depression was present. Stage 2 (88 out of 194 eyes, 45.4%) ERMs were associated with widening of the outer nuclear layer and loss of the foveal depression. Stage 3 (51 out of 194 eyes, 26.3%) ERMs were associated with continuous ectopic inner foveal layers crossing the entire foveal area. In stages 1, 2, and 3 all retinal layers were clearly defined on OCT. Stage 4 ERMs (12 out of 194 eyes, 6.2%) were thick and associated with continuous ectopic inner foveal layers. In addition, retinal layers were disrupted. Visual acuity progressively declined from stage 1 through stage 4 ($P < .001$).

• CONCLUSIONS: The presence of continuous ectopic inner foveal layers in ERMs is a newly described OCT finding associated with significant vision loss and is an essential element of a novel OCT-based grading scheme of ERMs that may influence visual prognosis. (Am J Ophthalmol 2017;175:99–113. © 2016 Elsevier Inc. All rights reserved.)

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EPIRETINAL MEMBRANE (ERM) FORMATION IS A COMmon retinal condition characterized by fibrocellular proliferation at the vitreoretinal interface, above the internal limiting membrane, with a prevalence that ranges between 2.2% and 28.9%, which increases with aging.[1–3]

ERMs are typically idiopathic, but can also be associated with retinal vascular or inflammatory diseases, trauma, tumors, intraocular surgery, or retinal detachment.[4] The precise pathophysiology of this clinical entity is not completely defined, although the proliferation of hyalocytes in the setting of anomalous posterior vitreous detachment and vitreoschisis has been suggested as a possible mechanism in the early development of idiopathic ERMs.[4]

Various classification schemes have been proposed,[5–7] including the original categorization by Gass, the most widely used.[7] Owing to dramatic improvements in image resolution and data acquisition speed, spectral-domain optical coherence tomography (SDOCT) has driven a transformative change in the study of ERMs, providing rapid cross-sectional imaging of the retina with near-histologic detail. OCT has become the gold standard in the evaluation of ERMs, but despite its universal application, a globally accepted OCT-based classification system is still lacking.[8]

In recent years OCT studies of the foveal microstructure associated with ERMs have flourished in order to identify the anatomic changes that may cause loss in visual acuity,[9–17] including disruption of the inner segment ellipsoid zone and photoreceptor outer segments.[9–12] More recently attention has shifted to the study of the inner retinal anatomy. In this regard, various reports have shown a significant association of the thickness of the inner retinal layers with vision loss in eyes with ERM.[13–17]

This study performed an in-depth SDOCT analysis of the development and evolution of ERMs and identified novel morphologic features that impacted visual acuity prognosis and were critical in the development of a new OCT-based staging system.

METHODS

A RETROSPECTIVE, OBSERVATIONAL, AND CONSECUTIVE chart review of patients diagnosed with ERM and seen by

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2 retina specialists (J.P.H. and M.S.F.) between January 1, 2010 and January 31, 2016 at the Stein Eye Institute, University of California Los Angeles and the Ramon y Cajal University Hospital was performed. This study was approved by the Institutional Review Board of the University of California Los Angeles and the Ramon y Cajal University Hospital, and the research project adhered to the tenets of the Declaration of Helsinki. Cases were identified by a medical billing record search, using the International Statistical Classification of Diseases and Related Health Problems, Ninth Revision (ICD-9) diagnosis code 362.56 for macular pucker.

The inclusion criterion was the presence of idiopathic unilateral or bilateral ERM. Exclusion criteria are summarized in Table 1. Both paper-based and electronic records were carefully reviewed to ascertain demographic and medical information of all the included patients. Best-corrected visual acuity (BCVA) was recorded at each visit and reported in Snellen fraction and was converted into logarithm of the minimal angle of resolution (logMAR) values for statistical analysis.

OCT images were obtained with the Spectralis SDOCT with eye-tracking dual-beam technology (Heidelberg Engineering GmbH, Heidelberg, Germany) and reviewed with the Heidelberg Eye Explorer (version 1.8.6.0) using the HRA/Spectralis Viewing Module (version 5.8.3.0).

Additionally, 43 patients were also imaged with OCT angiography (OCTA) using either the AngioPlex Cirrus 5000 HD-OCT system (Carl Zeiss AG, Oberkochen, Germany), with a light source at 840 nm, a bandwidth of 90 nm, and an A-scan rate of 68 000 scans per second (24 patients), or the AngioVue Imaging System (Optovue Inc, Freemont, California, USA), with a light source at 840 nm, a bandwidth of 45 nm, and an A-scan rate of 70 000 scans per second (19 patients). All patients imaged with OCTA underwent the 3 × 3-mm macular cube scanning protocol in each eye, containing 245 × 245 scans with the AngioPlex Cirrus 5000 and 304 × 304 scans with the AngioVue Imaging System. Each scan was automatically segmented by the AngioVue and AngioPlex software to visualize the superficial and deep retinal capillary plexus of the retina. The foveal avascular zone (FAZ) was qualitatively evaluated in all cases, and the presence of macular-foveal capillaries, defined as the presence of polygonal or straight anastomotic capillary segments crossing the entire foveal area, was assessed.[18,19]

Spectralis OCT scan patterns were used for all quantitative measurements. All eyes underwent at least 2 forms of OCT imaging at each visit: 19 B-scans administered over an area of 20 × 15 degrees with each B-scan spaced 242 μm apart and a single high-definition horizontal B-scan at 30 degrees. In addition, 51 eyes underwent high-density scanning over an area of 15 × 10 degrees with 97 B-scans each spaced 31 μm apart.

The thickness of the outer nuclear layer and ectopic inner foveal layers (defined below) in the foveal region was measured manually with the "caliper" function of the Heidelberg instrument, as shown in Figure 1. In all cases, the images were adjusted to an aspect ratio of 1:1 μm. Mean central foveal thickness as measured was obtained with the automated "thickness map" function of the Heidelberg Eye Explorer.

TABLE 1. Study of Ectopic Inner Foveal Layers in Epiretinal Membranes: Exclusion Criteria

Exclusion Criteria
• Any previous intraocular surgery with the exclusion of uncomplicated phacoemulsification
• History of retinal detachment
• Intermediate or advanced age-related macular degeneration
• History of choroidal neovascularization of any etiology
• Central serous chorioretinopathy
• Proliferative diabetic retinopathy
• Nonproliferative diabetic retinopathy with history of clinically significant diabetic macular edema
• Macular teleangectasias
• Tractional and degenerative lamellar macular holes
• History of central or branch retinal vein occlusion and central or branch retinal artery occlusion
• Advanced glaucoma, or optic neuropathy of any kind
• History of inflammatory eye disorders
• History of Irvine-Gass syndrome
• Visually significant cataract
• History of endophthalmitis or any other intraocular infection
• Retinal dystrophies
• Foveal hypoplasia/fovea plana
• History of ocular trauma
• Any other potential cause of vision loss other than epiretinal membranes

ERMs on OCT were defined as discrete, irregular, and hyperreflective lines above the inner retinal surface, frequently accompanied by wrinkling of the underlying retina with hyporeflective spaces between the ERM and the internal limiting membrane (Figure 2, Top, Center, Bottom). Retinal layers were identified according to the lexicon proposed by the IN•OCT Consensus.[20]

Continuous ectopic inner foveal layers were defined on OCT as the presence of a continuous hyporeflective or hyperreflective band, extending from the inner nuclear layer (INL) and inner plexiform layer (IPL) across the foveal region and visible in all OCT scans centered in the fovea (Figure 2, Top).

Disruption of the inner segment ellipsoid zone was defined as a discontinuous ellipsoid band in the foveal region, while the presence of a round or diffuse hyperreflective area between the ellipsoid zone and the cone outer segment tip line at the center of the fovea was defined as the "cotton ball" sign, as described by Tsunoda and associates,[21] and was not considered a disruption of the ellipsoid zone (Figure 2, Center).

