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Correlations between Clinical and Histopathologic Characteristics in Idiopathic Epiretinal Membrane

Lei-Chi Wang, MD,[1,2] Wen-Jung Lo, MD,[3,4] Ya-Yun Huang, MD,[3,5] Yu-Bai Chou, MD,[3,4] An-Fei Li, MD,[4,6] Shih-Jen Chen, MD, PhD,[3,4] Teh-Ying Chou, MD, PhD,[1,2] Tai-Chi Lin, MD, PhD[3,4]

Purpose: To investigate correlations between clinical and histopathologic characteristics of idiopathic epiretinal membrane (ERM).

Design: Retrospective interventional case series.

Participants: In total, 87 eyes from 87 patients with idiopathic ERM who underwent pars plana vitrectomy with peeling of the ERM from 2019 to 2020 were included.

Methods: The outcomes of clinical ophthalmic examination, including measurement of best-corrected visual acuity (BCVA) and spectral-domain OCT (SD-OCT), before and after surgery were reviewed. Surgical specimens were fixed in formalin and embedded in paraffin for histologic and immunohistochemical analysis.

Main Outcomes Measures: The association between morphological characteristics revealed on SD-OCT images and the cellular composition of the surgically excised ERM demonstrated with immunohistochemical staining were the main outcome measures. Changes in the BCVA and central macular thickness (CMT) were assessed through a comparison of preoperative and postoperative measurements.

Results: Based on SD-OCT morphological characteristics in the foveal area, 15 cases were classified into group 1A (mainly outer retinal thickening), 39 into group 1B (more tenting of the outer retina and distorted inner retina), and 33 into group 1C (prominent inner retina thickening). Overall, postoperative final BCVA and CMT at 1 year improved in all groups. Patients who presented with a better initial BCVA exhibited a more favorable final BCVA. Epiretinal membranes in group 1C demonstrated the greatest decrease in CMT compared with those in groups 1B and 1A, but the final CMT did not differ among the groups. A negative correlation between the density of hyalocytes ($P = 0.003$) and myofibroblasts ($P = 0.047$) was noted between the 3 groups. Total cell density and glial cell density of the ERMs were strongly associated with poor final BCVA and BCVA improvement.

Conclusions: The present study provides new histopathologic information regarding the formation and progression of idiopathic ERM. Glial cell proliferation plays a predominant role in these processes. Epiretinal membranes with high cellularity and glial cell density may cause damage to the retina structure, resulting in poor postoperative visual outcomes. These findings provide additional evidence supporting early surgical intervention in patients with idiopathic ERM reported with visual disturbance. *Ophthalmology 2022;129:1421-1428 © 2022 by the American Academy of Ophthalmology*

Idiopathic epiretinal membrane (ERM) is a pathologic fibrocellular membrane that is located at the vitreoretinal interface, and it grows on the inner surface of the retina,[1] with an incidence of approximately 5.3% to 18.5% in the general population.[2,3] Idiopathic ERM has been postulated to be caused by posterior vitreous detachment (PVD), which causes dehiscence in the internal limiting membrane (ILM) and subsequent cell proliferation on to the retinal surface to form the ERM.[4,5] Since Machemer first demonstrated the removal of ERMs by using vitrectomy techniques in 1978, several histopathological studies have indicated that various cell types, such as glial cells, retinal pigment epithelial (RPE) cells, myofibroblasts, hyalocytes, and macrophages, may play a crucial role in ERM formation.[6,7] However, the exact pathophysiology of ERM remains to be determined. To date, there is no consensus on the appropriate timing of surgical intervention.[8] Approximately 70% to 80% of patients regain vision after successful ERM removal, but some patients present with limited improvement of visual acuity, even in the absence of complications.[9]

The current indication for ERM surgery based on the clinical presentation of vision disturbance or structural classifications on OCT is not sufficient to evaluate functional prognosis. Therefore, to gain insight into the pathogenesis to balance the risks and benefits of surgical intervention, we investigated the correlations between clinical and histopathologic characteristics of idiopathic ERM by evaluating its morphological characteristics obtained from spectral-domain OCT (SD-OCT) and by assessing surgically removed ERM specimens.

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Methods

Study Subjects

This study was a nonrandomized, retrospective consecutive case series. The study protocol was approved by the Institutional Review Board of Taipei Veterans General Hospital and adhered to the tenets of the Declaration of Helsinki. Patients who underwent vitrectomy for idiopathic ERM from January 2019 to December 2020 at the Taipei Veterans General Hospital were enrolled. After surgery, the specimens were submitted to the pathology laboratory, as is routine for other surgical specimens. We excluded patients with ocular diseases such as retinal breaks, diabetic retinopathy, retinal vein occlusion, and uveitis. Eyes with decreased vision attributable to other pathologies such as glaucoma, optic nerve head changes, and age-related macular degeneration were also excluded.

