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REVIEW

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Epiretinal membrane: A review

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[Correction added on 14 February 2023, after first online publication: the copyright line was changed.]

Abstract

The prevalence of epiretinal membrane (ERM) is 7% to 11.8%, with increasing age being the most important risk factor. Although most ERM is idiopathic, common secondary causes include cataract surgery, retinal vascular disease, uveitis and retinal tears. The myofibroblastic pre-retinal cells are thought to transdifferentiate from glial and retinal pigment epithelial cells that reach the retinal surface via defects in the internal limiting membrane (ILM) or from the vitreous cavity. Grading schemes have evolved from clinical signs to ocular coherence tomography (OCT) based classification with associated features such as the cotton ball sign. Features predictive of better prognosis include absence of ectopic inner foveal layers, cystoid macular oedema, acquired vitelliform lesions and ellipsoid and cone outer segment termination defects. OCT-angiography shows reduced size of the foveal avascular zone. Vitrectomy with membrane peeling remains the mainstay of treatment for symptomatic ERMs. Additional ILM peeling reduces recurrence but is associated with anatomical changes including inner retinal dimpling.

KEYWORDS

ectopic inner foveal layer, epiretinal membrane, macular pucker, myofibroblasts, pre-macular fibrosis

1 | INTRODUCTION

Epiretinal membrane (ERM) can be defined as pre-retinal proliferation of myofibroblastic cells associated with extracellular matrix (ECM). Various aetiologies can lead to this final common pathway. Current imaging modalities are excellent at identifying and grading severity of ERMs, but do not yet differentiate histopathological variations which suggest that this is a heterogeneous group of diseases. This review discusses the latest evidence regarding the epidemiology, aetiology, histopathology, clinical findings, investigation and management of ERMs.

2 | EPIDEMIOLOGY

Epidemiology of ERMs was initially largely drawn from population-based studies using non-mydriatic retinal photography. Later studies incorporated the detection of ERM using ocular coherence tomography (OCT).[1,2] The Blue Mountains Eye Study (BMES)[3] and the Beaver Dam Eye Study (BDES)[4] were two early large population studies which reported a prevalence of 7%[3] and 11.8%,[4] respectively of idiopathic ERM (iERM) and a 5-year cumulative incidence of 5.3%[5] based on colour fundus photographs. iERMs were bilateral in 19.5%[4] to 31%[3] with a 13.5% 5-year incidence of second eye involvement.[5] In

the 20-year follow-up BDES, spectral domain (SD)-OCT was used for detection of ERM and the prevalence was found to be 34.1%,[2] much higher than the 11.8% detected on fundus photography.[2,4] A meta-analysis of 13 population-based studies has calculated an overall ERM prevalence of 9.1%.[6]

Increasing age is the most consistent risk-factor for ERM,[6-9] with most patients presenting over 50 years and a peak prevalence in the 7th decade.[3,4] In the BMES, the prevalence increased from 1.9% (<60 years) to 7.2% (60-69 years) to 11.6% (70-79 years), before declining to 9.3% in patients 80 years and older.[3] The Melbourne Collaborative Cohort Study (MCCS) found similar rates in these age groups but with a further increase in prevalence when 80 years or older (17%).[10]

Gender does not appear to be a major risk factor, with studies either showing equivalent prevalence in males and females,[4,10] or a slightly higher prevalence in females.[3,6,8,11]

There is great variability in the reported prevalence of ERM amongst different racial groups and countries. Reported rates are: Australia 7% (BMES),[3] 8.9% (MCCS)[10]; United States 11.8% (BDES),[4] 18.7% (Los Angeles Latino Eye Study)[11]; Singapore 7.6% (Singapore Indian Eye Study),[12] 7.9% (Singapore Malay Eye Study [SiMES] Group),[8] 12.1% (Singapore Epidemiology of Eye Disease [SEED] Study)[7]; China 1.02% (Beixinjing Blocks, Shanghai),[13] 2.2% (Beijing Eye Study),[14] 3.4% (Handan Study, rural China),[1] 7.3% (Jiangning Eye Study, urban Shanghai),[15] 7.6% (Kailuan Eye Study)[16]; Japan 4.0% (Hisayama Study),[17] 5.7% (Funagata Study)[18] and Korea 2.9% (Korea National Health and Nutrition Examination Survey).[9]