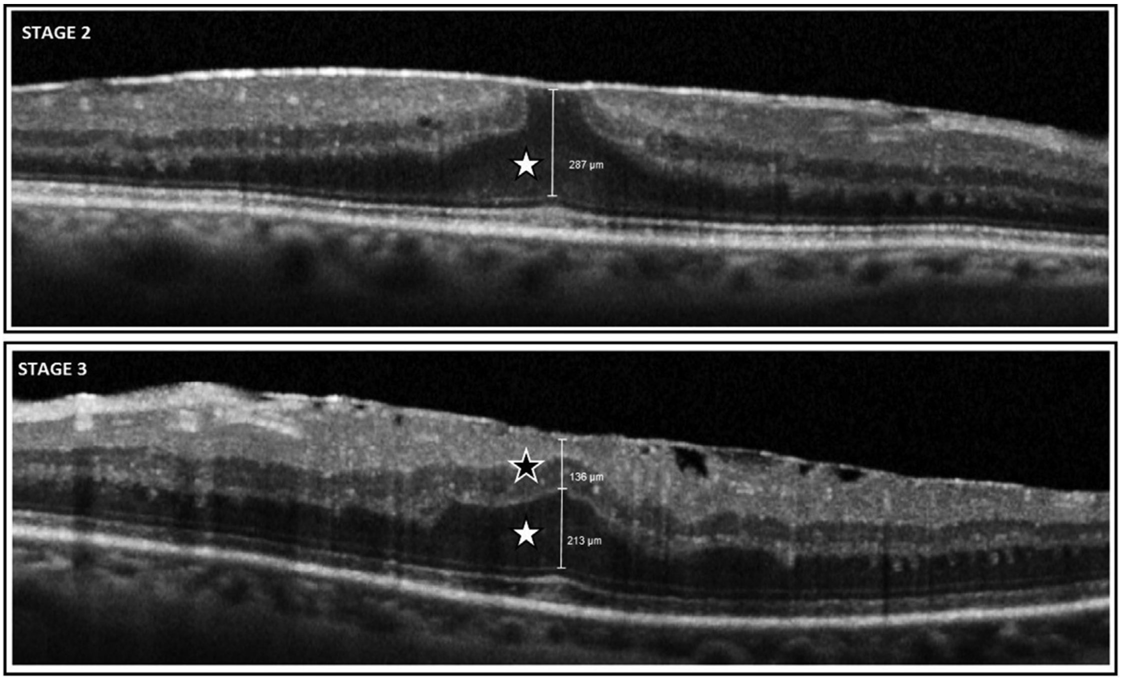

FIGURE 1. Optical coherence tomography measurements in epiretinal membranes. (Top) Measurement of the outer nuclear layer thickness in the central fovea (white star) in stage 2 epiretinal membrane. A straight line is traced with the caliper tool from the external limiting membrane to the internal limiting membrane. (Bottom) Measurement of the outer nuclear layer thickness in the central fovea (white star) in a stage 3 epiretinal membrane. The upper limit of the outer nuclear layer is the inferior border of the ectopic inner foveal layers. The thickness of the ectopic inner foveal layers (black star) is measured tracing a straight line from the upper limit of the outer nuclear layer to the internal limiting membrane.

The presence of hyporeflective intraretinal cystoid spaces in the setting of ERMs was considered as cystoid macular edema (CME) of presumably tractional origin, as defined by Johnson (Figure 2, Bottom).[22]

All OCT and OCTA images were qualitatively and quantitatively reviewed by 2 independent and masked observers (A.G., R.A.L.), and possible disagreements were resolved by a third observer (D.S., M.S.F.).

All the analyses were carried out using the SPSS V.15.0 and R package mgcv (R Development Core Team, available online at http://www.r-project.org). Descriptive statistics were first calculated for all variables of interest. Mean and standard deviation (SD) values were calculated for continuous variables, while frequency and percentage were calculated for categorical variables. Parametric and nonparametric test (Kruskal-Wallis, analysis of variance, Wilcoxon signed rank test) were used to compare quantitative variables, and χ^2 test was used to compare categorical variables. Univariate and multivariate logistic regression was used to evaluate associations of the ectopic inner foveal layers with BCVA. In the ERM staging process, the Cohen kappa coefficient was used to measure interobserver agreement for categorical variables. Differences were reported with 95% confidence intervals. A P value <.05 was considered statistically significant.

RESULTS

WE REVIEWED THE CLINICAL CHARTS OF 784 PATIENTS DIAGnosed with ERMs, of which 612 were excluded owing to the presence of 1 or more exclusion criteria. Of the remaining 172 patients (194 eyes) that met the inclusion criteria and were enrolled into the study, 97 (56.4%) were male and 75 (43.6%) were female. Mean age of the patients was 70.12 ± 8.7 years (range 36–90), and 22 out of 172 (12.8%) presented with bilateral ERM. Patients with unilateral ERM (150 out of 172, 87.2%) were found to have a normal foveal morphology in the fellow unaffected eye.

Of the 194 eyes with ERMs, 63 (32.5%) were directly scheduled for surgery after the first visit, without further follow-up, while the remaining 131 eyes (67.5%) were monitored for a mean period of 22.2 ± 18.3 months (range 3–84 months).

The presence of ectopic inner foveal layers extending continuously from the INL and IPL across the central fovea was diagnosed in 63 out of 194 eyes (32.5%), and the OCT reflectivity was similar to that of the normal INL (hyporeflective) and IPL (hyperreflective) in the perifoveal region.

In the majority of the ERMs (182 out of 194 eyes, 93.8%), all retinal layers were clearly defined and identified with OCT analysis, while in 12 out 194 cases (6.2%), the boundaries between the different retinal layers could not

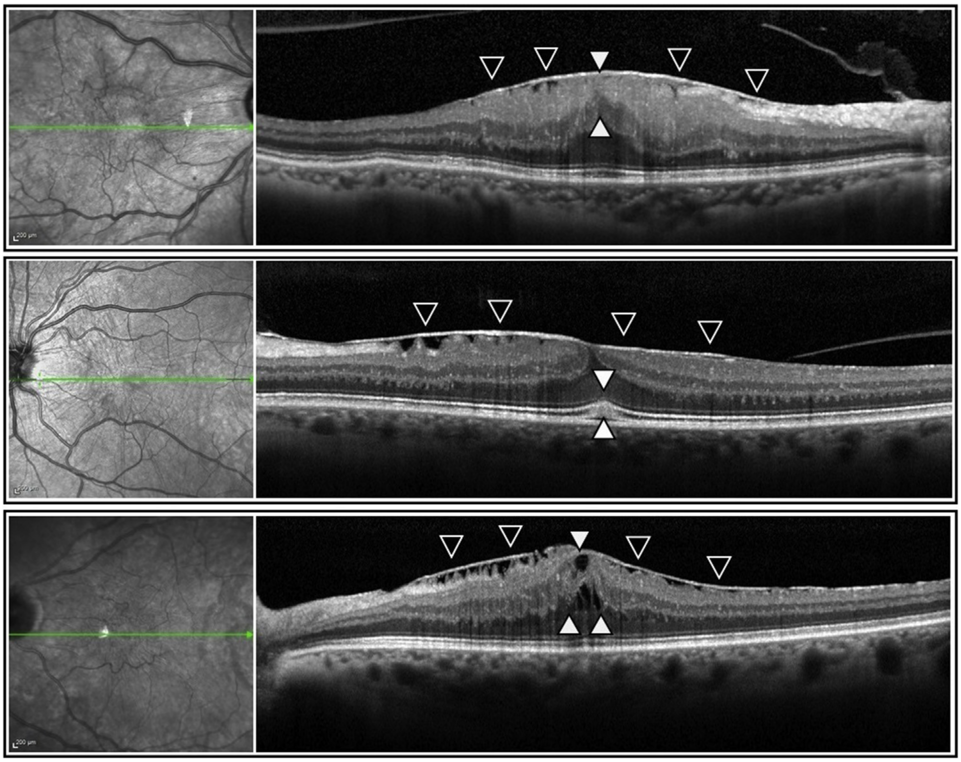

FIGURE 2. Morphologic characteristics of epiretinal membranes. (Top) Stage 3 epiretinal membrane (black arrows). The reflectivity of the ectopic inner foveal layers (white arrows) is similar to that of the inner nuclear layer (hyporeflective band over the outer plexiform layer) and that of the inner plexiform layer (hyperreflective band over the inner nuclear layer). The ectopic inner foveal layers appear continuous, cross the entire foveal area, and reside above the outer nuclear layer, which is not in apparent contact with the internal limiting membrane. (Center) Stage 2 epiretinal membrane (black arrows). Stretching of the outer nuclear layer is evident, and the foveal depression is absent. The inner nuclear and ganglion cell layers appear displaced, but a continuous layer of retinal tissue over the outer nuclear layer is absent. In the outer retina the cotton ball sign (white arrows) is identified as a hyperreflective area under the central ellipsoid zone, with poorly defined borders. (Bottom) Stage 3 epiretinal membrane (black arrows). Hyporeflective intraretinal cystoid spaces are illustrated between the outer nuclear and outer plexiform layers, and in the inner nuclear layer (white arrows).

be clearly identified owing to significant alterations in the normal retinal anatomy. The presence of a foveal depression was only present in 43 out of 194 eyes (22.1%).

These specific morphologic features were essential in developing a 4-stage classification scheme of ERMs, with clinical and prognostic relevance, as illustrated in Figure 3.

Stage 1 (43 out of 194 eyes, 22.1%) was defined as the presence of a mild ERM with negligible morphologic or anatomic disruption. All retinal layers were clearly identified with easily distinguishable boundaries (Figure 3, Top). In all stage 1 eyes, the foveal depression was identified, although it was shallower than the unaffected fellow eye in patients with unilateral ERM.

