Review

Surgical Treatment of Epiretinal Membrane

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Epiretinal membrane (ERM) is a common retinal disease characterized by cellular proliferation and metaplasia that lead to the formation of a pathological fibrocellular membrane immediately superjacent to the inner retinal surface. The vast majority of ERMs are considered idiopathic. However, ERM formation can result from various primary intraocular diseases, including retinal breaks and detachment, retinal vascular diseases, and vitreoretinal inflammatory conditions. Although ERMs are generally asymptomatic or cause mild metamorphopsia and/or a modest decrease in visual acuity, some can cause severe macular distortion and macular edema, resulting in significantly impaired function. Surgical removal of ERM is the only treatment, and improvements in vitrectomy systems have enabled less invasive treatment. However, there are currently no standardized criteria for ERM surgery, and the indications for surgery are determined from the patient's subjective symptoms. Another problem with ERM surgery is that not all patients show satisfactory postoperative recovery of visual function. Thus, further research is needed to determine the criteria for ERM surgery and methods to improve the postoperative prognosis.

Key words: epiretinal membrane, vitrectomy, optical coherence tomography, internal limiting membrane, lamellar macular hole

E piretinal membrane (ERM) is a common retinal disease characterized by cellular proliferation and metaplasia that lead to the formation of a pathological fibrocellular membrane immediately superjacent to the inner retinal surface (Figs. 1A and 1B). The terms epimacular membrane, macular pucker, cellophane maculopathy, and preretinal macular fibrosis have been used to describe this condition [1-7].

Of late, technology related to ERM surgery, including imaging analyses and surgical devices, has made rapid progress. In this review, we provide an overview of and recent insights into the surgical management of ERM.

Epidemiology and Pathogenesis of ERM

The vast majority of ERM cases are considered idiopathic and unassociated with other systemic or ocular diseases. They are found most frequently after 50 years of age, and several large clinical studies have reported a clinical prevalence of 7% to 11.8% [8, 9]. Most ERMs are asymptomatic, with many being extrafoveal in location. There appears to be no significant gender predilection, and ERM is bilateral in 20-30% of cases. Posterior vitreous detachment (PVD) is present in up to 90% of clinically significant ERMs, with spontaneous posterior hyaloid separation believed to be the causative factor. The Blue Mountains Eye Study reported second eye involvement over a 5-year period in 13.5% of patients [10].
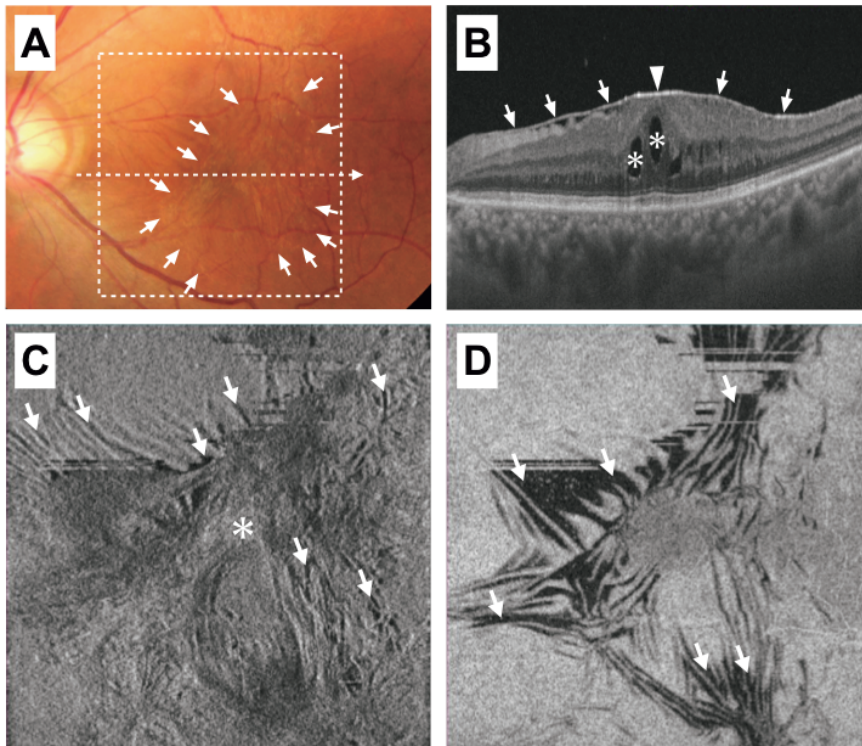
Fig. 1 Epiretinal membrane (ERM) with retinal folds. **A**, Representative color photograph of ERM. The *arrows* indicate the area of ERM. The *dotted arrow* indicates the scan direction of the B-scan optical coherence tomography (OCT) image shown in (B). The *dotted square* shows the scan area of the en face OCT images shown in (C) and (D); **B**, Horizontal B-scan OCT image. The hyperreflective line (*arrows*) on the retinal surface shows ERM. The foveal pit is absent (*arrowhead*), and several cysts are present in the retinal layers (*asterisks*); **C**, En face OCT image at the internal limiting membrane (ILM) level. ERM can be seen as a hyperreflective membrane-like structure (*asterisk*). The *arrows* indicate the retinal folds caused by traction from ERM; **D**, En face OCT image obtained 30 μm below ILM. The black linear structures (*arrows*) indicate the retinal folds.

