

Epiretinal membrane: optical coherence tomography-based diagnosis and classification

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Abstract: Epiretinal membrane (ERM) is a disorder of the vitreomacular interface characterized by symptoms of decreased visual acuity and metamorphopsia. The diagnosis and classification of ERM has traditionally been based on clinical examination findings. However, modern optical coherence tomography (OCT) has proven to be more sensitive than clinical examination for the diagnosis of ERM. Furthermore, OCT-derived findings, such as central foveal thickness and inner segment ellipsoid band integrity, have shown clinical relevance in the setting of ERM. To date, no OCT-based ERM classification scheme has been widely accepted for use in clinical practice and investigation. Herein, we review the pathogenesis, diagnosis, and classification of ERMs and propose an OCT-based ERM classification system.

Keywords: macular pucker, cellophane macular reflex, preretinal macular fibrosis, optical coherence tomography, central foveal thickness, inner segment ellipsoid band

Introduction

Epiretinal membrane (ERM), also known as macular pucker or cellophane maculopathy, is a disorder of the vitreomacular interface that can cause visual impairment. The clinical presentation of an ERM can range from completely asymptomatic, diagnosed on routine examination, to profoundly symptomatic with metamorphopsia, micropsia or macropsia, photopsia, decreased visual acuity (VA), and loss of central vision. The symptoms associated with ERMs, especially metamorphopsia, can impair vision-related quality of life.¹ It has been estimated that 30 million people of advanced age in the US have an ERM in at least one eye.² Numerous potential risk factors for the development of an ERM have been identified, including race, ethnicity, sex, smoking, diabetes, arteriolar narrowing, and hypercholesterolemia; however, the most consistently identified risk factor is age.³ Most ERMs occur in individuals older than 50 years, and the prevalence of ERM increases as age increases. The prevalence of ERM varies from 2.2% to 28.9% depending on the population being studied.^{4,5}

ERM is a pathologic fibrocellular membrane that lies immediately superjacent to the inner surface of the retina. Clinically, an ERM can be classified as either cellophane macular reflex or preretinal macular fibrosis based on severity.² Furthermore, an ERM can be classified as either idiopathic or secondary based on etiology.^{6–13} Historically, ERMs were diagnosed and classified based on clinical examination findings alone. However, recent advances in imaging have allowed clinicians to more accurately diagnose and characterize ERMs and their associated complications, such as vitreomacular traction and macular hole.¹⁴ Imaging techniques, such as spectral-domain optical coherence tomography (SD-OCT) with three-dimensional reconstruction, have been introduced for this purpose. In order to fully harness these technological advances, a

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standardized classification system must be devised. Herein, we review the basics of ERMs and propose an OCT-based classification system for ERMs.

Pathogenesis

The vitreous is the transparent gel that occupies the posterior segment of the eye and is composed primarily of water, collagen, hyaluronan, and hyalocytes.¹⁵ The vitreous adheres to the inside of the eye at the posterior lens capsule, peripheral retina, retinal vessels, perimacular region, and optic disk. As the vitreous ages, it liquefies and its retinal adhesions weaken. This can precipitate the separation of the vitreous from its posterior attachments, an occurrence known as posterior vitreous detachment (PVD). PVD has been described in up to 95% of cases of idiopathic ERM.¹⁶ Numerous theories have been proposed to explain the association between PVD and idiopathic ERM. A classically accepted theory is that PVD causes breaks in the internal limiting membrane (ILM) that allow cells to migrate to the inner surface of the retina where they form an idiopathic ERM.^{17,18} However, this theory has been challenged by the finding that breaks are exceedingly rare in the ILMs associated with ERMs.¹⁹ An alternative theory has been proposed that involves the concept of anomalous PVD.²⁰ Anomalous PVD occurs when vitreous liquefaction outpaces vitreoretinal adhesion weakening, resulting in vitreoschisis and vitreoretinal traction.²¹ When vitreoschisis occurs, remnants of the cortical vitreous are left in the premacular region.²² Vitreoretinal traction induces the production of cytokines, such as basic fibroblast growth factor and nerve growth factor, that stimulate the residual vitreous cells to proliferate.²³ Moreover, residual vitreous cells may promote the migration of cells or projection of cell processes through an otherwise intact ILM.²⁴