Stage 2 (88 out of 194 eyes, 45.4%) was defined as the presence of ERMs associated with more progressive retinal distortion. While the foveal depression was lost and a characteristic stretching of the outer nuclear layer was present, all retinal layers were defined and clearly identified with OCT (Figure 3, Top-center).

Stage 3 (51 out of 194 eyes, 26.3%) was defined as the presence of an ERM with continuous ectopic inner foveal layers anomalously crossing the central foveal area. The foveal depression was absent, and widening of the outer nuclear layer was often less pronounced if compared with stage 2 ERMs. In stage 3 ERMs all retinal layers were clearly identified on OCT (Figure 3, Center-bottom; Supplemental Video, available at AJO.com).

Finally, stage 4 (12 out of 194 eyes, 6.2%) was defined as an ERM complicated by significant retinal thickening and remarkable anatomic disruption of the macula. Continuous ectopic inner foveal layers extending from the INL and IPL and crossing the entire foveal area were again identified. Retinal layers were noted to be significantly distorted, disorganized, and not clearly identified with OCT (Figure 3, Bottom).

In the ERM staging process 2 masked graders independently evaluated all the OCT scans of the included ERMs, and the interobserver agreement was 89.12% with a Cohen kappa coefficient of 0.82 (excellent agreement).

BCVA correlation was performed and was greater in stage 1 (0.025 ± 0.06 logMAR, 20/21 Snellen equivalent)

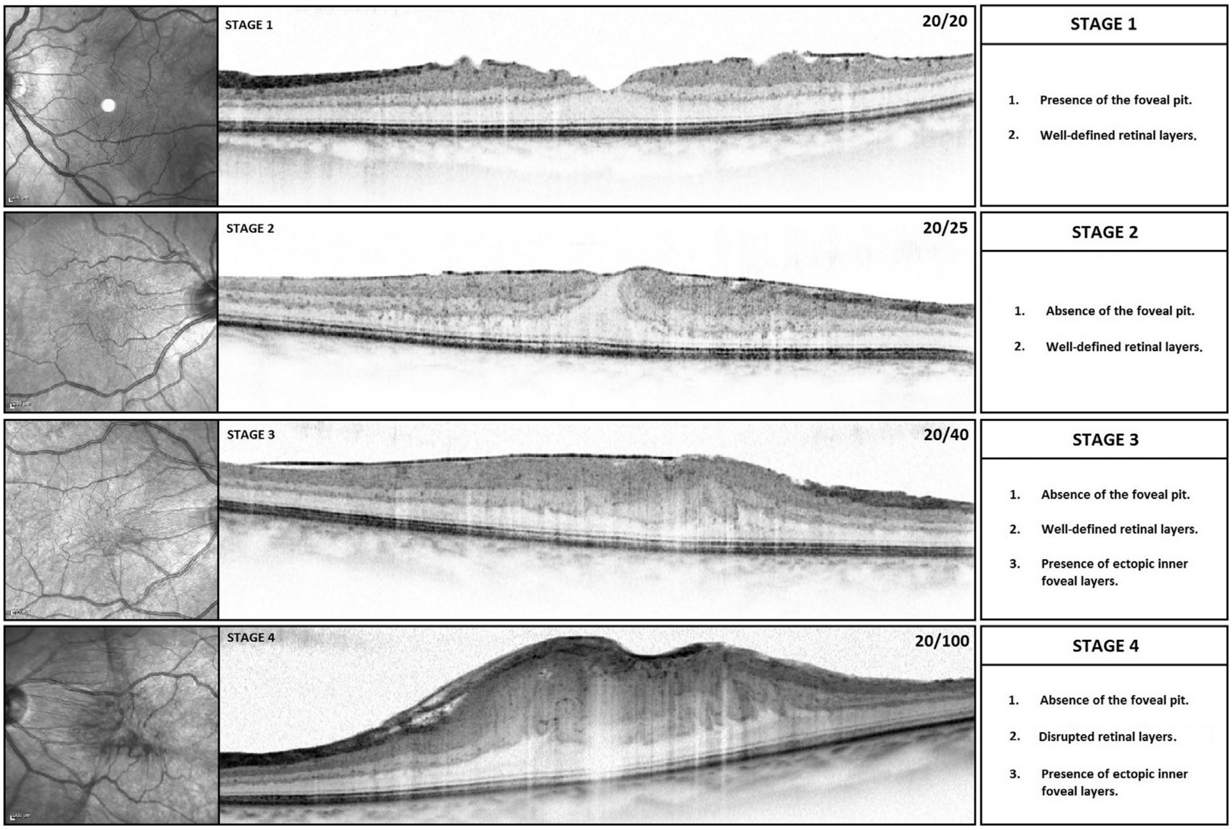

FIGURE 3. Proposed optical coherence tomography staging scheme of idiopathic epiretinal membranes.

TABLE 2. Baseline Characteristics of Studied Epiretinal Membranes (N = 194)

	Stage 1 (N = 43)	Stage 2 (N = 88)	Stage 3 (N = 51)	Stage 4 (N = 12)	*P* Value
Age (y)	69.1 ± 7.5	70.8 ± 9.4	70.2 ± 8.7	68.5 ± 8.7	.664[a]
Central foveal thickness (μm)	321.6 ± 60.1	412.4 ± 49.8	497.37 ± 64	639.25 ± 93.5	<.001[a]
Outer nuclear layer thickness (μm)	169.89 ± 66	267.47 ± 58	230.77 ± 61	-	<.001[a]
Ectopic inner foveal layer thickness (μm)	-	-	161.55 ± 63	-	-
Cystoid macular edema	0/43 (0%)	2/88 (2.3%)	7/51 (13.7%)	5/12 (41.7%)	<.001[b]
Ellipsoid disruption	1/43 (2.3%)	10/88 (11.4%)	11/51 (21.6%)	9/12 (75%)	<.001[b]
Cotton ball sign	3/43 (7%)	21/88 (23.9%)	11/51 (21.6%)	0/12 (0%)	.034[b]
BCVA, logMAR (Snellen)	0.02 ± 0.6 (20/21)	0.14 ± 0.13 (20/27)	0.33 ± 0.17 (20/43)	0.61 ± 0.26 (20/81)	<.001[c]

BCVA = best-corrected visual acuity.
[a]Analysis of variance test.
[b]χ^2 test.
[c]Kruskal-Wallis test.

and 2 (0.14 ± 0.13 logMAR, 20/27 Snellen equivalent) and significantly better than eyes in stage 3 (0.33 ± 0.17 logMAR, 20/42 Snellen equivalent) and 4 (0.61 ± 0.26 logMAR, 20/81 Snellen equivalent), with a *P* value <.001 (Table 2).

The presence of ectopic inner foveal layers was significantly associated with lower BCVA in a univariate linear regression model (*P* = .001). This significance was further confirmed with a multivariate linear regression model controlling for other possible causes of reduced BCVA, such as tractional CME, central foveal thickness, and disruption of the ellipsoid zone, suggesting that the sole presence of ectopic inner foveal layers may be an independent risk factor for lower visual acuity (*P* = .001).