With regard to the mechanism underlying idiopathic ERM formation, there are several possible theories. Some researchers have suggested that defects in the internal limiting membrane (ILM) created by PVD allow retinal glial cells (Müller cells and astrocytes) to migrate to the inner surface of the retina, where they form an idiopathic ERM [11,12]. Others suggest that, as a result of vitreoschisis and vitreoretinal traction caused by anomalous PVD, hyalocytes in the cortical vitreous remnants in the macular region are stimulated by various cytokines, such as basic fibroblast growth factor and nerve growth factor, after which they proliferate and differentiate into myofibroblasts, leading to idiopathic ERM formation [13-16]. However, the pathogenesis of ERM is not fully understood.

Nonidiopathic (secondary) ERMs have been associated with several vitreoretinal diseases, including retinal vascular diseases (*e.g.*, diabetic and hypertensive retinopathy, venous occlusive disease, angiomas, telangiectasis, *etc.*), vitreoretinal inflammatory conditions (*e.g.*, infectious or noninfectious uveitis), postoperative and post-traumatic states, inherited and congenital posterior segment anomalies and syndromes, intraocular tumors, and retinal breaks and detachment [17-41].

The pathogenesis of secondary ERMs differs from that of idiopathic ERMs because of the central role played by inflammation, which induces cellular proliferation and transdifferentiation to promote ERM formation and contraction. This mechanism is evidenced by an increase in the expression of cytokines such as interleukin-6 and 8 and monocyte chemoattractant protein-1 [42]. These cytokines are known to support inflammatory cells identified in secondary ERMs [43,44].

ERMs that occur following retinal breaks and detachment are thought to have a pathogenic mechanism in addition to inflammation; RPE cells gain access to the vitreous cavity through the retinal break and settle on the macular surface, subsequently developing into a membrane [45]. These membranes are architecturally enhanced by the presence of fibroblasts and macrophages, which are stimulated in part by the inflammation associated with vitreous hemorrhage and/or surgical repair.

Visual Function in ERM

ERMs are usually asymptomatic or cause mild

symptoms of metamorphopsia and/or a modest decrease in visual acuity. Among patients with idiopathic ERMs, two-thirds exhibit a visual acuity of 20/30 or better, while 85% display a visual acuity of 20/70 or better [7,46]. A visual acuity of 20/200 or lower may be observed in a small number of patients (approximately 5%) [47-49]. A few of these membranes can cause macular distortion and edema to the extent that clinicians recommend their removal via pars plana vitrectomy.