The precise identification of the cells and cell lineages involved in the pathogenesis of idiopathic ERMs has been hindered by the ability of these cells to transdifferentiate.²⁵ Glial cells are thought to predominate in early idiopathic ERMs.²⁶ However, the exact etiology of these glial cells remains unclear; there is evidence that these glial cells derive from Müller cells or astrocytes.^{26–28} Hyalocytes, likely originating from cortical vitreous remnants following anomalous PVD, have been identified in ERMs, and the transdifferentiation of hyalocytes may play a central role in ERM formation.^{28,29} The role of macrophages in the pathogenesis of idiopathic ERMs has yet to be determined; hyalocytes are of macrophage lineage, and some glial cells are specialized macrophages.^{29,30} The presence of retinal pigment epithelial cells in idiopathic ERMs is a subject of debate, and there is

evidence that retinal pigment epithelial cells may only be found in secondary ERMs following retinal detachment.^{31,32} Fibroblasts likely contribute to the pathogenesis of idiopathic ERMs by producing collagen.³³ Myofibroblasts, possibly of hyalocyte, Müller cell, or retinal pigment epithelial cell origin, are thought to predominate in late idiopathic ERMs.^{28,33–35} Myofibroblasts can deposit collagen, secrete contractile proteins, and induce intracellular contraction that may account for the contractile properties of late idiopathic ERMs.

Extracellular matrix production and remodeling plays a central role in the pathogenesis of idiopathic ERM. Given the proposed involvement of anomalous PVD, the extracellular matrix of early idiopathic ERM is likely composed primarily of type II collagen. The ultrastructure of idiopathic ERMs is characterized by a dense, irregular network of extracellular fibrils that are oriented at random.³⁶ The diameter of these extracellular fibrils varies based on the stage of idiopathic ERM, suggesting that there are differences in collagen composition. Cellophane macular reflex fibrils are thin, ranging from 6 nm to 15 nm in diameter, while in preretinal macular fibrosis, the fibers are thick, ranging from 18–26 nm to 36–56 nm in diameter.³⁶ The extracellular matrix components that have been described in ERMs include collagen types I, II, III, IV, and VI, fibronectin, and laminin.^{36–38} Collagen types III and IV, fibronectin, and laminin are present in both early and late idiopathic ERMs.³⁶ Cellophane macular reflex has been shown to contain large amounts of collagen type VI.³⁶ Type VI collagen presumably anchors the ERM to the ILM of the retina. Preretinal macular fibrosis has been shown to contain large amounts of collagen types I and II.³⁶ Collagen types I and II presumably form the bulk of the extracellular matrix in late ERMs. The retinal distortions induced by ERM contraction are thought to be the primary reason for visual impairment in idiopathic ERM.

Like idiopathic ERMs, secondary ERMs are frequently associated with PVD, suggesting that idiopathic and secondary ERMs share some pathogenic mechanisms.³⁹ However, secondary ERMs differ in that they are associated with etiologies, such as posterior uveitis, cytomegalovirus retinitis, diabetic retinopathy, retinal vein occlusion, blunt force trauma, retinal detachment and repair, argon laser photocoagulation, and cataract surgery.^{7–12} The involvement of cellular proliferation, migration, and adhesion suggests that secondary ERM formation may be an abnormal wound healing response.⁴⁰ Inflammation is a central component of many of the disorders associated with secondary ERMs, as evidenced by the increased expression of cytokines, such as interleukin (IL)-6, IL-8, and monocyte chemoattractant

protein-1.⁴¹ These cytokines support the inflammatory cells that have been identified in secondary ERMs, including macrophages, T-cells, and B-cells.^{42,43} Interestingly, glial cells are thought to predominate in both idiopathic and secondary ERMs, and IL-6 has been implicated in glial cell activation and proliferation.^{43,44} Some of the disorders associated with secondary ERMs involve angiogenesis, and the resultant secondary ERMs have been shown to contain proangiogenic factors, such as vascular endothelial growth factor, and variable amounts of vascular tissue.^{45,46} As compared to idiopathic ERMs, secondary ERMs tend to occur in younger patients and be associated with worse VA and greater central foveal thickness (CFT).³⁹