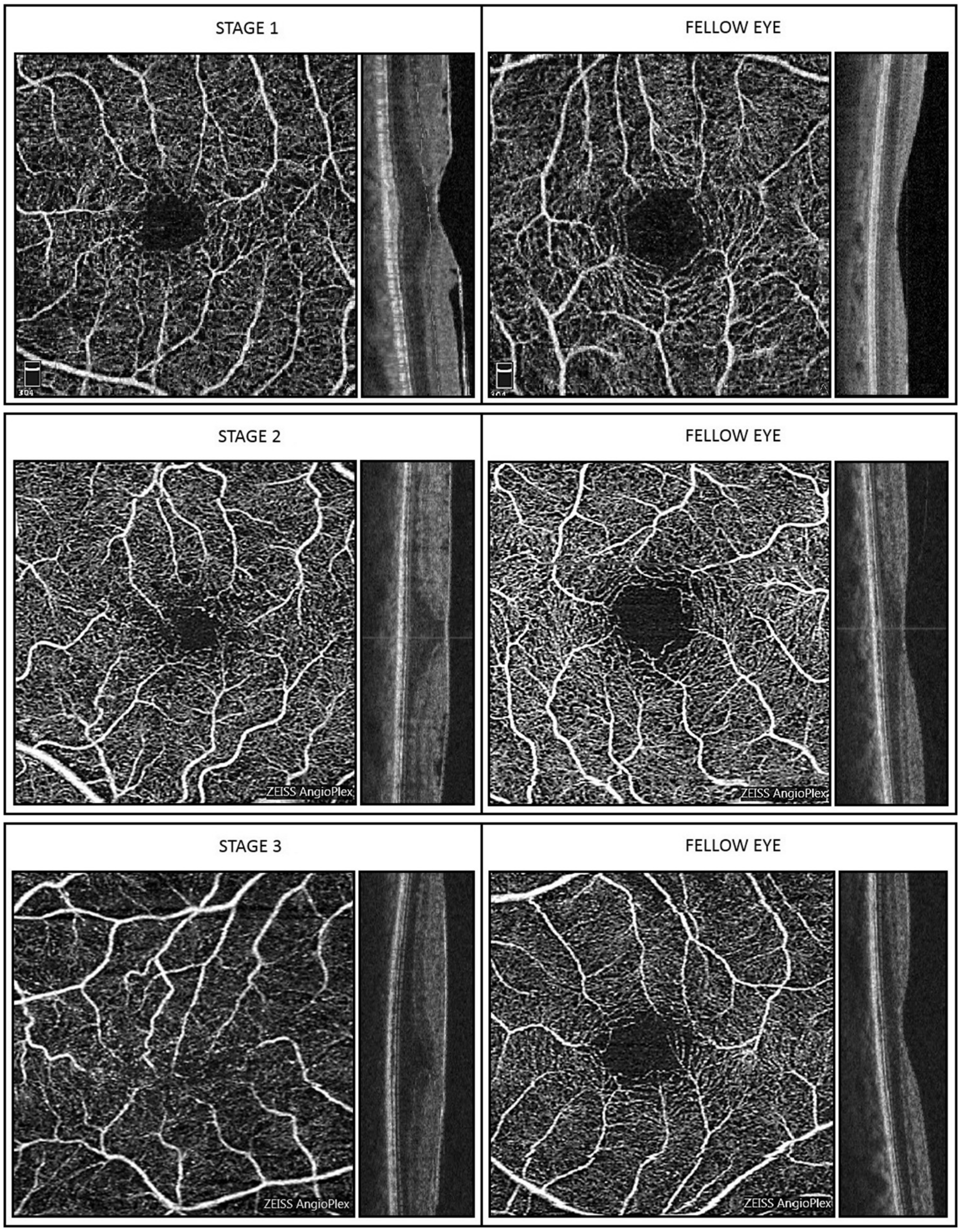

FIGURE 4. Optical coherence tomography angiography of idiopathic epiretinal membranes and unaffected fellow eyes. Foveal avascular zone and deep and superficial retinal capillary plexus are imaged with 3 × 3-mm scans. (Top) Stage 1 epiretinal membrane. Variation of the foveal avascular zone is minimal, but is slightly reduced upon comparison to the unaffected fellow eye. Mild deformation of the vessels owing to epiretinal membrane traction is noted. (Center) Stage 2 epiretinal membrane. Reduction of the foveal avascular zone is evident, and is significantly decreased if compared with the fellow eye. The deformation of the vessels and their displacement toward the foveal center is remarkable. (Bottom) Stage 3 epiretinal membrane. The foveal avascular zone is nearly absent. Severe deformation and displacement of the vessels is noted.

Statistically significant differences in central foveal thickness were encountered between the 4 subgroups. Retinal thickness was lowest in eyes with stage 1 ERMs and was greatest in eyes with stage 4 ERMs ($P < .001$, Table 2).

The prevalence of tractional CME and ellipsoid disruption increased according to the ERM stage and was lowest in stages 1 and 2 and highest in stages 3 and 4, with statistically significant differences between the 4 groups ($P < 2.001$, Table 2).

OCTA was performed in 9 eyes with stage 1, 18 eyes with stage 2, and 14 eyes with stage 3 ERMs. In stage 1 ERMs variations in the FAZ size were minimal, while in stage 2 and stage 3 ERMs the FAZ was significantly reduced if

TABLE 3. Natural History of Epiretinal Membranes During the Follow-up Period: Epiretinal Membranes Without Anatomic Signs of Progression to Later Stages

	Stage 1 (N = 23)	Stage 2 (N = 67)	Stage 3 (N = 15)	Stage 4 (N = 3)
Central foveal thickness (μm)				
Baseline	328.35 ± 67.7	401.9 ± 39.2	469.9 ± 73.6	690 ± 155
End of follow-up	334.13 ± 69.6	408.06 ± 44.3	480.13 ± 73.5	735 ± 129.7
P value[a]	.47	.1	.03	.1
Outer nuclear layer thickness (μm)				
Baseline	177.56 ± 71	257.45 ± 46	222.9 ± 70.3	-
End of follow-up	171.4 ± 67.5	268.4 ± 57.5	223.13 ± 70.3	-
P value[a]	.6	.04	.8	-
Ectopic inner foveal layer thickness (μm)				
Baseline	-	-	135.7 ± 52	-
End of follow-up	-	-	146.06 ± 51	-
P value[a]	-	-	.15	-
BCVA, logMAR (Snellen)				
Baseline	0.02 ± 0.07 (20/21)	0.13 ± 0.12 (20/27)	0.21 ± 0.17 (20/32)	0.9 ± 0.36 (20/158)
End of follow-up	0.02 ± 0.07 (20/21)	0.17 ± 0.13 (20/29)	0.27 ± 0.13 (20/37)	1 ± 0.27 (20/200)
P value[a]	.99	<.001	.018	.31

BCVA = best-corrected visual acuity.
[a]Wilcoxon signed rank test.

compared with the unaffected fellow eye (Figure 4, Top, Center, Bottom). Notably, this finding was more pronounced in stage 3 ERMs, in which the FAZ was nearly entirely absent in certain cases (Figure 4, Bottom). Macular-foveal capillaries were not identified in any of these cases. OCTA was also performed in 2 stage 4 ERMs, but the scans were excluded from the analysis owing to poor imaging quality.

The majority of eyes with ERMs in which surgery was deferred (108 out of 131, 82.5%) failed to show signs of morphologic progression to later stages during the mean follow-up of 22.2 ± 18.3 months (Table 3). Incidence of tractional CME and ellipsoid disruption did not change significantly in the 4 groups ($P = .5$ and $P = .125$, respectively), but in stage 2 ERMs the presence of the cotton ball sign was significantly higher at the end of the follow-up period ($P = .02$). Functionally, even in the absence of anatomic progression a slight but statistically significant decrease in visual acuity was registered in ERMs stage 2 ($P < .001$) and 3 ($P = .018$) at the end of the follow-up period, as demonstrated in Table 3.

Anatomic progression to more advanced stages was described in 23 out of 131 ERMs (17.5%). Specifically, 9 out of 32 stage 1 ERMs (28.1%) progressed to stage 2 (Figure 5, Top), 10 out of 77 stage 2 ERMs (13%) progressed to stage 3 (Figure 5, Center), and 2 out of 17 stage 3 ERMs (11.1%) progressed to stage 4 during the follow-up (Figure 5, Bottom). In 1 case, it was possible to record the gradual evolution of an ERM through stages 1, 2, and 3 (Figure 6). Finally, in 1 case a stage 1 ERM progressed directly to stage 3. No cases of ERM regression were noted.

The progression to more advanced stages was associated with a substantial and statistically significant drop in BCVA in all cases, which was particularly evident in those membranes that progressed from type 2 to type 3 ($P = .012$), as shown in Figure 7 and Table 3.

Interestingly, during the follow-up period the thickness of the outer nuclear layer increased significantly in eyes with ERMs that evolved from type 1 to type 2 ($P = .008$), while in eyes with type 2 ERMs that progressed to type 3, significant thinning of the same layer was identified ($P = .011$), presumably owing to the development of ectopic inner foveal layers (Table 4). The thickness of the ectopic inner foveal layers was not assessed in stage 4 ERMs, as the measurements were not considered reliable.

DISCUSSION

THE TRACTIONAL STRESS INDUCED BY ERMS CAN INVOLVE all retinal layers, causing a broad clinical spectrum of macular complications that ranges from increased retinal thickness with or without macular schisis to the formation of lamellar and full-thickness macular defects.[21–25] Causes of visual reduction include macular distortion and/or edema,[26] but an accurate prediction of vision loss may be elusive.