At each patient's first visit, a complete ophthalmic examination, including best-corrected visual acuity (BCVA) measurement, slit-lamp biomicroscopy, noncontact tonometer measurement, dilated fundus evaluation and photography, and SD-OCT (Avanti; Optovue), was conducted. Idiopathic ERM was further classified based on the SD-OCT morphological characteristics of the foveal area.[9] Fovea-attached ERMs were classified as group 1A (ERM with outer retinal thickening and a nearly normal configuration in the inner retina), group 1B (more exaggerated tenting of the outer retinal layer in the foveal area and the inner retina distorted by centripetal and anteroposterior forces caused by the ERM), or group 1C (prominent inner retina thickening, with inward tenting of the outer retinal reflectivity in the foveal area). Cases with fovea-sparing ERM were excluded owing to their small number (16 eyes).

Surgery for ERM involves creating a complete PVD to release the anteroposterior traction, complete removal of the ERM, and peeling of the ILM.

Clinical data from patients, including BCVA, SD-OCT measurements, and lens status, were recorded postoperatively during the 1-year follow-up. Outcome measures were changes in the BCVA and central macular thickness (CMT). During the follow-up period, cataract surgery was arranged if the cataract obscured vision. Additional visits were arranged after cataract surgery.

Specimen Preparation, Tissue Processing, and Staining

A total of 87 specimens were collected during the study period. After peeling off the membrane, the specimens were fixed in 10% neutral formalin and embedded in paraffin. During the first sectioning of the paraffin-embedded specimen, in addition to 1 blank slide for hematoxylin and eosin staining, 3 positive-charged blank slides were prepared for further immunohistochemical staining against antibodies including glial fibrillary acidic protein (dilution 1:300, clone 6F2; Dako), smooth muscle actin (dilution 1:100, clone 1A4; Dako), and CD68 (dilution 1:50, clone PG-M1; Dako). All of the immunohistochemistry were performed on a BOND-MAX autostainer (Leica Microsystems) with recommended heat-induced epitope retrieval conditions and a BOND Polymer Refine Red Detection kit.

Histologic Evaluation and Image Acquisition

All formalin-fixated, paraffin-embedded specimens were evaluated using light microscopy. The cellularity of glial cells, hyalocytes, and myofibroblasts was calculated under a 40× objective lens (1 high-power field) in the hot spot area and was categorized as absent, low, medium, or high if the number of cell was 0, < 10, 10 to 20, or > 20 in 1 high-power field. For the remaining less predominant cell types, namely, RPE cells and red blood cells (RBCs), cellularity was categorized into absent, few, and many based on the evaluation of the whole specimen. Whole-slide images of the 4-μm sections from the specimens were also scanned with a Philips Ultra Fast Scanner 1.8 (Philips IntelliSite Pathology Solution 3.2). The images were acquired using the Philips Image Management System 3.3 (Philips IntelliSite Pathology Solution 3.2). For the specimens that could not be scanned owing to their small size, the images were acquired using a Nikon Eclipse 80i microscope equipped with a Nikon DS-Fi3 camera.

Statistical Analysis

Statistical analysis was performed using JASP software (version 0.16.1; JASP Team [2022]). A P value of < 0.05 was considered statistically significant in all analyses. To evaluate the potential factors related to visual performance and CMT on initial presentation and at the end of follow-up, independent variables including OCT classification and numbers of total cells, glia cells, hyalocytes, myofibroblasts, RPE cells, and RBCs were analyzed in age- and sex-adjusted multiple linear regression models. In addition, to evaluate the influence of lens status on visual performance, a 2-sample t test was used to analyze the difference between patients with and without cataract and between patients receiving and not receiving cataract surgery.

Table 1. Demographic Characteristics and OCT Classification of All Patients

Group	1A	1B	1C	P Value
Number	15	39	33	
Sex (female/male)	7/8	21/18	18/15	
Age, years	68.67 ± 4.85	65.80 ± 10.48	63.75 ± 6.27	0.168
Lens status (phakic/pseudophakic)	7/8	25/14	23/10	
BCVA (logMAR)				
Initial	0.32 ± 0.17	0.54 ± 0.21	0.70 ± 0.31	<0.001*
Final	0.20 ± 0.17	0.29 ± 0.24	0.44 ± 0.34	0.009*
CMT (μm)				
Initial	449.20 ± 44.72	521.10 ± 72.73	577.38 ± 117.44	<0.001*
Final	383.60 ± 41.21	374.10 ± 60.70	390.00 ± 3.29	0.613
Mean BCVA change (logMAR)	−0.127 ± 0.189	−0.250 ± 0.272	−0.261 ± 0.280	0.334
Mean CMT change (μm)	−65.6 ± 37.35	−147 ± 102.6	−187 ± 96.7	0.034*

BCVA = best-corrected visual acuity; CMT = central macular thickness; logMAR = logarithm of the minimum angle of resolution.
*Statistically significant.