Diagnosis and classification

The diagnosis and classification of ERMs has historically been based on clinical examination findings.⁴⁷ In clinical practice, ERMs are frequently classified as either cellophane macular reflex, the early form, or preretinal macular fibrosis, the late form.^{2,13} Cellophane macular reflex denotes a thin transparent membrane overlying the macula. Because this membrane does not distort the retina, it typically does not cause visual impairment; therefore, cellophane macular reflex

can be an incidental finding on routine clinical examination. Slit lamp biomicroscopy of cellophane macular reflex reveals a glinting, water-silk, shifting light reflex from the inner surface of the retina (Figure 1).⁴⁸ In select cases, preretinal macular fibrosis develops as the membrane thickens and contracts, with the appearance of superficial retinal folds or traction lines, becoming opaque and gray.⁴⁸ Preretinal macular fibrosis can distort the retina, resulting in visual impairment in ~80% of cases.⁴⁹ Slit lamp biomicroscopy of preretinal macular fibrosis reveals a semitranslucent membrane that obscures the underlying retinal features and may be associated with superficial or full-thickness retinal folds or traction lines and vascular tortuosity or dilation (Figure 1). Severe cases can involve retinal hemorrhages, exudates, vascular abnormalities, edema, macular pseudoholes, and macular holes, resulting in further visual impairment.² In addition to clinical examination, a variety of ancillary tests can assist in the diagnosis and classification of ERM; for example, fluorescein angiography can demonstrate retinal edema. However, OCT is the ancillary test that has had the greatest impact on clinical practice.

OCT is a medical imaging technique used to produce noninvasive high-resolution cross-sectional images of

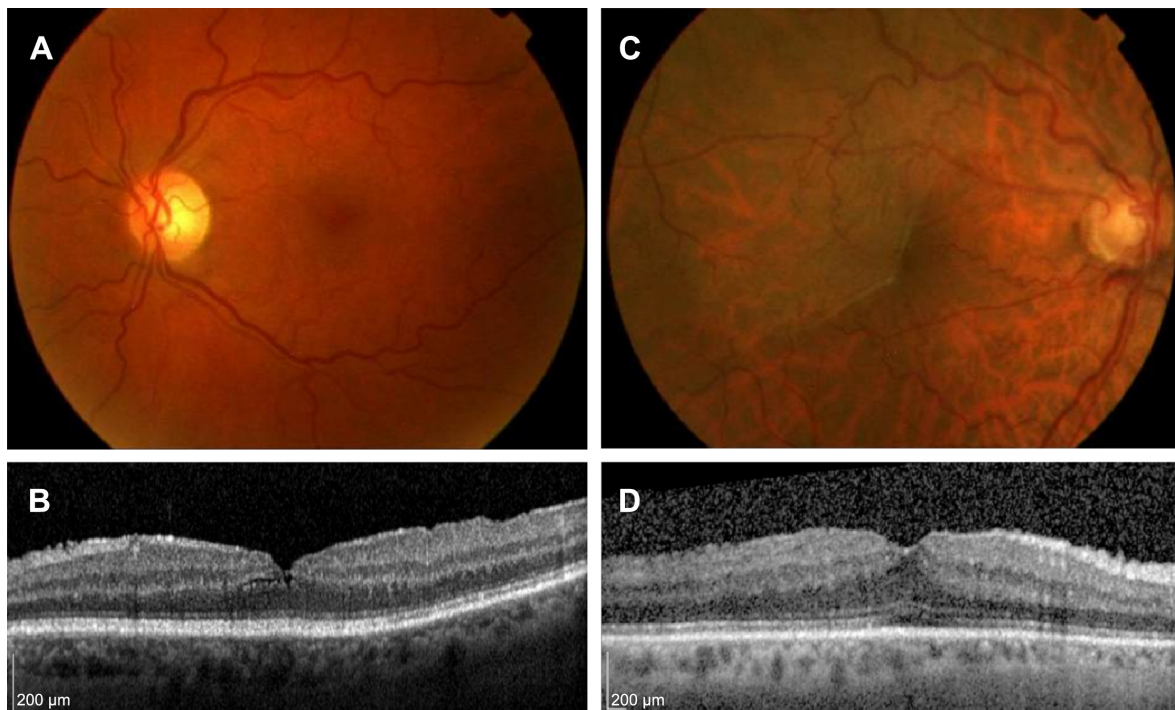


Figure 1 Epiretinal membrane examples.