Caution is advised when comparing ethnic prevalence across studies. Not only do imaging modalities and reading methodologies differ, but also differences in retinal pigmentation may affect the ability to detect ERMs on fundus photography or lead to incorrect assignment of an ERM due to retinal reflex artefacts.[7] Nevertheless some conclusions may be drawn by studies with multi-ethnic populations or with identical methodologies. The Multi-Ethnic Study of Atherosclerosis[19] of 5960 US citizens found that Chinese persons (39.0%) had a significantly higher prevalence of ERM than Hispanics (29.3%), whites (27.5%) or blacks (26.2%). The SEED study also found the highest prevalence in Chinese (13.0%), when compared to Indians (8.7%) and Malays (7.9%).[7] In the SiMES, the age-standardised prevalence of ERM was over twice as high in Malays (15.8%) compared with Caucasians in the BMES (6.8%).[8] Both studies used the same graders, reading centre and grading protocols. The Funagata Study[18] also used the BMES protocol but found a similar prevalence in Japanese (5.7%) as for Caucasians. The MCCS found that the prevalence of ERMs in Australians of Southern European origin (15.3%) was nearly twice that of persons of Northern European origin (7.8%).[10] It is possible that any true ethnic differences in the prevalence of ERMs may be due to genetic or lifestyle differences,[7] but epidemiological evidence for this does not yet exist.

Refractive associations with ERM are inconsistent, with some studies showing an association with myopia,[1] and others with hyperopia.[8]

3 | AETIOLOGY

ERMs have been classified according to aetiology despite often identical clinical appearances. iERMs occur when there are no associated ocular abnormalities, or a posterior vitreous detachment (PVD) only. Some authors attempt to further differentiate patients in which a PVD exists as having a "primary," rather than iERM.[20] A PVD is present in 78%[21] to 95%[22] of iERMs, suggesting its importance in the pathogenic process.

Secondary ERM refers to ERMs thought to be due to coexisting or preceding ocular disease. Of all ERMs, 32.3% may be secondary,[8] with the most frequent causes being previous cataract surgery[3,4] (odds ratio 2.82[9] to 10.6[7]; up to 77%[8]), diabetic retinopathy[4] (odds ratio 1.84[18] to 2.48[7]) and retinal vein occlusion.[3,8] One study found that 11.2% of eyes without ERM 1-month post-cataract surgery may develop ERM over 3 years.[23] A list of causes of ERM is outlined in Table 1.

4 | HISTOPATHOLOGY AND PATHOGENESIS

ERMs are generally composed of two layers overlying the internal limiting membrane (ILM). The outermost layer sits on top of the ILM and consists of non-cellular ECM proteins containing bundles of extracellular fibrils randomly orientated. Overlying this is an inner cellular sheet consisting of a single or multi-layer of epiretinal cells. As ERMs progress, accumulation of myofibroblast-like cells and ECM deposition increase its contractile properties.[24]

In iERM, transdifferentiation of various precursor cells to myofibroblasts is considered the key pathogenic process. Precursor cell types may be difficult to identify as they rapidly lose their characteristic features when undergoing transdifferentiation.[24] However, immunohistochemical studies have shown that the myofibroblasts originate from frequently found cellular constituents of ERMs including: retinal glial cells, hyalocytes, retinal pigment epithelial (RPE) cells and fibroblasts.[25-31] Evidence of myofibroblastic transdifferentiation is characterised by