Table 2. Immunohistochemical Analysis of Histopathologic Features

Group	1A	1B	1C	*P* Value	Coefficient, *P* Value
Number	15	39	33		
Total cell density					
Low/medium/high	2/2/11	5/8/26	5/5/23	0.066	−0.064, 0.564
Glial cells					
Low/medium/high	3/3/8	5/7/25	5/4/24	0.373	0.094, 0.407
Hyalocytes					
Low/medium/high	3/2/3	19/9/9	25/2/6	0.006*	−0.326, 0.003*
Myofibroblasts					
Low/medium/high	8/4/3	24/7/8	26/3/4	0.043*	−0.221, 0.047*
RPE cells					
Absent/few/many	11/3/1	34/4/1	30/1/2	0.429	−0.054, 0.629
RBCs					
Absent/few/many	7/4/4	25/8/6	23/7/3	0.238	−0.115, 0.304

RBC = red blood cell; RPE = retinal pigment epithelium.
*Statistically significant.

Results

A total of 87 patients with idiopathic ERM met our inclusion criteria (Table 1). The ERMs were classified according to their SD-OCT morphological characteristics in the foveal area. Fifteen eyes (17%) were categorized into group 1A, 39 eyes (45%) were categorized into group 1B, and 33 eyes (38%) were categorized into group 1C. Age and sex were balanced among the groups. The initial BCVA and CMT progressively worsened from group 1A to group 1C, with statistically significant differences among the 3 groups ($P < 0.001$).

Postoperative Clinical Outcomes

Postoperatively, an outcome analysis demonstrated an improvement in BCVA and CMT compared with their initial presentation in all the groups (Table 1). The final BCVA at 1 year progressively decreased from group 1A (0.20 ± 0.17) to group 1B (0.29 ± 0.24) and group 1C (0.44 ± 0.34) ($P = 0.009$). However, no significant difference in the final CMT was noted among the groups. A subgroup analysis revealed that the postoperative mean BCVA change was −0.127 ± 0.189, −0.250 ± 0.272, and −0.261 ± 0.280 in the 3 groups; however, the difference was not significant ($P = 0.334$). By contrast, the decrease in CMT was greater in group 1C than in groups 1B and 1A ($P = 0.034$).

Immunohistochemical Analysis of Surgical Samples

A microscopic examination and immunohistochemical analysis revealed glial cells, hyalocytes, myofibroblasts, RPE cells, and RBCs on the surgically removed ERMs. The outcome analysis revealed no significant difference in the total cell density and the density of glial cells, RPE cells, and RBCs among the groups. By contrast, the density of hyalocytes and myofibroblasts progressively decreased from group 1A to group 1C ($P = 0.006$ and 0.043, respectively). A