Factors such as ellipsoid zone disruption[9–12] and alterations in the photoreceptor outer segment length[27]

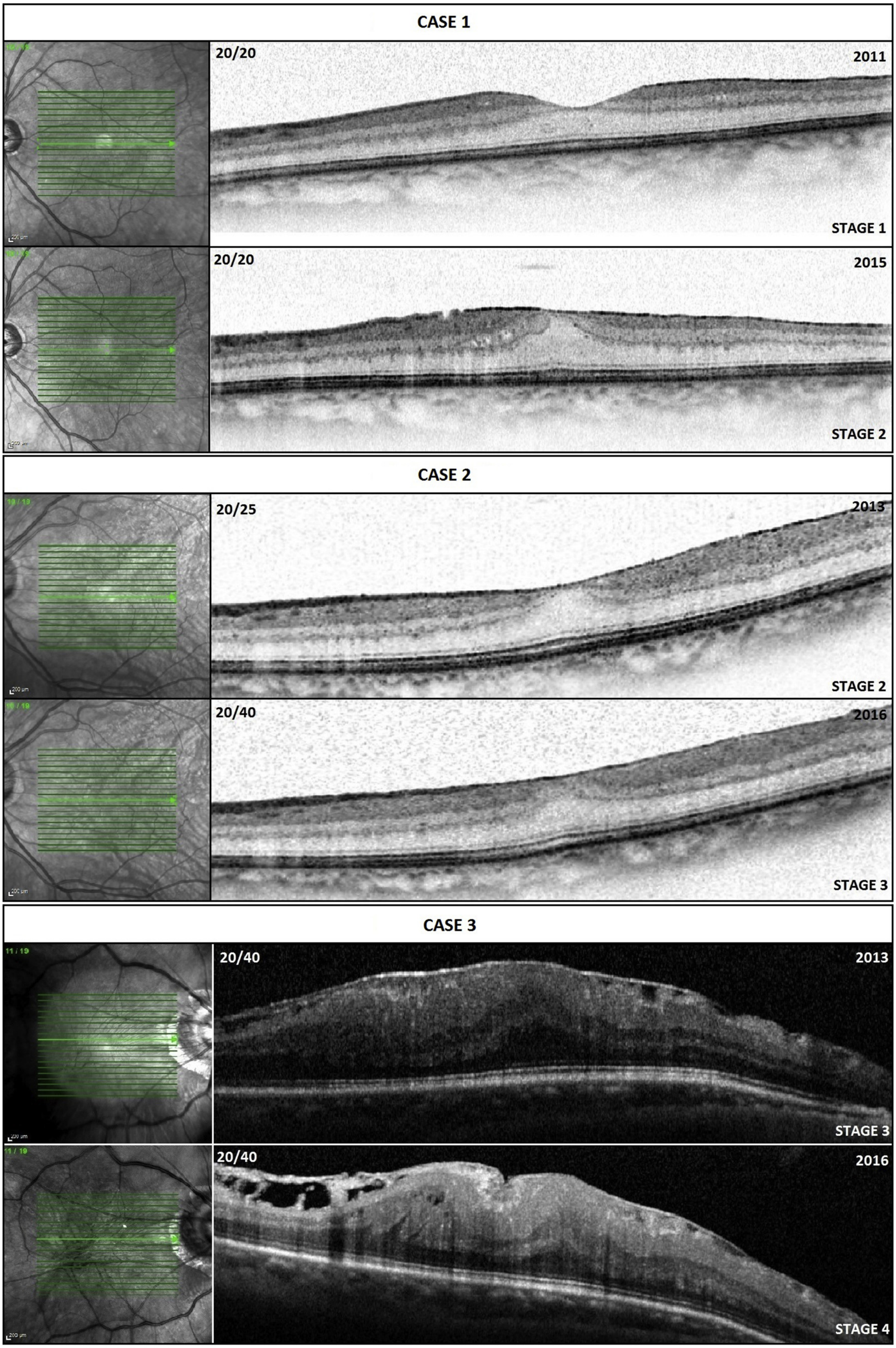

FIGURE 5. Cases of epiretinal membrane progression to later stages. (Top) Case 1: progression from stage 1 to stage 2 epiretinal membrane. After 4 years of follow-up, the retina is thicker, and the foveal depression is lost. Small intraretinal cystoid spaces are

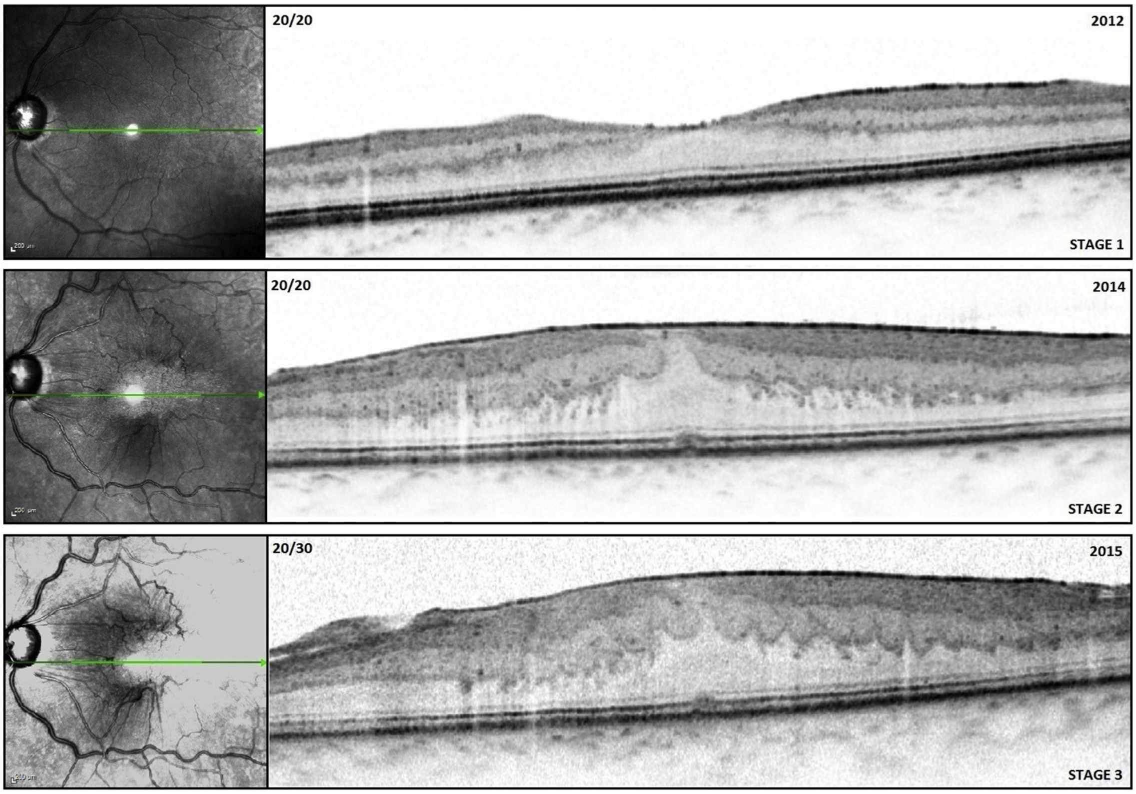

FIGURE 6. A case of epiretinal membrane progression through stages 1, 2, and 3. (Top) At baseline a stage 1 epiretinal membrane is noted. The optic pit is present and no ectopic layers over the fovea are identified. Vision is 20/20 Snellen equivalent. (Center) Two years later, the optic pit is lost, the epiretinal membrane is thicker, and stretching of the outer nuclear layer is present. A cotton ball sign has developed but there are no ectopic inner layers across the fovea. Visual acuity remained stable. (Bottom) In the same eye-tracked optical coherence tomography scan, a continuous layer of ectopic retinal tissue across the fovea is illustrated. The ectopic inner foveal layers are continuous with the inner nuclear and inner plexiform layers (with similar reflectivity) and reside above the outer nuclear layer, which appears shallower. The cotton ball sign is still present. Visual acuity dropped to 20/30 Snellen equivalent.

have also been correlated with lower preoperative and postoperative visual acuity.

More recently, the role of the inner retinal layers in visual acuity loss has been studied more closely, as these more proximal layers may be the primary affected site of ERM-associated mechanical stress. Ganglion cell–inner plexiform layer complex thickening was significantly associated with visual acuity reduction in various reports,[15,16] while some authors have proposed the inner retinal irregularity index as a valid tool for postoperative visual prognosis in eyes with ERMs.[17]

The present study confirms that the inner retinal layers of the macula may be especially sensitive to tractional stress and illustrates that ERM formation may significantly alter the inner foveal microanatomy. We propose that the chronic anteroposterior and centripetal traction caused by the ERM may induce the displacement and reorganization of the inner retinal layers, creating a continuous floor of inner retinal

noted in the inner nuclear layer. The ellipsoid zone is preserved. In this case the visual acuity remained stable. (Center) Case 2: progression from stage 2 to stage 3 epiretinal membrane. After 3 years of follow-up, ectopic inner foveal layers continue across the entire foveal area. The outer nuclear layer appears thinner, and is no longer in contact with the internal limiting membrane. The ellipsoid zone is preserved. The visual acuity decreased from 20/20 to 20/40 Snellen equivalent. (Bottom) Case 3: progression from stage 3 to stage 4 epiretinal membrane. After 3 years of follow-up, the retinal layers are disrupted, with ill-defined borders. The epiretinal membrane is thicker, with clear signs of traction affecting the underlying retina. There are alterations of the external limiting membrane and the ellipsoid zone. Visual acuity remained stable.