TABLE 1 Aetiology of epiretinal membranes

1. Idiopathic
   - No pathology
   - Posterior vitreous detachment only[a]
2. Secondary
   - Iatrogenic
     - Cataract surgery
     - Vitrectomy surgery
     - Retinopexy (laser or cryotherapy)
   - Retinal vascular disease
     - Diabetic retinopathy
     - Retinal vascular occlusive disease
     - Coat's disease
     - Retinal arteriolar macroaneurysm
     - Radiation retinopathy
     - Sickle-cell retinopathy
   - Uveitis
   - Retinal tears and/or detachment
   - Associated with other vitreomacular traction disorders
     - Macular hole
     - Vitreomacular traction syndrome
   - Pathological myopia
   - Trauma
   - Intraocular tumours
     - Retinal ("capillary") haemangioblastoma
     - Vasoproliferative tumour
     - Choroidal melanoma
     - Combined hamartoma of the retina and retinal pigment epithelium
     - Retinal astrocytic hamartoma
   - Age-related macular degeneration
   - Retinal dystrophies
     - Retinitis pigmentosa
   - Neurofibromatosis Type 2

[a]Considered by some as "primary" rather than "idiopathic."[20]

a reduction in cell-specific proteins such as glial fibrillary acidic protein (GFAP), and the upregulation of proteins involved in myofibroblast proliferation and membrane contractility such as α-smooth muscle actin (α-SMA).[32-35] The predominant cell-types in ERMs differ between studies. This may reflect different aetiological factors involved in ERM formation, as well as different methods (such as histology, electron microscopy and immunofluorescence) in identifying cell types.

How the precursor cells initially reach the inner retinal surface is still under debate. Histopathological evidence suggests three main theories describing this initial event in ERM pathogenesis. A classic theory was proposed in 1974 by Foos.[36] He proposed that retinal glial cells migrated to the retinal surface via microdefects in the ILM occurring after PVD.[37-39] Although glial cell proliferation has been demonstrated in direct association with these ILM defects, it has been found to occur too rarely to account as a general theory for iERM formation. A more widely accepted theory proposes that ERM is precipitated by an anomalous PVD whereby residual hyalocytes on the retinal surface undergo growth and metaplasia to form ERM.[40] These theories however do not explain the presence of ERMs in the absence of PVD. A third theory attempts to explain the frequent finding of RPE cells in iERM and proposes their involvement by transdifferentiation and migration through the retina and microdefects in the ILM.[30] With deficiencies in each of these theories, there is currently no universal agreement of this initial process. A summary of current ERM histology and pathogenesis hypotheses is presented in Figure 1, and histopathology presented in Figure 2.

4.1 | ECM components

ECM is synthesised and secreted by cells including glial cells and myofibroblasts from the inner cellular layer of the ERM. Epithelial cells such as RPE are particularly efficient in secreting ECM, including basement membrane line material. The non-cellular ECM in turn forms the main structural framework that facilitates adhesion and proliferation of epiretinal cells. Unlike the numerous studies on the cellular components of ERMs, there are fewer studies on the ECM.[41-43]

The main component of the ECM is extracellular collagen fibrils with fragments of ILM.[44] Early studies divided the collagen types into native vitreous collagen (NVC), left on the retinal surface following vitreoschis or partial PVD, and newly formed collagen (NFC), presumably secreted by the cellular layer.[41,45] The two collagens differ in that NVC has smaller fibrils (<16 nm diameter) with a more regular fibrillar arrangement than NFC.[41,45,46]

More recent ultrastructural studies have identified the collagens to consist predominantly of types I, II, III, IV and VI.[41,47,48] The exact location and distribution of these collagen types within the extracellular layer are still unclear. Type I, II and III collagens have been identified as NFC, whereas type II and IV mainly represent NVC that are often found covering the ILM.[49] Type IV collagen has also been found to be a component of the ILM and additionally has been found to form a basement membrane-like layer for the epiretinal cells.[39] Type VI