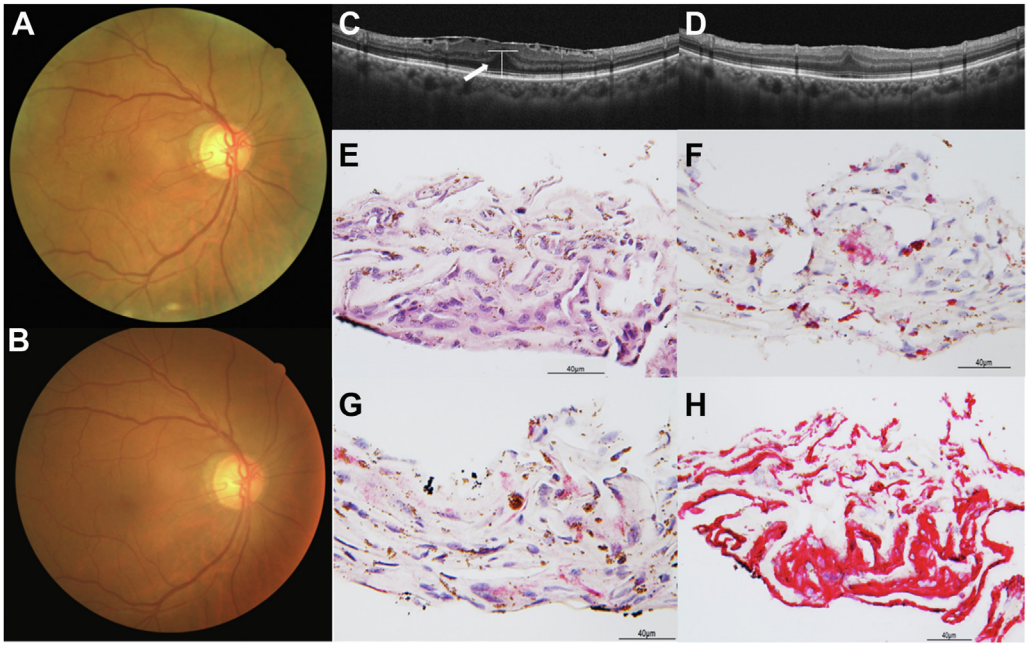

Figure 1. **(A)** Preoperative and **(B)** postoperative fundus color photographs of a representative case of group 1A. **C**, Epiretinal membrane (ERM) with outer retinal thickening (arrow) and nearly normal inner retina on spectral domain (SD)-OCT image. **D,** Free of ERM after surgery on SD-OCT image. **E,** The standard hematoxylin and eosin staining performed on 4-μm sections showed relatively low total cell density. Immunohistochemical staining for **(F)** CD68 and **(G)** smooth muscle actin showed moderate cellularity of hyalocytes and myofibroblasts, respectively. **H,** The majority of the cells were glial cells highlighted with glial fibrillary acidic protein. Scale bar, E–H, 40 μm.

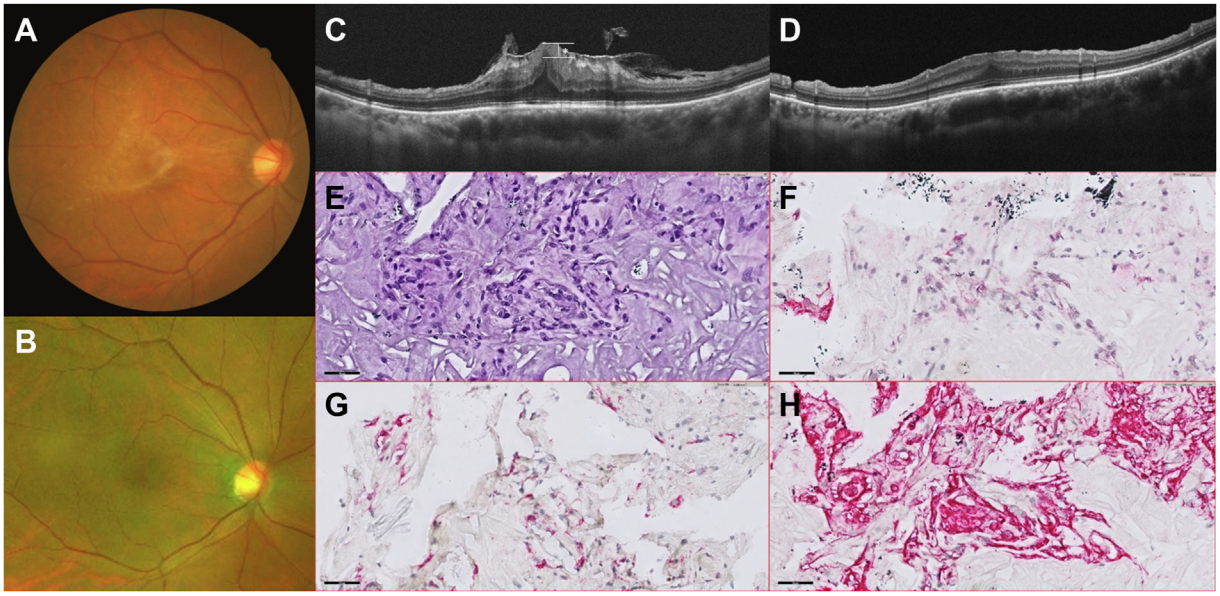

Figure 2. (A) Preoperative and **(B)** postoperative fundus color photographs of a representative case of group 1B. **C,** Epiretinal membrane (ERM) with exaggerated tenting of the outer retinal layer in the foveal area; the inner retinal layer was thickened and its configuration was distorted by centripetal and anteroposterior tractional forces caused by ERM on spectral domain (SD)-OCT image. *Inner retinal layer thickness. **D,** Free of ERM after surgery on SD-OCT image. **E,** The standard hematoxylin and eosin staining performed on 4-μm sections. Immunohistochemical staining for **(F)** CD68 and **(G)** smooth muscle actin showed lower cellularity of hyalocytes and myofibroblasts. **H,** The majority of the cells were glial cells highlighted with glial fibrillary acidic protein. Scale bar, E–H, 50 μm.

multivariate regression analysis demonstrated a negative correlation of the density of hyalocytes ($P = 0.003$) and myofibroblasts ($P = 0.047$) among the 3 groups. The aforementioned results are presented in Table 2. Representative cases from each group that illustrate the correlations between clinical and histopathologic characteristics are presented in Figures 1 through 3.