Notes: (A) Color fundus photograph demonstrating subtle cellophane macular reflex. (B) Spectralis OCT scan through the central fovea of (A) demonstrating a primary epiretinal membrane without significant retinal thickening (central foveal thickness of 274 μm) with an intact inner segment ellipsoid band. (C) Color fundus photograph demonstrating preretinal macular fibrosis. (D) Spectralis OCT scan through the central fovea of (C) demonstrating a primary epiretinal membrane with significant retinal thickening (central foveal thickness of 364 μm) with an intact inner segment ellipsoid band.

Abbreviation: OCT, optical coherence tomography.

biological tissues. OCT has proven to be more sensitive than clinical examination for the diagnosis of numerous disorders of the vitreomacular interface, including ERM.⁵⁰ In clinical practice, time-domain OCT has largely been supplanted by SD-OCT, also known as Fourier-domain OCT, because of the improved scanning speed and detection sensitivity of the latter technique.⁵¹ The use of broadband light has significantly improved axial resolution, and there are now several commercially available SD-OCT systems with axial resolutions of ~4 μm .^{52,53} To perform SD-OCT, broadband light is split into several arms: the measurement arm is backscattered by the tissue of interest, and the reference arm is backscattered by a stationary mirror of a known distance.⁵⁴ The backscattered light from both sources is combined, and the interference spectrum is recorded using a spectrometer and a charge-coupled device camera. Fourier transform of the interference spectrum provides data on the echo time delay of light that is used to form a tissue reconstruction. Transverse scanning is used to form a two-dimensional tissue reconstruction, and the augmented speed of SD-OCT now allows for volumetric three-dimensional tissue reconstruction.¹⁴

The International Vitreomacular Traction Study Group recently proposed definitions and classification systems for several disorders of the vitreomacular interface based entirely on OCT findings.⁵⁵ Vitreomacular adhesion (VMA) was defined as perifoveal vitreous separation with residual vitreomacular attachment and normal foveal morphology. VMA was subclassified as isolated or concurrent based on the absence or presence of associated macular abnormalities, such as diabetic macular edema. Furthermore, VMA was subclassified as either focal ($\leq 1,500 \mu\text{m}$) or broad ($> 1,500 \mu\text{m}$) based on the diameter of its vitreous attachment. Vitreomacular traction (VMT) was defined as anomalous PVD in association with an anatomic distortion of the normal foveal morphology, and VMT was subclassified as isolated or concurrent and focal or broad in the same manner as VMA. Full-thickness macular hole (FTMH) was defined as a foveal lesion that interrupts all layers of the macula from the ILM to the retinal pigment epithelium. FTMH was subclassified based on the presence or absence of VMT. FTMH was also subclassified as primary if it was initiated by VMT or secondary if it was associated with a disorder known to cause macular hole in the absence of prior VMT. Furthermore, FTMH was subclassified as small ($\leq 250 \mu\text{m}$), medium ($> 250 \mu\text{m}$ to $\leq 400 \mu\text{m}$), or large ($> 400 \mu\text{m}$) based on its narrowest diameter. The International Vitreomacular Traction Study Group made note of the relationship between anomalous PVD and idiopathic ERM; however, an ERM classification system was not proposed.