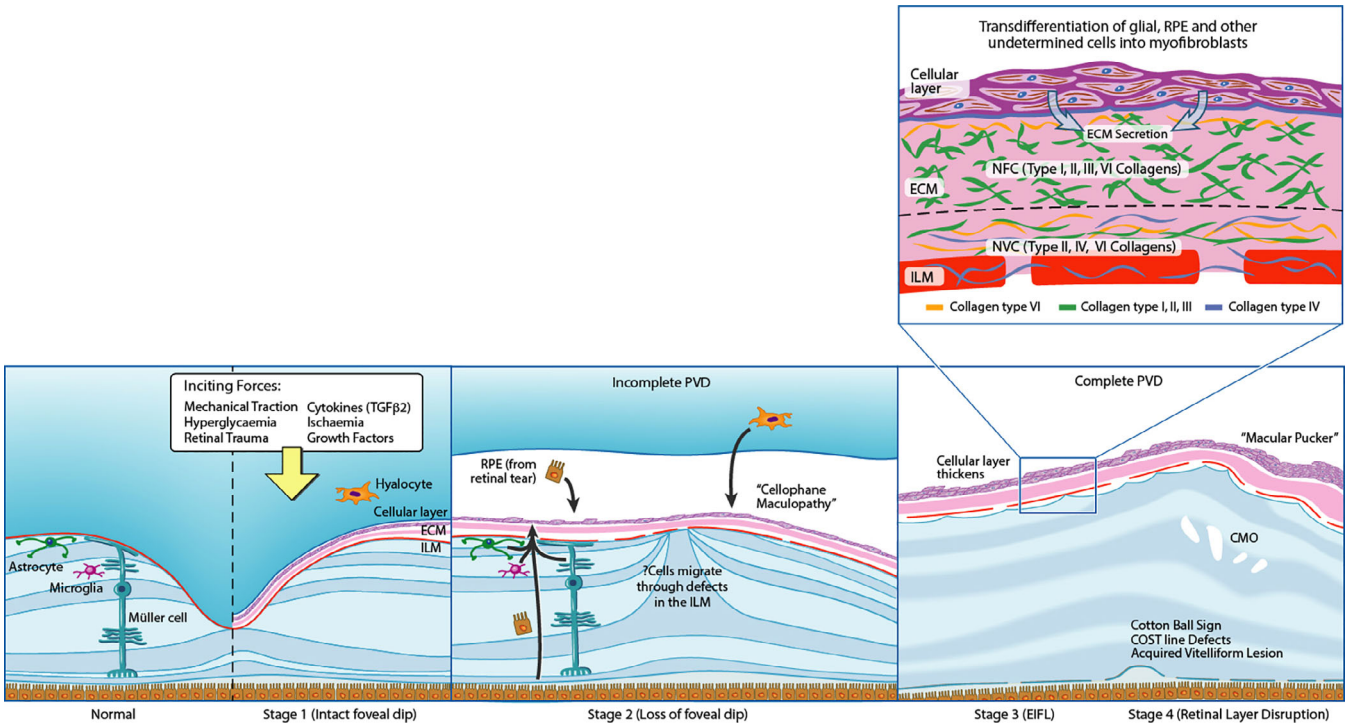

FIGURE 1 Pathogenesis of epiretinal membrane (ERM) formation. Glial cells (astrocytes, microglia and Müller cells), retinal pigment epithelial cells and hyalocytes are all thought to contribute to a cellular layer on top of the internal limiting membrane (ILM). Some of these may reach the epiretinal surface via defects in the ILM. Inciting forces may include posterior vitreous detachment, hyperglycaemia and ischaemia. The epiretinal cells then transdifferentiate into myofibroblasts and secrete an extracellular matrix containing collagens I-VI. Progression of the ERM causes progressive loss of the foveal dip, ectopic inner foveal layers, disruption of retinal layers, cystoid macular oedema and foveal pathology