One of the most common symptoms in ERM patients is metamorphopsia, which is a subjective symptom characterized by distortion of viewed objects. In patients with ERM, metamorphopsia is thought to result from the displacement of photoreceptors due to retinal traction and/or visual cortex reorganization as well as perceptual adjustment in response to disrupted sensory input from the retina [50-56]. Metamorphopsia is quantitatively evaluated using M-CHARTS (Inami Co., Tokyo). The severity of distorted vision in normal eyes is 0 in both the vertical and horizontal directions. In general, difficulties in daily life start to occur when the severity of distorted vision exceeds 0.5, and ERM surgery might be indicated at this point [57].

Imaging Analyses of ERM

Optical coherence tomography (OCT) plays an important role in the clinical assessment of eyes with ERMs. OCT can detect ERMs and can also assist in topographic localization, identification of vitreoretinal relationships (such as vitreomacular traction syndrome), detection of lamellar or full-thickness macular holes and retinal folds, and quantitation of macular thickness and macular volume (Figs.1B-1D) [58]. In addition to its value in clinical characterization, OCT has therapeutic value in preoperative planning. The co-existence of a macular hole, the presence of a bilaminar ERM, or knowledge of substantive macular edema may lead the surgeon to modify his or her approach. OCT also shows considerable prognostic value in terms of counseling patients regarding the visual potential of the affected eye. Finally, it can assist in postoperative management via assessments of the macular thickness and membrane regrowth.

Treatment of ERM

Surgical excision is the only available treatment option for ERM. The aim of surgical intervention is to improve traction-induced visual disturbance via removal of ERM, which relieves the macular traction. In recent years, the increased resolution of OCT has enabled the early detection of asymptomatic ERMs [58-60]. However, no objective or quantitative criteria for indicating surgical removal of ERM have been established. Therefore, it is essential to conduct a thorough risk/benefit analysis and carefully judge whether surgery is indicated based on the results of subjective visual function tests as well as the patient's lifestyle and environment.

Surgical Procedure

Surgical setting. In recent years, several advancements have facilitated safe and relatively fast vitrectomy; these include the availability of better microincision vitrectomy surgery (MIVS) systems, development of small-gauge forceps and chandelier illumination, improvements in light-emitting diodes and other light sources, and availability of microscope systems with wide fields of vision. When performed using the new MIVS system, vitrectomy uses three or four ports. The size of the vitrectomy device can be either 20-, 23-, 25-, or 27-gauge. The 25-gauge system is the principal vitrectomy system in international use, although the 27-gauge system is gradually seeing wider adoption. In recent years, digitally assisted vitrectomy surgery has become available, and it has become possible to perform macular surgery, including surgery for ERM, at higher magnifications and lower illumination intensities. If cataracts are clinically present before ERM surgery and/or the patient is aged over 50 years and his/her cataracts are expected to progress after surgery, the cataract surgery system should be prepared such that cataract surgery and intraocular lens (IOL) implantation can be performed simultaneously with vitrectomy.

Visualization of vitreous, induction of posterior vitreous detachment, and core and peripheral vitrectomy. After core vitrectomy, the vitreous body is visualized by steroid particles (triamcinolone acetonide) to confirm the occurrence of PVD [61,62]. PVD occurs spontaneously in approximately 70% of cases of

ERM [63]. However, when it has not occurred, it is induced by aspiration of the vitreous body. The adhesion between the vitreous body and ERM is sometimes extremely strong; therefore, when the vitreous body is aspirated, care must be taken to avoid macular damage from excessive traction. After PVD, core and peripheral vitrectomy is performed. Any vitreous body remaining in the area surrounding the trocar can lead to an increased risk of retinal tears due to traction from the vitreous body when instruments are inserted or extracted. Therefore, it is safer to excise the part of the vitreous body surrounding the trocar. In phakic eyes, the lens should not be allowed to come in contact with the vitreous cutter. The combined use of chandelier illumination and a wide-angle viewing system can facilitate safe and efficient surgery with a wide field of vision.