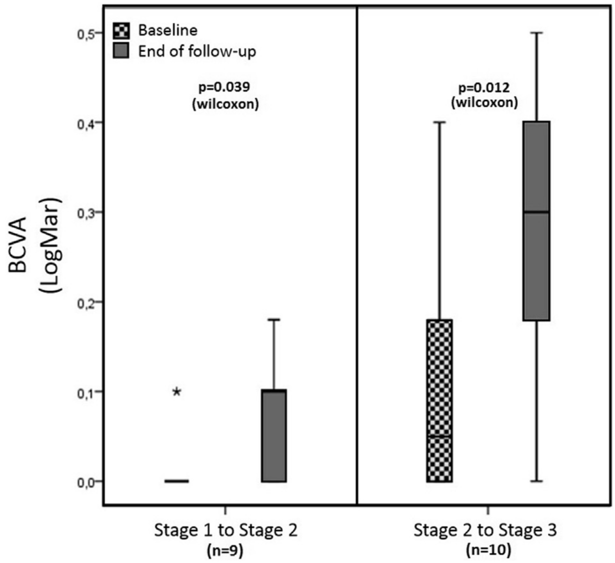

FIGURE 7. Best-corrected visual acuity correlations according to epiretinal membrane stage. Asterisks represents the maximum value of the BCVA in that subgroup (ie, 0.1 LogMAR).

tissue extending from the INL and IPL across the central fovea and referred to as ectopic inner foveal layers.

Previous studies using autofluorescence,[28] color,[29] infrared,[30] and red-free[31] fundus imaging demonstrated that ERMs commonly result in centripetal forces and contraction of the posterior pole. However, such reports described the gross movement of the macular region, without analyzing the tractional effect of ERMs on the different retinal layers.

It is unclear whether mechanical forces alone are sufficient to promote the ectopic inner foveal layers, or if other concurrent pathologic mechanisms are necessary. Retinal injury can activate Müller cells by various mechanisms and can trigger different signal pathways, leading to proliferation and migration or reactive gliosis.[32] Recent in vitro experimental studies in animal models have demonstrated that Müller cells may activate and proliferate in response to tractional stress over the retina.[33] High levels of extracellular signal–regulated kinase (ERK) have been found in the INL of guinea pig and rat retinas after mechanical stretch.[33] ERK is a protein downstream in the mitogen-activated protein kinase cascade, which regulates Müller cell proliferation and neuroprotection.[34] According to this hypothesis, in the setting of an ERM the development of ectopic inner foveal layers may result from the combination of both physical displacement of the inner retinal layers and Müller cell–driven proliferation.

The presence of ectopic inner foveal layers is the keystone of the proposed OCT-based staging scheme, which classifies ERMs into 4 stages with distinct morphologic and functional characteristics. The observation of our study population over the follow-up period illustrated that ERMs can progress sequentially from one stage to another and that the development of ectopic inner foveal layers was accompanied by a significant drop in visual acuity. This fact may be clinically relevant with prognostic implications and may influence the surgical decision in ERM patients, as lower preoperative visual acuity has been significantly associated with limited postoperative functional recovery.[35]

In the present study, the OCTA analysis in eyes with ERM showed marked alterations of the FAZ, ranging from a slight reduction in the area of the capillary-free zone to the near-complete disappearance in eyes with stage 3 ERMs and ectopic inner foveal layers (Figure 4). The architecture of both the superficial and deep retinal capillary plexus appeared to be altered, presumably owing to the central displacement of vessels.

The absence of an FAZ has been demonstrated in fovea plana and foveal hypoplasia, in which there is bilateral anatomic absence of the foveal pit with persistence of the inner retinal layers over the fovea.[36] In these conditions, macular-foveal capillaries crossing the fovea may be identified with OCTA (Figure 8, Top), as reported by recent papers.[36]

By contrast, we did not identify the presence of macular-foveal capillaries in any included case, suggesting that the displacement of the superficial and deep plexus may be mainly mechanical, without the formation of anastomotic capillary segments (Figure 8, Bottom). This is in contradistinction to the study of Cicinelli and associates, who observed a cohort of 10 patients with various ocular pathologies and described 2 cases of macular-foveal capillaries in ERM eyes.[18] However, the small size and the heterogeneity of their study population, as well as the lack of a fellow-eye control group, may have biased this analysis.

In contrast to fovea plana, which is a bilateral finding, all the fellow eyes in our study without ERM imaged with OCTA illustrated a physiological pit with a normal FAZ in the absence of macular-foveal capillaries, supporting the hypothesis that in the setting of an ERM the presence of ectopic inner foveal layers is an acquired condition.

The pathophysiological mechanism leading to vision loss in the presence of ectopic inner foveal layers is speculative, but may lead to new interrogations on the visual significance of the foveal pit. Physiologically, the outward displacement of the inner layers during foveal development creates a clear optical zone overlying a region of higher cone specialization, which may facilitate the development of a central area of greater visual resolution.[37]

However, the functional advantage of the foveal pit is challenged by the cases of fovea plana in which visual acuity is preserved. Some authors proposed that neither the development of a foveal pit nor the FAZ is necessary to achieve good visual acuity.[38,39] Nevertheless, these assumptions are based on the study of congenital conditions in which the development of a pit never

TABLE 4. Natural History of Epiretinal Membranes During the Follow-up Period: Epiretinal Membranes With Anatomic Signs of Progression to Later Stages[a]

	Stage 1 to Stage 2 (N = 9)	Stage 2 to Stage 3 (N = 10)
Central foveal thickness (μm)		
Baseline	330.7 ± 32.03	413 ± 55.2
End of follow-up	399 ± 56.8	442.4 ± 47
P value[b]	.012	.005
Outer nuclear layer thickness (μm)		
Baseline	153.11 ± 41.3	273 ± 79.7
End of follow-up	247.5 ± 55.8	213.4 ± 63.5
P value[b]	.008	.011
Ectopic inner foveal layer thickness (μm)		
Baseline	-	-
End of follow-up	-	120.9 ± 31.3
BCVA, logMAR (Snellen)		
Baseline	0.022 ± 0.04 (20/21)	0.09 ± 0.13 (20/24)
End of follow-up	0.08 ± 0.07 (20/24)	0.27 ± 0.14 (20/37)
P value[b]	.039	.012

BCVA = best-corrected visual acuity.
[a]Statistical analysis was performed only in epiretinal membranes progressing from stage 1 to 2, and from stage 2 to 3.
[b]Wilcoxon signed rank test.

occurs and, in such context, the elongation and packing of cones and other adaptation phenomena may negate the need for a clear optical zone in the fovea.

The present study allows the analysis of this issue from a different perspective, as in our case the presence of ectopic inner foveal layers occurred in patients with a presumably physiological pit prior to ERM formation, in which the foveal cones developed without any overlying retinal tissue. In stage 3 and 4 ERMs, the ectopic inner foveal layer interposed between the afferent light and the photoreceptors, and may obstruct or degrade the visual image projected on the cone photoreceptors. Moreover, the chronic displacement of the retinal layers may cause photoreceptor damage and deformation, contributing to the visual alterations and distortion in eyes with ERM.

The analysis of surgical results in those eyes that underwent pars plana vitrectomy and ERM peel was not the objective of this descriptive study, and will be assessed in a future study. However, preliminary evidence suggests that the ectopic inner foveal layers may persist even after surgical ERM removal, as illustrated in Figure 9.

Limitations of this study include its retrospective nature, the limited follow-up, and the lack of high-density macular raster scanning and OCTA for all cases. It is possible that the normal foveal anatomy may have been missed by the standard 20 × 15-degree macular raster, biasing the ERM staging process. High-density tracking was, however, performed in stage 3 ERMs in a significant subset of eyes and we were able to confirm the presence of continuous ectopic inner foveal layers in all scans through the central fovea. Moreover, the eye tracking system was applied in all those eyes with progression to stage 3 ERMs and illustrated, in all cases, the development of the ectopic inner foveal layers across the fovea in a precisely aligned B-scan at baseline and follow-up.

In conclusion, this report gives new insights into the pathophysiology of ERMs and the visual significance of the optic pit by describing a previously unreported clinical entity referred to as ectopic inner foveal layers. The presence of this acquired condition, the pathophysiology of which is still poorly defined, was associated with significant vision loss and is the centerpiece of a new OCT-based grading scheme of ERMs that may influence the surgical decision in these patients.

Larger, prospective studies with longer follow-up are necessary to support our hypothesis and reduce bias, while further investigations are required for a better understanding of the pathologic mechanisms leading to the formation of the ectopic inner foveal layers. Improvements in OCT resolution and OCTA technology will be useful tools for this purpose. Furthermore, the analysis of surgical results will be critical to explore possible postoperative functional and anatomic differences between the 4 stages of ERMs.

We hope that our results and proposed staging scheme will encourage future study so as to achieve a broader consensus, and ultimately improve the management of ERMs.