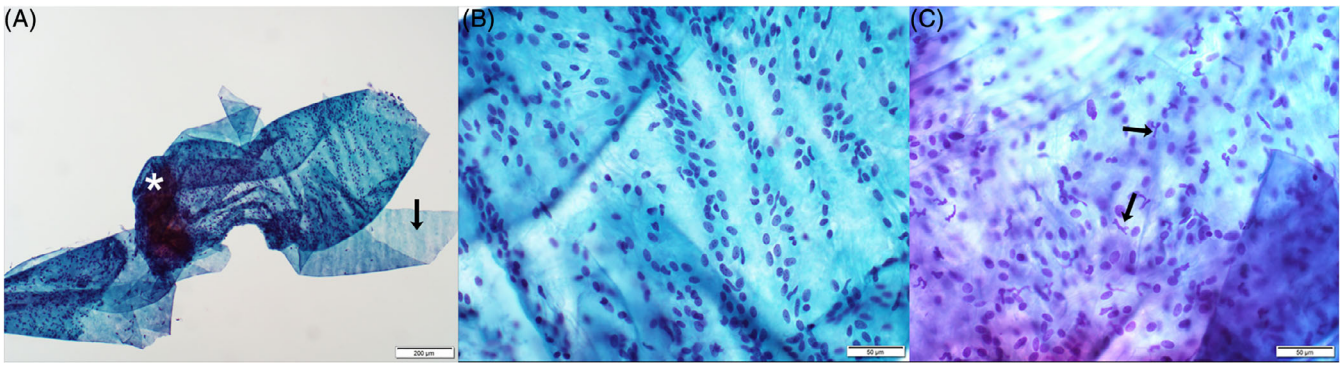

FIGURE 2 Idiopathic epiretinal membrane (ERM) cytopathology. A, An ERM (*) is visible with high and moderate cellularity areas attached to internal limiting membrane (arrow). ThinPrep Papanicolaou stain ×100. B, Higher magnification of the moderate cellularity area of ERM (×400) showing spindled cells arranged in rows. C, ×400 magnification of high cellularity area of ERM, focused to best demonstrate microglia with twisted nuclei (arrowheads) intermixed with the spindled cells. Images courtesy of Dr Svetlana Cherepanoff

collagen, a ubiquitous ECM protein, has been shown to be responsible for the fine fibrillar network of the ECM and is thought to strongly interact with type IV collagens of both the inner cellular and the outer ILM boundaries of the ECM layer to account for its biomechanical stability during surgical removal.[47] In ERMs, epiretinal cells secrete collagen type VI, which is also normally produced by retinal glial cells (Müller cells and astrocytes). With ERM progression and further myofibroblastic-transdifferentiation, the ECM layer contains more abundant collagen types I, III and IV that are normally produced by myofibroblasts.[41] Thus, the change of collagen secretion with ERM development reflects myofibroblastic transdifferentiation of epiretinal cells.

4.2 | Cellular components

4.2.1 | Glial cells

Each type of retinal glial cell including microglia (of monocyte-macrophage lineage) and astrocytes and Müller cells (of neuroepithelial lineage) have been implicated in the formation of ERMs. Their response to injury is characterised by reactive gliosis and is thought to be a major factor in the formation of fibroproliferative tissues of ERMs and proliferative vitreoretinopathy (PVR).[26,50] After gaining access to the inner retinal surface, the cells proliferate and act as a scaffold for extracellular collagen production and transdifferentiation into myofibroblasts.[31,36]

Retinal microglia are small, round, fast unidirectional moving cells that represent a relatively larger proportion of ERMs than once thought. In ERM and PVR, they secrete transforming growth factor beta (TGF-β)-1 that stimulates myofibroblast-like transdifferentiation of epithelial cells.[45]

Retinal astrocytes have a flattened cell body with fibrous radiating processes filled with distinct intermediate filaments that stain intensely with GFAP antibodies.[31,36] The three morphologic subtypes include: protoplasmic, fibrous and gemistocytic. It is thought that retinal astrocytes may act as a scaffold for fibroblast differentiation and collagen production.[31] Although fibrous astrocytes are highly implicated, they are not consistently the predominant cell type in iERMs. Their presence appears more prominent in other vitreomacular traction disorders such as vitreomacular traction syndrome (VMTS),[51] lamellar macular holes (LMHs),[52] myopic traction maculopathies[53] and ERMs associated with proliferative diabetic retinopathy (PDR).[48]