Visualization and peeling of ERM.   It is generally difficult to distinguish the boundary between ERM and the retina; therefore, triamcinolone acetonide and vital dyes are used to enhance ERM visualization so that safe and complete ERM peeling can be achieved. Commonly used vital dyes include trypan blue, indocyanine green (ICG), and brilliant blue G (BBG) [64-72]. Triamcinolone acetonide adheres to ERM but not to ILM (Figs. 2A and 2B), whereas trypan blue passes through cell membranes and stains the cells, with greater affinity for ERM than for ILM. Therefore, use of these 2 visualizing agents enables positive visualization of ERM. In contrast, ICG and BBG stain ILM but not ERM, enabling negative staining of ERM. Appropriate use of these agents based on an understanding of their properties allows for effective visualization of the relevant structures during ERM surgery. Removal of ILM, the scaffold for myofibroblast proliferation, enables complete removal of ERM and has been suggested to reduce the risk of ERM recurrence [73-77]. If ILM peeling is performed at the same time as ERM surgery, retinal staining with ICG and BBG should be performed multiple times before and after ERM and ILM peeling to
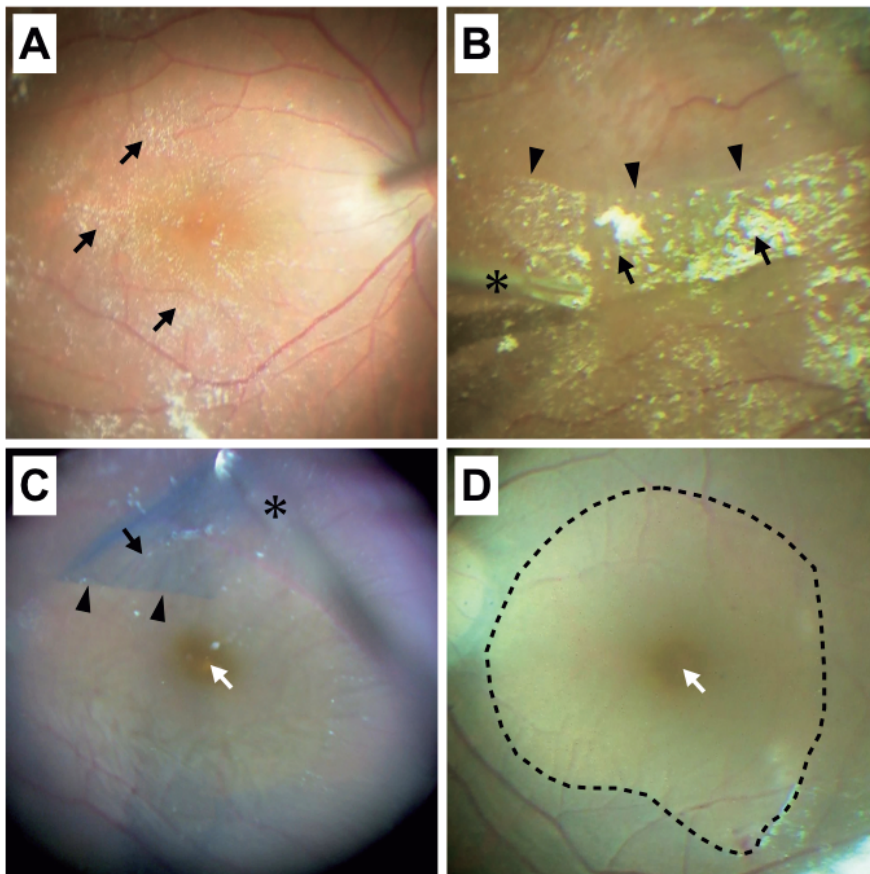
Fig. 2   Images captured during epiretinal membrane (ERM) surgery. **A**, ERM is visualized with triamcinolone acetonide (*arrows*); **B**, ERM visualized with triamcinolone acetonide (*arrows*) is peeled with end-grabbing forceps (*asterisk*). The *arrowheads* indicate the edge of the peeled ERM; **C**, The internal limiting membrane (ILM) visualized with brilliant blue G (BBG) (*black arrow*) around the fovea (*white arrow*) is peeled with end-grabbing forceps (*asterisk*). The *arrowheads* indicate the edge of the peeled ILM; **D**, The region without BBG staining (*dotted area*) is the ILM-peeled area. The *arrow* indicates the fovea.