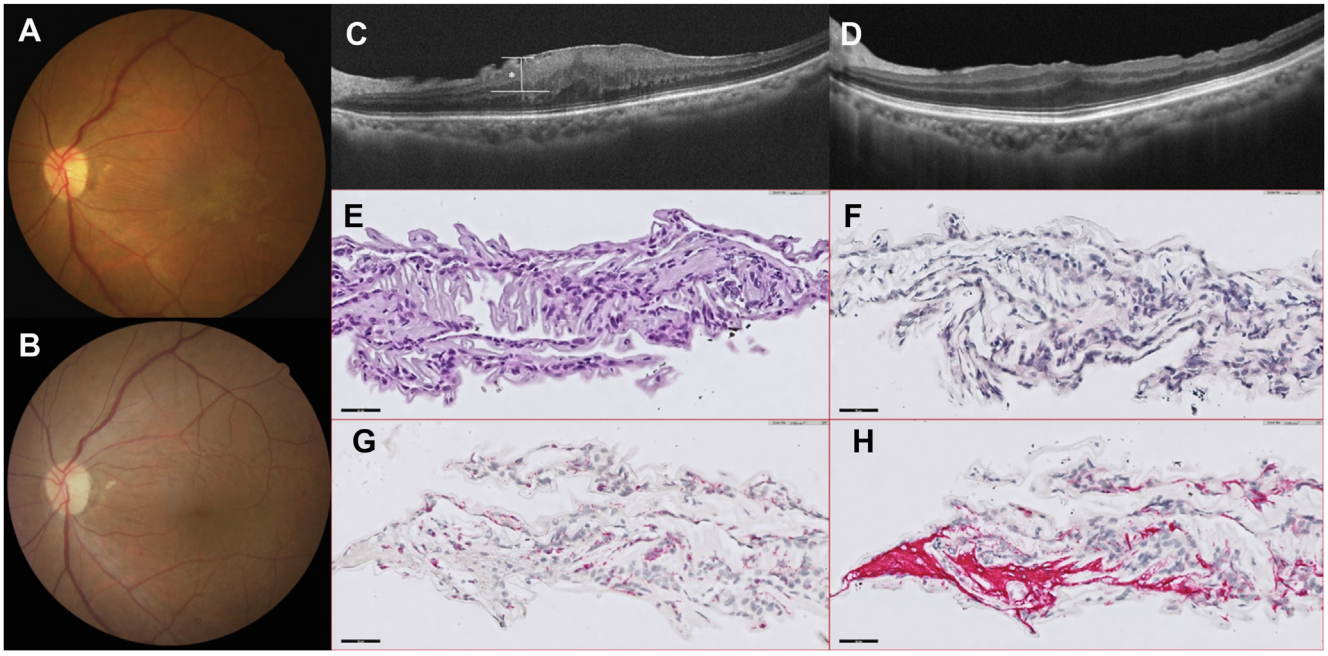

Figure 3. (A) Preoperative and **(B)** postoperative fundus color photographs of a representative case of group 1C. **C**, Epiretinal membrane (ERM) with prominent inner retinal thickening on spectral domain (SD)-OCT image. *Inner retinal layer thickness. **D,** Free of ERM after surgery on SD-OCT image. **E,** The standard hematoxylin and eosin staining performed on 4-μm sections. Immunohistochemical staining for CD68 **(F)** showed absence of hyalocytes in this case, whereas there were few myofibroblasts highlighted with smooth muscle actin **(G)**. **H,** Most of the cells were glial cells, demonstrated with glial fibrillary acidic protein immunohistochemistry. Scale bar, E–H, 50 μm.

Table 3. Multivariate Regression Analysis of Final BCVA and CMT on Preoperative Factors

Variables	Final BCVA Correlation Coefficient, *P* Value	Final CMT Correlation Coefficient, *P* Value
Initial BCVA	0.674, <0.001*	−0.137, 0.296
Initial CMT	0.023, 0.862	0.252, 0.051
Total cell density	0.234, 0.040*	0.191, 0.080
Glial cells	0.253, 0.028*	−0.079, 0.488
Hyalocytes	−0.144, 0.212	−0.180, 0.103
Myofibroblasts	−0.078, 0.501	−0.121, 0.286
RPE cells	−0.036, 0.753	−0.072, 0.515
RBCs	0.119, 0.379	−0.043, 0.753

BCVA = best-corrected visual acuity; CMT = central macular thickness; RBC = red blood cell; RPE = retinal pigment epithelium.
*Statistically significant.