Müller cells normally elaborate the ILM, which is a modified basement membrane. Their processes can grow towards the vitreous surface where they are thought to contribute to the formation of ERMs and proliferative vitreoretinopathies.[54] They undergo reactive gliosis in response to injury by cellular hypertrophy, proliferation and upregulation of intermediate filaments including nestin, vimentin and GFAP.[32] This aberrant proliferation of Müller cells is a major factor in the formation of fibroproliferative membranes associated with PVR, PDR and iERMs.[31] As glial cells undergo mitosis, they migrate onto the retinal surface through breaks in the ILM and spread as a monolayer on the ILM surface. This is supported by the observation of GFAP positive Müller cells traversing the ILM and extending into ERMs,[54] where they then upregulate collagen and ECM production.[47]

Müller cells may be activated by various pathogenic factors including mechanical traction, retinal trauma, ischaemia, hyperglycaemia and by cytokines and growth factors.[32] As Müller cells are mechanosensitive, mechanical stress from epiretinal traction may activate them, perpetuating reactive gliosis and myofibroblastic transdifferentiation.[47]

4.2.2 | Hyalocytes

Hyalocytes are mononuclear phagocytes embedded in the vitreous cortex with higher populations at the posterior pole and vitreous base.[55] At the posterior pole, they are widely spread apart in a single layer positioned 20 to 50 μm from the ILM.[40] Their origin is of monocyte/macrophage lineage, and in ERMs they express monocyte/macrophage cell markers including cluster of differentiation (CD) CD35, CD45, CD64 and CD163 but not CD68.[49] Multiple investigators have established the presence or predominance of hyalocytes in ERMs with their long cell fibres located in cellular agglomerations next to fibroblasts.[26,40,56]

In vitro studies have demonstrated stronger contractile responses of hyalocytes by TGF-β2 stimulation compared to other epiretinal cells, suggesting an important role of hyalocytes in exacerbating ERM contractility.[57]

Kishi and Shimizu[58] proposed that after a PVD, patients may develop ERMs due to a remnant pre-macular layer of posterior vitreous cortex. Sebag et al,[40] further proposed that vitreoschisis occurs as a consequence of anomalous PVD, and the level of splitting within the posterior vitreous lamellae, whether occurring anteriorly or posteriorly to the hyalocytes, determines whether a thick cellular pre-macular membrane of hyalocytes remains to promote the formation ERMs. Multiple studies have also provided evidence of myofibroblastic differentiation from hyalocytes in ERMs, VMTS, LMHs and other proliferative-vitreoretinal diseases.[40,56,57,59,60]

4.2.3 | RPE cells

RPE cells can migrate through retinal breaks and attach to the inner retina.[61] They are the predominant cell type in PVR and ERMs associated with retinal tears and detachments but are not typically seen in iERM or traction vitreo-maculopathies.[26,51] Smiddy et al[30] first demonstrated a predominance of RPE cells in iERMs, however this has not been found in most other studies.[37,45,46,49,53,59,62] How RPE cells reach the retinal surface is still unclear and postulations are mentioned earlier. On the retinal surface, they may undergo myofibroblastic transdifferentiation via TGF-β2 stimulation like glial cells and hyalocytes.[63] Another intriguing possibility is that retinal cells may be undergoing transdifferentiation into pigment epithelial cells.[64]