enable timely assessment of the presence of any residual ERM or ILM (Figs. 2C and 2D) [78-80]. Although it was recently reported that trypan blue and BBG show lower cytotoxicity than does ICG, any of these staining agents can be cytotoxic if used at too high a concentration [80-82]. Thus, the appropriate concentrations must be used, and the agents must be sufficiently washed out after use.

If the boundary between ERM and the retina is clear, ERM peeling can be performed by directly grasping the ERM margin using end-grabbing forceps. Initiation of ERM peeling in the space between ERM and the retina reduces the risk of retinal damage during surgery. The site at which ERM peeling is initiated can be determined using either preoperative OCT or a surgical microscope in combination with integrated intraoperative OCT. If the boundary between ERM and the retina as well as any space between ERM and the retina is not clear, ERM peeling should be preferably initiated at the temporal inferior area of the macula, not in the area of the papillomacular bundle or any site in close proximity to the macula; this avoids damage to the central and lower parts of the field of vision.

The appropriate area of ERM peeling has not been established. Hirano *et al.* reported that ERM and ILM peeling completely resolved retinal traction caused by ERM, and that the traction outside the parafoveal area, a 3-mm-diameter circle centered at the fovea, did not affect the postoperative improvement in visual function [58]. Kanzaki *et al.* reported that ERM formation did not affect visual function when the area of ILM peeling was larger than the parafoveal area [83]. In consideration of these reports, a 3-mm-diameter circle centered at the fovea may be the minimum area required for ERM and ILM peeling.

Complications of Surgery

Posterior retinal breaks, macular hole, and retinal hemorrhage.   When peeling ERM and/or ILM, retinal traction can cause posterior retinal breaks, macular holes, and retinal hemorrhages. For a minor posterior retinal break, gas tamponade with subsequent monitoring for progression is sufficient. In contrast, if the retinal break is distant from the macula, or if a major retinal break is likely to cause postoperative retinal detachment, it is necessary to perform laser treatment around the break, followed by gas tamponade. If a macular hole forms, ILM peeling and gas tamponade are performed. Retinal hemorrhage is generally self-limiting and does not require treatment; however, it can be stopped if necessary by increasing the irrigation pressure or applying diathermy.

Intraoperative lens damage.   Devices that are inserted into phakic eyes, including trocars, vitreous cutters, light pipes, and end-grabbing forceps, rarely come in contact with the lens and damage it. In case these devices touch the lens, ERM peeling is still feasible if the damage to the lens is minor. However, lensectomy is required if the damage results in reduced retinal visibility. Depending on the condition of the lens capsule, IOL can be simultaneously implanted. If the lens capsule is severely damaged, IOL is implanted with sutured fixation or sutureless intrascleral fixation, generally as a secondary treatment. Postoperative progression of cataracts frequently occurs when surgery is completed in the phakic state. Secondary cataract surgery is performed in these cases, but these surgeries are somewhat difficult because of a higher probability of posterior capsule rupture.

Postoperative cataracts.   Postoperative nuclear sclerotic cataracts develop in 10-70% of phakic eyes after completion of lens-sparing surgery [73, 84-88]. The probability of this complication occurring in an earlier postoperative phase is higher in older patients; thus, patients aged over 50 and/or those with pre-existing nuclear sclerosis are treated with phacoemulsification and IOL implantation simultaneously with ERM surgery [89, 90]. In most cases, phacoemulsification is performed first, followed by vitrectomy. IOL implantation is performed before or after vitrectomy depending on the surgeon's preference.