Clinical studies have utilized various disparate systems to classify ERMs based on OCT findings.⁵⁶⁻⁵⁹ For example, an OCT-based idiopathic ERM classification system has been proposed based on foveal morphology.⁵⁸ The proposed classifications include (1A) fovea-involving ERM with outer retinal thickening and minimal inner retinal change, (1B) fovea-involving ERM with outer retinal inward projection and inner retinal thickening, (1C) fovea-involving ERM with prominent thickening of the inner retinal layer, (2A) fovea-sparing ERM with formation of a macular pseudohole, and (2B) fovea-sparing ERM with schisis-like intraretinal splitting (Table 1). To validate this classification system, multifocal electroretinography was used to demonstrate the functional differences among the various classifications. Another OCT-based ERM classification system has been proposed based on the extensive morphologic classification and subclassification.⁵⁹ The proposed primary classifications include (A) with PVD and (B) without PVD. Classification (A) was subclassified as (A1) without contraction of the ERM and (A2) with contraction of the ERM; subclassification (A2) was further subclassified as (A2.1) with retinal folding, (A2.2) with edema, (A2.3) with cystoid macular edema, and (A2.4) with lamellar macular hole. Classification (B) was subclassified as (B1) without VMT and (B2) with VMT; subclassification (B2) was further subclassified as (B2.1) with edema, (B2.2) with retinal detachment, and (B2.3) with schisis (Table 2). This classification system provides a framework for thoroughly describing the morphologic characteristics of an ERM; however, it has yet to be validated, and its clinical relevance remains unclear.

OCT-based classification systems such as the abovementioned ones are poised to supplant the clinical examination-based classification systems currently utilized in clinical practice. In order for an OCT-based ERM classification system to be meaningful, the OCT findings that are included should be evidence-based. CFT is one of the most extensively studied OCT findings, in large part because it was measurable

Table 1 OCT-based morphologic classification of idiopathic ERMs

Group 1: fovea-involving ERM	
1A	Outer retinal thickening and minimal inner retinal change
1B	Outer retinal inward projection and inner retinal thickening
1C	Prominent thickening of the inner retinal layer
Group 2: fovea-sparing ERM	
2A	Formation of a macular pseudohole
2B	Schisis-like intraretinal splitting

Note: Data from Hwang et al.⁵⁸

Abbreviations: ERMs, epiretinal membranes; OCT, optical coherence tomography.

Table 2 OCT-based morphologic classification of ERMs

Group A: with posterior vitreous detachment	
A1	No contraction
A2	Contraction
A2.1	With retinal folding
A2.2	With edema
A2.3	With cystoid macular edema
A2.4	With lamellar macular hole
Group B: with vitreous attachment	
B1	No traction
B2	Vitreomacular traction
B2.1	With edema
B2.2	With retinal detachment
B2.3	With schisis

Note: Data from Konidaris et al.⁵⁹

Abbreviations: ERMs, epiretinal membranes; OCT, optical coherence tomography.

with early iterations of time-domain OCT. CFT is the distance between the inner surface of the retina and the inner surface of the retinal pigment epithelium as measured at the central fovea. At baseline, most ERMs are associated with both increased CFT and worsened VA, and there is overwhelming evidence that successful surgical intervention is associated with both decreased CFT and improved VA.^{60–78} However, variable and inconsistent findings have been reported regarding the correlation between preoperative CFT and postoperative VA. Overall, these findings suggest that CFT may be useful for evaluating the impact of ERM on baseline VA, but CFT is probably not useful for predicting postoperative VA. Contemporary SD-OCT allows for the characterization of subtle OCT findings, such as the inner segment ellipsoid (ISE) band. The ISE band is the second innermost of the four hyperreflective outer retinal bands on OCT; in the past, this band was erroneously attributed to the boundary between the inner and outer segments of the photoreceptors.⁷⁹ ISE band integrity is the preoperative OCT finding that has been most consistently associated with postoperative VA.⁸⁰ A majority of studies have reported that an intact preoperative ISE band is associated with a better postoperative VA than a disrupted preoperative ISE band.^{60–78} These findings regarding CFT and ISE band integrity are likely applicable to both idiopathic and secondary ERMs.^{76–78}

An ERM classification system should take into account the contemporary understanding of the pathogenesis of ERMs and the clinically relevant SD-OCT findings (Table 3). The diagnosis of ERM is contingent on the recognition of a highly reflective membranous structure at the vitreomacular interface on clinical examination or OCT imaging. An ERM can be classified as idiopathic, primary, or secondary based on its underlying etiology. Idiopathic ERMs are those that occur

Table 3 ERM classification scheme that takes into account pathogenesis and clinically relevant SD-OCT findings