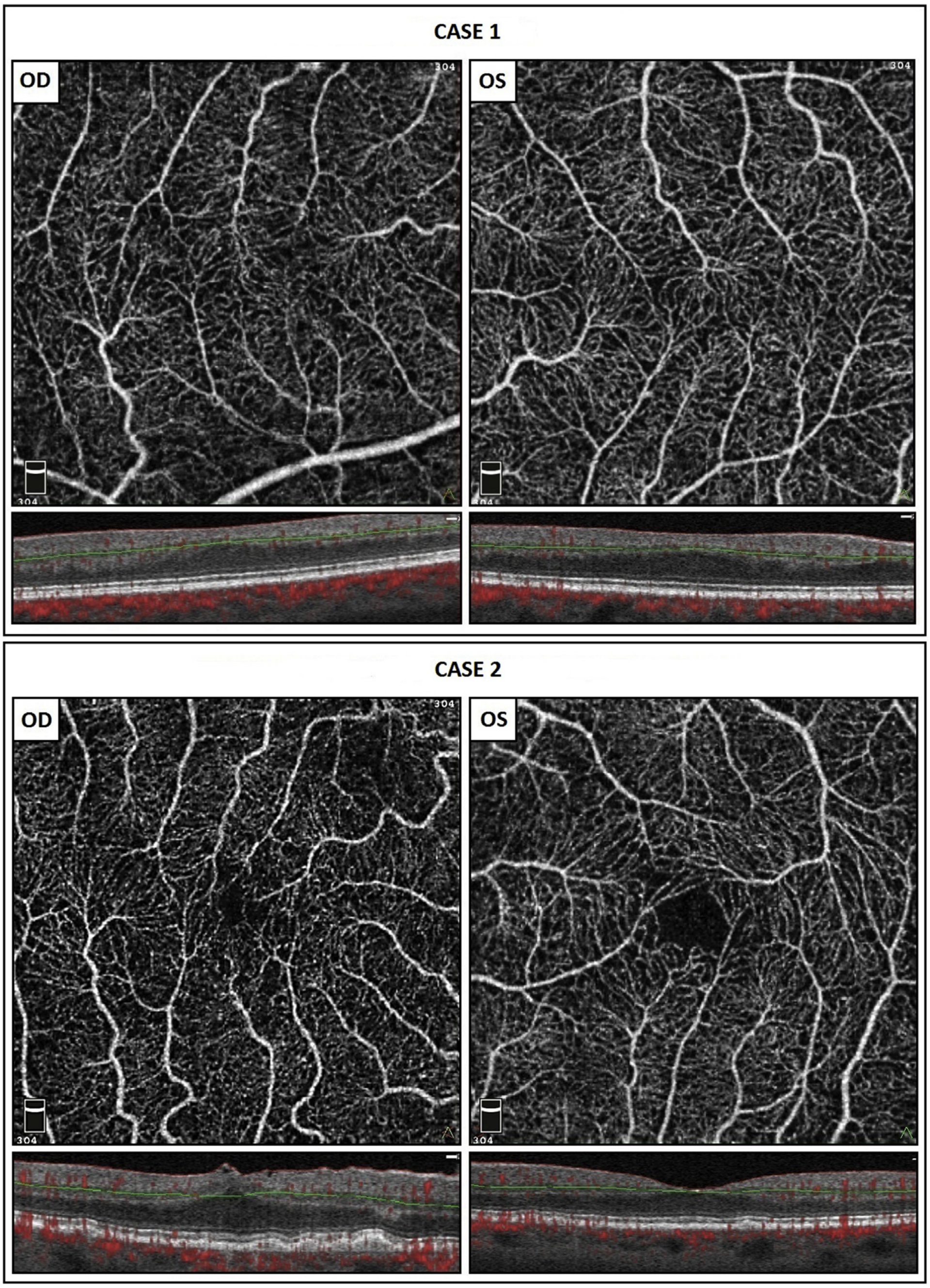

FIGURE 8. Morphologic differences between foveal microvasculature in fovea plana and idiopathic epiretinal membrane. Foveal avascular zone and deep and superficial retinal capillary plexus are imaged with 3 × 3-mm scans. (Top) Case 1: optical coherence tomography angiography in fovea plana. In both eyes, the foveal avascular zone in absent. Macular-foveal capillaries crossing the entire foveal area are identified. The morphology of the vessels is similar in both eyes. (Bottom) Case 2: optical coherence tomography angiography in stage 3 epiretinal membrane (right eye) and unaffected fellow eye (left eye). In the right eye, the foveal avascular zone is severely reduced, although still present. The ectopic layers are present across the entire foveal area, but no flow is seen in the center of the fovea. Macular foveal capillaries are absent and the vessels appear displaced and stretched, and their morphology is different from the fellow eye. The foveal avascular zone in the fellow eye is normal.

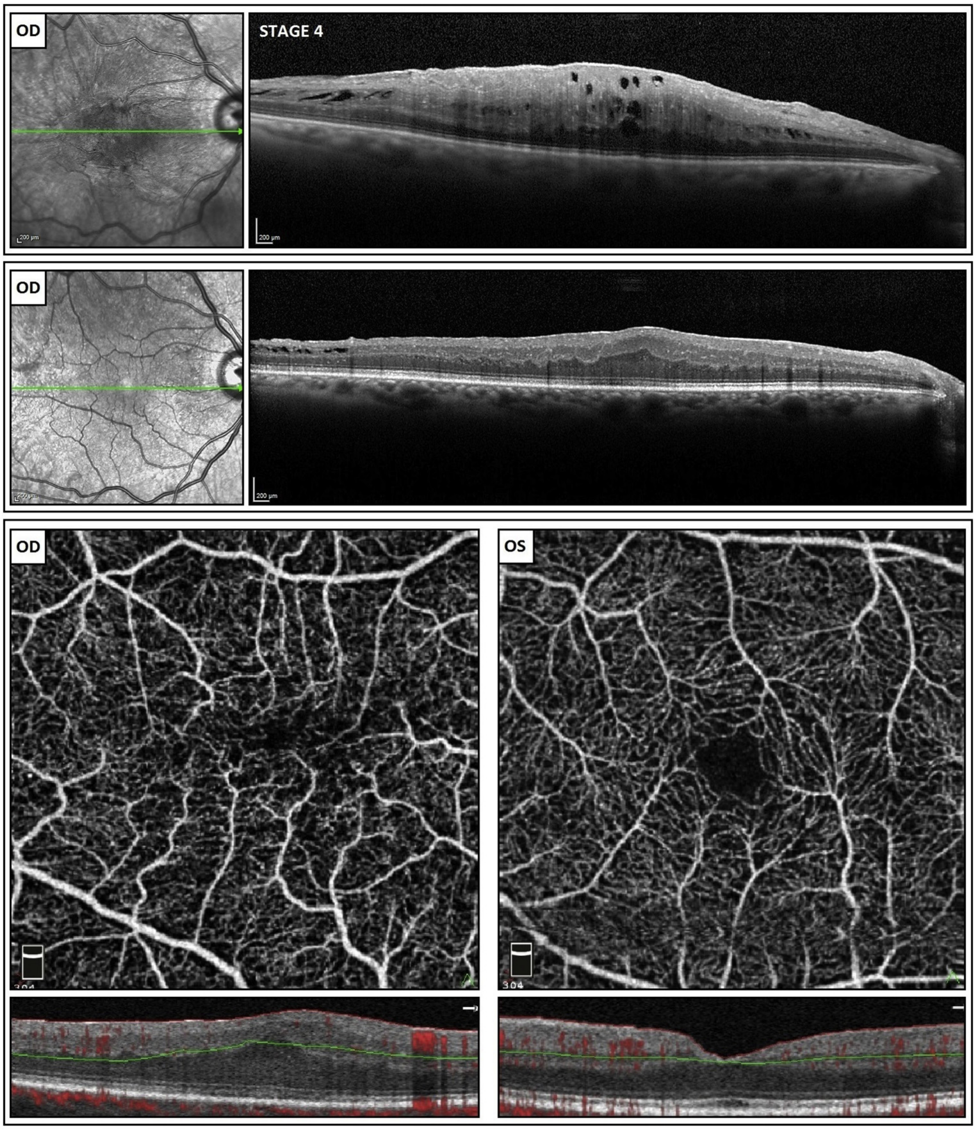

FIGURE 9. Postoperative multimodal imaging of a stage 4 epiretinal membrane. (Top) Preoperative optical coherence tomography. The retina is thickened, with disrupted retinal layers and the presence of intraretinal cystoid spaces. The ectopic inner foveal layers are continuous across the entire foveal area. (Center) Postoperative optical coherence tomography. Twelve months after pars plana vitrectomy with epiretinal membrane and internal limiting membrane peeling, the ectopic inner foveal layers are still present and continuous across the entire foveal area. The thickness of the retina and the ectopic inner foveal layers is decreased. (Bottom) Postoperative optical coherence tomography angiography of the vitrectomized eye (right eye) and the unaffected fellow eye (left eye). At 12 months from surgery, the foveal avascular zone of the vitrectomized eye is severely reduced but foveal capillaries are notably absent. The morphology of the retinal vessels appears distorted. The foveal avascular zone and the retinal vasculature in the fellow eye are normal.