Factors for Visual and Anatomical Recovery

Table 3 presents the results of the multivariate regression analysis of the final BCVA and CMT for each preoperative factor after adjustment for age and sex. The final BCVA was strongly correlated with initial BCVA ($P < 0.001$), total cell density ($P = 0.040$), and glial cell density ($P = 0.028$). Although not statistically significant, the initial CMT and final CMT were positively correlated ($P = 0.051$).

Table 4 presents the results of a subanalysis of the initial and final BCVA for preoperative lens status and a comparison of eyes with or without subsequent cataract surgery during the follow-up period. Cataract surgery was performed on 47 eyes. Moreover, 32 eyes were pseudophakic before ERM surgery, and 8 eyes had no cataract. Our results revealed that the initial status of the lens and cataract extraction was not related to visual acuity.

Correlations between Visual Improvement and Histopathologic Features

Compared with the initial visual acuity, at the 1-year follow-up, 39 (44.8%) of our patients presented with improved vision for ≥ 3 lines, 17 (19.5%) presented improved vision for 1 to 3 lines, 25 (28.7%) retained the same vision for ≤ 1 line, 4 (4.6%) patients lost their vision for 1 to 3 lines, and 1 (1.1%) patient lost their vision for ≥ 3 lines (Fig 4). OCT classification was not correlated with postoperative BCVA improvement. Postoperative changes in BCVA based on OCT classification are illustrated in Figure 5. The density of hyalocytes, myofibroblasts, RPE cells, and RBCs was not correlated with postoperative BCVA changes. However, the presence of lower total cell ($P = 0.022$) and glial cell densities ($P = 0.030$) was correlated with greater visual improvement at 1 year (Table 5).

Discussion

Numerous studies have investigated the etiology,[7,10] cellular pathogenesis,[6,7,11,12] classification,[5] and surgical outcomes[13–16] of ERM. However, the correlations between its clinical presentation and histopathologic characteristics remain unclear. Clinically, ERM appears on ophthalmoscopic examination as a translucent, transparent, or pigmented membrane on the inner retinal surface.[7] Early-stage ERMs are usually asymptomatic, whereas advanced ERMs are likely to cause visual impairments that may affect quality of life. Surgical intervention was usually reserved for patients with severely affected visual functions in the past. However, with advances in minimally invasive vitreoretinal surgery and imaging techniques, safer and more effective surgeries are now being increasingly performed.[17,18] Moreover, researchers classify ERM based on OCT findings rather than based on clinical scales to identify the factors affecting prognosis after surgery.[5,15] However, despite successful ERM removal, the BCVA of some patients may not be restored completely. In idiopathic ERM surgery nowadays, choosing the correct surgical indication and timing is challenging. Thus, elucidating the association between morphological presentation on OCT and cell components of ERMs, and the impact of this association on visual prognosis, may help surgeons to take measures to prevent irreversible retinal damage and to achieve favorable postoperative visual outcomes.

In the present study, we used the OCT-based ERM classification system proposed by Hwang et al[9] to grade the severity of preoperative idiopathic ERMs. Our results revealed that the initial BCVA and CMT progressively worsened from group 1A to group 1C. We only included preoperative and 1-year postoperative data in the analysis because the best final visual outcomes are obtained and stabilized at 12 months after surgery.[19,20] Overall, the final BCVA and CMT at 1 year improved after peeling of the ERMs in all groups. The mean BCVA improvement was similar in all groups. Therefore, eyes in groups 1A and 1B that exhibited a better baseline BCVA achieved more

Table 4. Preoperative and Postoperative BCVA in Terms of Lens Status and Cataract Surgery

	Initial BCVA logMAR	*P* Value	Final BCVA logMAR	*P* Value
Initial lens status		0.9454		0.5805
Phakia, 55 (63%)	0.5588/0.5229		0.3253/0.2218	
Pseudophakia, 32 (37%)	0.5629/0.5229		0.3324/0.3010	
Cataract surgery		0.6724		0.3067
Yes, 47 (85.5%)	0.5750/0.5229		0.3169/0.2218	
No, 8 (14.5%)	0.5426/0.5229		0.3410/0.3010	

BCVA = best-corrected visual acuity; logMAR = logarithm of the minim angle of resolution.
Values are mean/median.