Peripheral retinal tear and postoperative retinal detachment.   Peripheral retinal tears are found in up to 6% of cases [63, 73, 86, 87, 91-94], but the frequency of this complication appears to be lower when MIVS is applied [95, 96]. Peripheral retinal tears often develop in association with surgical equipment insertion, which can cause traction from the vitreous body in the vitreous base. Therefore, peripheral retinal tears can be prevented by excising the vitreous body surrounding the trocar. In patients who show lattice degeneration and strong adherence between the vitreous body and retina, excessive aspiration of the vitreous body during PVD induction should be avoided for the prevention of peripheral retinal tears. A search for retinal tears

should be carefully performed using a wide-angle viewing system and scleral indentation to ensure that no peripheral retinal tears are overlooked. If peripheral retinal tears are found, the vitreous body surrounding them should be shaved; in addition, laser photocoagulation or transscleral cryotherapy should be applied to the retinal tears. Fluid–air or fluid–gas exchange can then be performed to complete the surgery. Postoperative retinal detachment occurs in up to 14% of patients undergoing vitrectomy surgery, and this complication is usually associated with overlooked peripheral tears or later contraction of the vitreous base [85,86,92,93,97]. If postoperative retinal detachment occurs, retinal detachment repair surgery should be performed as soon as possible, depending on the state of the retinal detachment.

Other complications associated with ERM peeling. Other complications associated with ERM peeling have also been reported, including endophthalmitis, retinal phototoxicity, choroidal neovascularization, and visual field defects. Acute-onset endophthalmitis is a serious complication with an incidence rate of 0.030-0.070% [98-100]. In general, thorough sterilization of equipment as well as the use of disposable items and topical antibiotics are encouraged. Additionally, an important practice to prevent endophthalmitis when performing MIVS is to suture the scleral incision site if the self-sealing of the scleral incision is judged to be insufficient at the completion of surgery [101].

ERM recurrence. Recurrence of epiretinal tissue formation after vitrectomy is observed in less than 20% of patients and rarely has a significant effect on vision [73,76,86,87,92,102]. ERM recurrence is thought to be caused by the residual vitreous cortex and/or insufficient ERM removal. Additionally, the current body of evidence suggests that ILM provides a scaffold for ERM recurrence [102]. In their 2017 meta-analysis, Chang *et al.* reported that vitrectomy with ILM peeling is associated with lower rates of ERM recurrence [103], although the proportion of cases with vision-limiting recurrent ERM is small. If ERM recurrence reduces visual function, ERM peeling is repeated.

Controversies related to ILM peeling. There are several reasons that ILM peeling should be avoided. One is that ILM is the basal lamina connected to the end feet of the Muller cells; thus, ILM peeling can cause mechanical damage to the retinal tissues, which could potentially lead to dissociation of the nerve fiber layer

and inner retinal dimpling. Other reasons are that ILM peeling can affect Müller cell function, and that the stains used to visualize ILM have cytotoxic effects [104-110].

Several meta-analyses to investigate the safety and efficacy of ILM peeling have recently been published [103,111,112]. However, it remains unclear whether ILM peeling should be routinely performed for patients with ERM; to clarify this point, it will be necessary to monitor a larger number of patients for extended periods and conduct prospective randomized clinical trials.

Postoperative Changes in Visual Function

Visual acuity. In most patients, the macular surface architecture is greatly improved immediately after surgery, although a short-term decrease in the visual acuity to below the preoperative level is not uncommon. While immediate and significant improvements in the visual acuity may occur, it often takes 4 to 6 weeks for the patient's vision to return to the preoperative level, and subsequent improvement continues over the following 3 to 6 months. It has been reported that 60-90% of patients show a visual acuity improvement of two or more lines by 6 to 12 months after surgery [84,86,87,92,97,113-116].