Definition		
A highly reflective membranous structure at the vitreomacular interface		
Classification		
Idiopathic	No identifiable etiology	
Primary	Secondary to posterior vitreous detachment	
Secondary	Secondary to another disorder known to cause epiretinal membrane formation	
Central foveal thickness ^a		
	Stratus OCT ^b (μm)	Spectralis OCT ^c (μm)
Normal	<250	<320
Thickened	≥250	≥320
Inner segment ellipsoid band integrity		
Intact	Clear and consistent	
Disrupted	Blurred, interrupted, or absent	

Notes: ^aCentral subfield mean thickness as measured using the device-specific scan protocols publicly available at www.drcr.net. ^bStratus OCT-derived central foveal thickness normal and thickened values derived from Bressler et al.⁸² ^cSpectralis OCT-derived central foveal thickness normal and thickened values derived from Chalam et al.⁸³

Abbreviations: ERM, epiretinal membrane; OCT, optical coherence tomography; SD-OCT, spectral-domain optical coherence tomography.

in the absence of an identifiable etiology. Primary ERMs are those that occur secondary to PVD in the absence of another identifiable etiology. Secondary ERMs are those that occur secondary to other disorders known to cause ERMs regardless of the occurrence of PVD. In the setting of ERM, the SD-OCT findings with the strongest evidence of clinical relevance are CFT and ISE band integrity. CFT is generally reported as either center point thickness or central subfield mean thickness. Although these measures are highly correlated, central subfield mean thickness is preferred because it is the average of more data points and is less dependent on scan centration.⁸¹ CFT can be classified as either normal or thickened based on previously reported SD-OCT device-specific values. For the Stratus OCT (Carl Zeiss Meditec AG, Jena, Germany), normal CFT is <250 μm and thickened CFT is ≥250 μm; for the Spectralis OCT (Heidelberg Engineering Inc., Heidelberg, Germany), normal CFT is <320 μm and thickened CFT is ≥320 μm.^{82,83} Although sex and racial differences in CFT can be disregarded in general clinical practice, these differences should be taken into account when performing rigorous clinical investigation. ISE band integrity on SD-OCT should be evaluated when considering surgical intervention. The ISE band is intact when it is clear and consistent and is disrupted when it is blurred, interrupted, or absent.

Treatment

The management options for ERM are currently limited and consist of either observation or surgical intervention. Surgical intervention entails pars plana vitrectomy with ERM removal

with or without ILM removal.⁸⁴ Surgical peeling of the ILM may help decrease the risk of ERM recurrence.⁸⁴ The surgical techniques used in the treatment of ERM generally afford excellent postoperative visual outcomes.⁸⁵ However, there are definite risks associated with surgical intervention for ERM, including recurrence, endophthalmitis, and retinal detachment.⁸⁶ Conservative management is supported by the fact that most ERMs are asymptomatic and do not progress, and some ERMs even regress. Aggressive management has been proposed for select cases of ERM based on the fact that patients with better preoperative VA tend to have better postoperative results.⁸⁷ Surgical ERM removal may be more beneficial for patients with secondary ERM than patients with idiopathic ERM.⁸⁸ However, secondary ERMs are more likely to recur, potentially because of more extensive damage or ongoing inflammation at the vitreoretinal interface. In clinical practice, surgical intervention is generally deferred until symptoms interfere with daily life. However, this is unlikely to reflect the time at which surgery must be performed to prevent irreversible retinal damage.

Conclusion

OCT has revolutionized the clinical management of numerous disorders of the eye. OCT offers distinct advantages over clinical examination for the diagnosis and classification of disorders of the vitreomacular interface. The OCT-based classification schemes proposed by the International Vitreomacular Traction Study Group will assist in the clinical management and investigation of VMA, VMT, and macular hole. OCT-based classification schemes such as these could potentially allow clinicians to identify cases of VMA or VMT that are at risk of developing anomalous PVD and idiopathic ERM. Managing these cases with prophylactic surgical or pharmacologic intervention could theoretically prevent the formation of primary ERMs. The adoption of a standardized OCT-based classification system for ERMs has the potential to assist in clinical practice and investigation. The inclusion of clinically relevant, objective measures, such as CFT and ISe band integrity, could assist clinicians in identifying the optimal time to perform surgery and predicting postoperative outcomes. Further work will be required to demonstrate the clinical utility of OCT-based ERM classification schemes.

Disclosure

The authors report no conflicts of interest in this work.

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