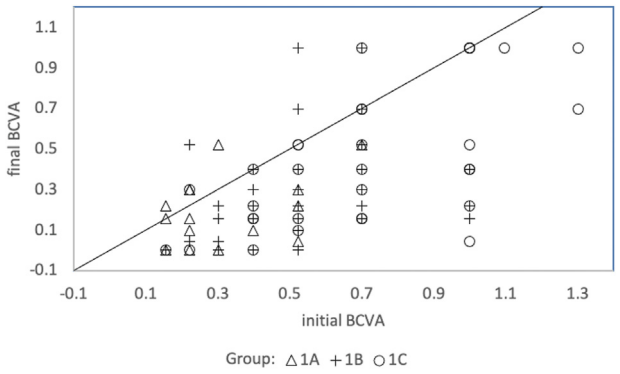

Figure 4. The 1-year visual outcome (logMAR) regarding OCT classification compared with baseline in all patients. BCVA = best-corrected visual acuity; logMAR = logarithm of the minim angle of resolution.

favorable final BCVA than those in group 1C. This finding is in agreement with the results of Rice et al.[21] Thus, we suggest early surgical intervention before BCVA deterioration for the restoration of optimal postoperative vision.

Eyes in group 1C showed the greatest decrease in CMT owing to the greater thickness of ERMs at baseline, but the final CMT was similar among all groups. The anatomic structures of all eyes recovered well. Central macular thickness and BCVA were not significantly correlated, which is consistent with previous findings.[22,23]

Numerous theories regarding the pathogenesis of ERM have been proposed.[7] Migration of retinal tissue–derived glial cells, together with microdefects in the ILM, which occur during PVD and spread to the inner surface of the retina, contributes to ERM formation.[4,24] In contrast, researchers have suggested that anomalous PVD enables the growth and fibrous metaplasia of vitreous cells between the vitreous and the retina, resulting in the formation of ERM.[6,25] Similar to previous studies, we identified glial cells, hyalocytes, myofibroblasts, and RPE cells in the removed ERM samples. However, determining the total cell density on SD-OCT images is difficult because the cellularity of the majority of the membrane specimens was high when observed under a microscope for all groups. Bu et al[26] reported that the cell density in ERM was not associated with preoperative and postoperative visual function, but it has influenced the difficulty involved in ERM peeling. In contrast, we found that a high total cell density in ERMs was associated with a poor final BCVA.

An analysis of cell components revealed that the density of glial cells was high in all groups, whereas the densities of hyalocytes and myofibroblasts were significantly lower in groups 1C and 1B than in group 1A. Studies have reported that glial cells are predominantly found during the early formation of idiopathic ERM,[5,27] along with hyalocytes, which is the primary component of the contacted ERM foci with the posterior hyaloid during incomplete PVD.[6,25] Subsequently, myofibroblasts that may be transdifferentiated from either Müller cells, hyalocytes, or RPE cells with contractile properties contribute to the formation process.[5,6,10,28] As ERMs thicken and contract, they cause superficial retinal folds or traction lines on the inner retina, resulting in visual impairment.[5] In the present study, we demonstrated that the cellularity of glial cells, hyalocytes, and myofibroblasts was predominant in group 1A. However, in groups 1B and 1C, glial cells accounted for the majority of the cell components. Although no significant differences in the total cell density and the density of glial cells were noted among the 3 groups, we found a trend of increasing total cellularity and glial cell density as ERM progressed from group 1A to 1C. Therefore, our results suggest that glial cells, hyalocytes, and myofibroblasts contribute to the formation of ERM, but glial cell proliferation plays a major role in ERM progression. Moreover, we propose that glial cell proliferation rather than myofibroblast contraction may result in morphological changes such as outer retinal inward projection and inner retinal thickening on SD-OCT images. In addition, glial cell proliferation, but not myofibroblast contraction, causes visual deterioration, as evidenced by a study that demonstrated that the thickening of the inner retinal layer at the fovea was strongly correlated with decreased responses on multifocal electroretinography.[9] We also found that a high glial cell density was associated with poor final BCVA after surgery.

A subanalysis of the correlation between visual improvement and histopathologic features revealed that the vision of most of our patients was restored after surgery, regardless of their OCT classification. In all 3 groups, an increase in total cellularity and glial cell density led to poor visual improvement. Thus, predicting visual prognosis based on OCT classification is insufficient because it fails to distinguish the cellularity of ERMs. According to our findings, glial cell proliferation may occur before the

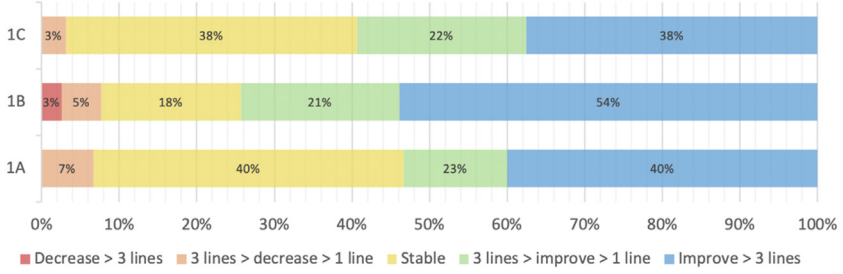

Figure 5. Postoperative changes in best-corrected visual acuity based on OCT classification.