Numerous studies have been conducted to elucidate the factors associated with visual acuity prognosis. Previously reported preoperative factors associated with better postoperative visual acuity include better preoperative visual acuity [113,114,117-122], greater inner nuclear layer (INL) thickness [123], greater photoreceptor outer segment length [121], ellipsoid zone integrity [113,118,119,124-126], and lesser central foveal thickness [120,123,125,127].

Metamorphopsia. Metamorphopsia is alleviated by ERM peeling, but it is not completely cured by the procedure, probably because the photoreceptor cell arrangement does not revert to its exact original state following ERM peeling. According to a report by Kinoshita *et al.*, metamorphopsia is present at approximately 50% and 30% of the preoperative level at 3 months and 1 year after surgery, respectively [114]. In particular, the INL thickness has been reported to be significantly associated with metamorphopsia, with a thicker INL being associated with more severe metamorphopsia both preoperatively and postoperatively [128-130].

A Peculiar Type of ERM: Lamellar Hole-Associated Epiretinal Proliferation (LHEP)

LHEP is a membranous tissue seen on the surface of the retina and was first reported by Witkin *et al.* [131]. LHEP is mainly observed in patients with macular hole and degenerative lamellar macular hole (LMH), which is a type of LMH that involves very little retinal traction in its pathology [59,132,133]. The term "LHEP" was coined by Pang *et al.*, and the condition has also been termed "dense non-tractional ERM" and "atypical epiretinal tissue" [133-135]. Recently, it was reported that the presence of LHEP is not exclusive to LMH [136], and Hubschman *et al.* proposed to delete the prefix "lamellar-hole associated" from LHEP and term the membrane "epiretinal proliferation" [137]. However, LHEP remains the best-known and most frequently used term.

Unlike idiopathic ERMs, LHEPs are yellow because of the presence of carotenoids [138]. In addition, LHEPs appear thick with moderate reflectivity in OCT [133], whereas idiopathic ERMs are thin and highly reflective. Although LHEPs are highly extensible and can be readily peeled off the retinal surface, complete removal is difficult because they are closely associated with retinal tissue at the LMH and macular hole margins [134,135,139-141], a feature not shared with idiopathic ERMs.

Histological studies have shown that LHEPs contain cells that are positive for specific markers of glial cells or hyalocytes. These cells are therefore considered to be the major components of LHEPs [139,142-148]. On the other hand, LHEPs do not stain with α-smooth muscle actin antibody, suggesting that they do not have contractile properties [139,146].

Treatment of degenerative LMH leads to challenges regarding the approach to LHEPs [132]. Until now, degenerative LMH has been treated by both ILM and LHEP removal. However, it has been reported that visual acuity improvements following surgery are insufficient, and postoperative macular holes develop in 16% of cases [134,149,150]. Recently, Shiraga *et al.* proposed a new surgical technique to treat LHEP associated with degenerative LMH, wherein LHEP is embedded into the macular aperture such that it fills the retinal gap [140,151,152]. The same group reported postoperative improvements in the macular contour and visual acuity [140,151,152]. Similar to the inverted ILM flap technique, the mechanism of action of the LHEP embedding technique is thought to be restoration of the macular structure by glial cells within LHEP [153,154]. Although the results thus far are promising, further research on this treatment approach for degenerative LMH is necessary.

Conclusions

The efficacy of surgical removal of ERMs by vitrectomy for improving visual function was first reported by Machemer in 1978 [155]. In the more than 40 years since, progress in OCT technology and vitrectomy systems has resulted in detailed elucidation of the ERM pathology and enabled less invasive treatment. However, clear criteria indicating surgery remain to be established, and indications for surgery are, therefore, still based on the patient's subjective symptoms along with the physician's judgment. Another problem is that not all patients show satisfactory recovery of visual function after surgery. Further research regarding the criteria for indicating ERM surgery and the factors associated with the visual prognosis is necessary.

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