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REFERENCES

1. Ng CH, Cheung N, Wang JJ, et al. Prevalence and risk factors for epiretinal membranes in a multi-ethnic United States population. *Ophthalmology* 2011;118(4):694–699.
2. Cheung N, Tan SP, Lee SY, et al. Prevalence and risk factors for epiretinal membrane: the Singapore Epidemiology of Eye Disease study. *Br J Ophthalmol* 2016; http://dx.doi.org/10.1136/bjophthalmol-2016-308563.
3. You Q, Xu L, Jonas JB. Prevalence and associations of epiretinal membranes in adult Chinese: the Beijing eye study. *Eye (Lond)* 2008;22(7):874–879.
4. Schumann RG, Gandorfer A, Ziada J, et al. Hyalocytes in idiopathic epiretinal membranes: a correlative light and electron microscopic study. *Graefes Arch Clin Exp Ophthalmol* 2014;252(12):1887–1894.
5. Mitchell P, Smith W, Chey T, Wang JJ, Chang A. Prevalence and associations of epiretinal membranes. The Blue Mountains Eye Study, Australia. *Ophthalmology* 1997;104(6): 1033–1040.
6. Klein R, Klein BE, Wang Q, Moss SE. The epidemiology of epiretinal membranes. *Trans Am Ophthalmol Soc* 1994;92: 403–425.
7. Gass JDM. Macular dysfunction caused by epiretinal membrane contraction. In: . Stereoscopic Atlas of Macular Diseases: Diagnosis and Treatment. 4th ed., Vol 2. St Louis, Mo: Mosby; 1997:938–950.
8. Stevenson W, Prospero Ponce CM, Agarwal DR, Gelman R, Christoforidis JB. Epiretinal membrane: optical coherence tomography-based diagnosis and classification. *Clin Ophthalmol* 2016;29(10):527–534.
9. Kim JH, Kim YM, Chung EJ, Lee SY, Koh HJ. Structural and functional predictors of visual outcome of epiretinal membrane surgery. *Am J Ophthalmol* 2012;153(1):103–110.
10. Shimozono M, Oishi A, Hata M, et al. The significance of cone outer segment tips as a prognostic factor in epiretinal membrane surgery. *Am J Ophthalmol* 2012;153(4):698–704.
11. Itoh Y, Inoue M, Rii T, Hirota K, Hirakata A. Correlation between foveal cone outer segment tips line and visual recovery after epiretinal membrane surgery. *Invest Ophthalmol Vis Sci* 2013;54(12):7302–7308.
12. Watanabe K, Tsunoda K, Mizuno Y, Akiyama K, Noda T. Outer retinal morphology and visual function in patients with idiopathic epiretinal membrane. *JAMA Ophthalmol* 2013;131(2):172–177.
13. Okamoto F, Sugiura Y, Okamoto Y, Hiraoka T, Oshika T. Inner nuclear layer thickness as a prognostic factor for metamorphopsia after epiretinal membrane surgery. *Retina* 2015; 35(10):2107–2114.
14. Okamoto F, Sugiura Y, Okamoto Y, Hiraoka T, Oshika T. Associations between metamorphopsia and foveal microstructure in patients with epiretinal membrane. *Invest Ophthalmol Vis Sci* 2012;53(11):6770–6775.
15. Koo HC, Rhim WI, Lee EK. Morphologic and functional association of retinal layers beneath the epiretinal membrane with spectral-domain optical coherence tomography in eyes without photoreceptor abnormality. *Graefes Arch Clin Exp Ophthalmol* 2012;250(4):491–498.
16. Song SJ, Lee MY, Smiddy WE. Ganglion cell layer thickness and visual improvement after epiretinal membrane surgery. *Retina* 2016;36(2):305–310.
17. Cho KH, Park SJ, Cho JH, Woo SJ, Park KH. Inner-retinal irregularity index predicts postoperative visual prognosis in idiopathic epiretinal membrane. *Am J Ophthalmol* 2016;168: 139–149.
18. Cicinelli MV, Carnevali A, Rabiolo A, et al. Clinical spectrum of macular-foveal capillaries evaluated with optical coherence tomography angiography. *Retina* 2016; http://dx.doi.org/10.1097/IAE.0000000000001199.
19. Yeung J, Crock G, Cairns J, Heinze J, Troski S, Billson F. Macular-foveal capillaries in human retina. *Aust J Ophthalmol* 1973;1(1):17–23.
20. Staurenghi G, Sadda S, Chakravarthy U, Spaide RF. International Nomenclature for Optical Coherence Tomography (IN•OCT) Panel. Proposed lexicon for anatomic landmarks in normal posterior segment spectral-domain optical coherence tomography: the IN•OCT consensus. *Ophthalmology* 2014;121(8):1572–1578.
21. Tsunoda K, Watanabe K, Akiyama K, Usui T, Noda T. Highly reflective foveal region in optical coherence tomography in eyes with vitreomacular traction or epiretinal membrane. *Ophthalmology* 2012;119(3):581–587.
22. Johnson MW. Tractional cystoid macular edema: a subtle variant of the vitreomacular traction syndrome. *Am J Ophthalmol* 2005;140(2):184–192.
23. Bu SC, Kuijer R, Li XR, Hooymans JM, Los LI. Idiopathic epiretinal membrane. *Retina* 2014;34(12):2317–2335.
24. Govetto A, Dacquay Y, Farajzadeh M, et al. Lamellar macular hole: two distinct clinical entities? *Am J Ophthalmol* 2016; 164:99–109.
25. Tsai CY, Hsieh YT, Yang CM. Epiretinal membrane-induced full-thickness macular holes: The Clinical Features and Surgical Outcomes. *Retina* 2016;36(9):1679–1687.
26. Pilli S, Lim P, Zawadzki RJ, Choi SS, Werner JS, Park SS. Fourier-domain optical coherence tomography of eyes with idiopathic epiretinal membrane: correlation between macular morphology and visual function. *Eye (Lond)* 2011;25(6): 775–783.
27. Shiono A, Kogo J, Klose G, et al. Photoreceptor outer segment length: a prognostic factor for idiopathic epiretinal membrane surgery. *Ophthalmology* 2013;120(4):788–794.
28. Rodrigues IA, Lee EJ, Williamson TH. Measurement of retinal displacement and metamorphopsia after epiretinal membrane or macular hole surgery. *Retina* 2016;36(4):695–702.
29. Yang HK, Kim SJ, Jung YS, Kim KG, Kim JH, Yu HG. Improvement of horizontal macular contraction after surgical removal of epiretinal membranes. *Eye (Lond)* 2011;25(6):754–761.
30. Kofod M, La Cour M. Quantification of retinal tangential movement in epiretinal membranes. *Ophthalmology* 2012; 119(9):1886–1891.
31. Weinberger D, Stiebel-Kalish H, Priel E, Barash D, Axer-Siegel R, Yassur Y. Digital red-free photography for the evaluation of retinal blood vessel displacement in epiretinal membrane. *Ophthalmology* 1999;106(7):1380–1383.
32. Dyer MA, Cepko CL. Control of Müller glial cell proliferation and activation following retinal injury. *Nat Neurosci* 2000;3(9):873–880.
33. Lindqvist N, Liu Q, Zajadacz J, Franze K, Reichenbach A. Retinal glial (Müller) cells: sensing and responding to tissue stretch. *Invest Ophthalmol Vis Sci* 2010;51(3):1683–1690.
34. Fischer AJ, Scott MA, Ritchey ER, Sherwood P. Mitogen-activated protein kinase-signaling regulates the ability of

Müller glia to proliferate and protect retinal neurons against excitotoxicity. *Glia* 2009;57(14):1538–1552.

35. Laban KG, Scheerlinck LM, van Leeuwen R. Prognostic factors associated with visual outcome after pars plana vitrectomy with internal limiting membrane peeling for idiopathic epiretinal membrane. *Ophthalmologica* 2015;234(3):119–126.
36. Dolz-Marco R, Phasukkijwatana N, Sarraf D, Freund KB. Optical coherence tomography angiography in fovea plana. *Ophthalmic Surg Lasers Imaging Retina* 2016;47(7): 670–673.
37. Hendrickson A, Possin D, Vajzovic L, Toth CA. Histologic development of the human fovea from midgestation to maturity. *Am J Ophthalmol* 2012;154(5):767–778.
38. Marmor MF, Choi SS, Zawadzki RJ, Werner JS. Visual insignificance of the foveal pit: reassessment of foveal hypoplasia as fovea plana. *Arch Ophthalmol* 2008;126(7):907–913.
39. Mohammad S, Gottlob I, Kumar A, et al. The functional significance of foveal abnormalities in albinism measured using spectral-domain optical coherence tomography. *Ophthalmology* 2011;118(8):1645–1652.