Table 5. Multivariate Regression Analysis of Postoperative BCVA changes on Histopathologic Features

BCVA Changes	β Coefficient	*P* Value
Total cell density	−0.259	0.022*
Glial cells	−0.247	0.030*
Hyalocytes	−0.040	0.210
Myofibroblasts	0.110	0.339
RPE cells	0.089	0.434
RBCs	0.146	0.200

BCVA = best-corrected visual acuity; RBC = red blood cell; RPE = retinal pigment epithelium.
*Statistically significant.

detection of morphological changes in the retina on OCT images. In addition, the increase in the total cellularity and glial cell density of ERMs may cause vision deterioration and damage to the retina structure, hindering BCVA improvement. Therefore, early surgical intervention before the occurrence of massive glial cell proliferation is recommended.

Whether RPE cells are present in idiopathic ERMs is debated.[5,7,12] In the present study, RPE cells were occasionally observed in all groups and were not associated with preoperative and postoperative visual function. Similarly, a few RBCs were occasionally detected in all groups. We believed that these RBCs were derived from the hemorrhage that occurred during ILM peeling. Eyes with adjunctive ILM peeling showed more favorable visual outcomes than nonpeeled eyes, and adjunctive ILM peeling was associated with a lower risk of recurrent ERM.[14,29,30] Therefore, adjunctive ILM peeling was performed in all the ERM surgery cases in this study. The presence of RBCs did not affect the initial or final visual outcomes.

This study has several limitations. First, we enrolled only patients who underwent surgical intervention but not patients with subclinical ERM. We also did not include patients with secondary ERM or fovea-sparing ERM. Thus, our results may not be representative of all the morphological subtypes of ERMs. Second, 8 eyes remained phakic and may have some degree of cataract at 1 year of follow-up. This outcome might have resulted in the underestimation of visual recovery after ERM surgery. However, after adjustment for the initial and final lens status, we found that lens status was not significantly related to visual acuity, which may be because cataract extraction would be arranged once vision was significantly affected. Third, ERM durations were not analyzed in this study, which might be one of the factors affecting visual outcomes.[5] Finally, subjective visual distortion is an indication for ERM peeling. The severity of metamorphopsia was not evaluated in this study, which may have compromised the data analysis.

In conclusion, the present study provides new insights into the formation and progression of idiopathic ERM. The correlations between clinical and histopathologic characteristics of ERM suggest that current surgical indications based on BCVA or OCT classification are insufficient. Glial cell proliferation and increased total cellularity, which are observed before vision deterioration and retinal structure changes, are the most crucial factors for visual prognosis. These findings provide additional evidence supporting early surgical intervention in patients with idiopathic ERM reported with visual disturbance.

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Footnotes and Disclosures

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[1] Department of Pathology and Laboratory Medicine, Taipei Veterans General Hospital, Taipei, Taiwan.

[2] Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan.

[3] Department of Ophthalmology, Taipei Veterans General Hospital, Taipei, Taiwan.

[4] Department of Ophthalmology, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan.

[5] Department of Medical Education and Research, Taipei Veterans General Hospital, Taipei, Taiwan.

[6] Department of Ophthalmology, Cheng Hsin General Hospital, Taipei, Taiwan.

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All authors have completed and submitted the ICMJE disclosures form.

The authors have no proprietary or commercial interest in any materials discussed in this article.

HUMAN SUBJECTS: Human subjects were included in this study. The study protocol was approved by the Institutional Review Board of Taipei Veterans General Hospital. The study was conducted according to the principles described in the Declaration of Helsinki and complied with Health Insurance Portability and Accountability Act and local patient privacy protection regulations. Informed consent from all patients is waived in this study protocol.

No animal subjects were included in this study.

Author Contributions

Conception and design: Wang, Chen, TY Chou, Lin

Analysis and interpretation: Wang, Lo, Huang, YB Chou, Li, Chen, TY Chou, Lin

Data collection: Wang, Lo, Huang, YB Chou, Li, Chen, TY Chou, Lin

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Overall responsibility: Wang, Lo, Huang, YB Chou, Li, Chen, TY Chou, Lin

Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **CMT** = central macular thickness; **ERM** = epiretinal membrane; **ILM** = internal limiting membrane;

PVD = posterior vitreous detachment; **RBC** = red blood cell; **RPE** = retinal pigment epithelial; **SD-OCT** = spectral-domain OCT.

Key Words:
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Correspondence:
Tai-Chi Lin, MD, PhD, Department of Ophthalmology, Taipei Veterans General Hospital, 201, Sec. 2, Shih-Pai Road, Taipei, Taiwan, 11217. E-mail: tclin6@vghtpe.gov.tw.

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