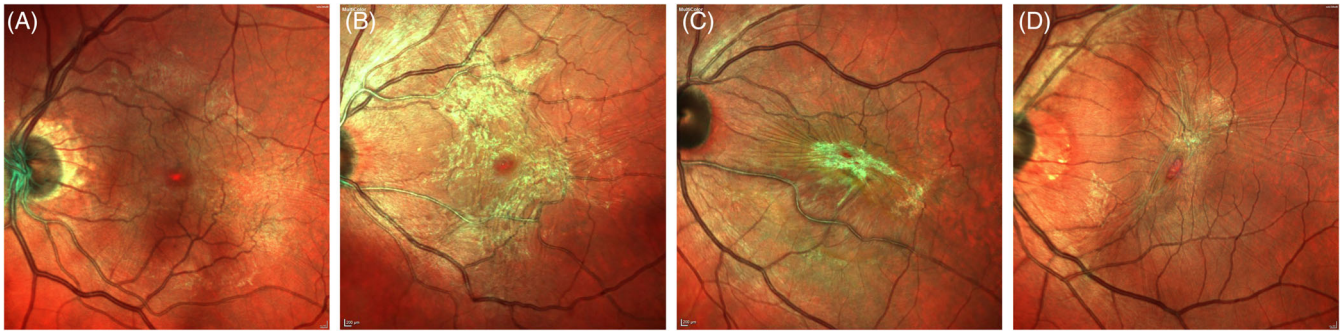

FIGURE 3 Clinical grading of epiretinal membrane with synonymous names based on the Gass[75] classification

4.2.4 | Macrophages

The presence of macrophages has been demonstrated in iERMs but appear more apparent in secondary causes associated with vitreous haemorrhages.[32] Macrophages derive from monocyte lineage, including microglia, hyalocytes and blood derived monocytes. Their role in ERM formation is unclear, however macrophages are known to secrete cytokines and growth factors such as TGF-β, insulin-like growth factor-1, fibroblast growth factor and platelet derivative growth factor that contribute to myofibroblastic transdifferentiation.[65]

4.2.5 | Fibroblasts and myofibroblasts

The process of ERM formation resembles the hallmarks of fibrosis, where exuberant production of ECM proteins by myofibroblasts eventually causes fibrotic contraction, distorting normal structure and function of tissue. Collagen can be produced by RPE and Müller cells, because basement membrane production is part of their normal function. The expression of α-SMA is a constant finding in ERMs and gives cells contractile properties.[66] It is de novo expression marks the event of myofibroblast activation, the fundamental event to allow the production of collagen and generation of contractile forces in ERMs.[47]

4.3 | TGF-β

TGF-β is the most implicated mediator of myofibroblastic transdifferentiation and fibrosis in ERMs,[47] PDR membranes and PVR.[67] TGF-β is a cytokine with important homeostatic functions in proliferation, differentiation and apoptosis.[68] Activation of TGF-β1 triggers signal transduction pathways promoting the transcription of TGF-β target genes needed for fibrogenesis.[69] Interestingly, myofibroblasts themselves can release latent TGF-β that bind to ECM proteins forming a reservoir of TGF-β, and extracellular mechanical stress transmitted by integrins induces release of TGF-β.[70] Hence, both increased mechanical stress and contraction on ECM can release further TGF-β, perpetuating myofibroblastic activity.[70]

5 | SYMPTOMS AND SIGNS

In many cases, ERMs can be asymptomatic.[71] The development of symptoms depends on the location, duration, severity and type of ERM. Vision can be affected when there is involvement of the macular or peri-macular region, when there is retinal traction or oedema, and with more opaque membranes. Common symptoms include reduced visual acuity (VA), blurred vision, metamorphopsia, loss of stereopsis and aniseikonia. Standard acuity charts and less commonly specialised testing including M-CHARTS for metamorphopsia and new aniseikonia test charts for aniseikonia can be used to evaluate symptoms.[72] A newly recognised symptom of ERM has been coined binocular interference and occurs when the affected subject needs to close one eye to improve their overall vision in the absence of either diplopia or strabismus. In a study by Hatt et al[73] the most common associations in patients with ERM and who reported monocular eye closure were binocular interference and central-peripheral rivalry-type diplopia. These patients had significantly reduced quality of life.

The diagnosis of ERM relies on clinical examination in combination with OCT. Early ERMs may be an incidental finding seen as a glistening fundus reflex. Progression of the ERM can lead to inner retinal distortion from contraction seen as superficial radial folds and either straightening or increased tortuosity of the retinal vessels.[74] Up to 95% of eyes with ERM may have an associated PVD.[24] There may be other findings associated with the ERM such as cystoid macular oedema (CMO), foveal ectopia, blunting of the foveal reflex, lamellar or full-

thickness macular holes (MHs) and/or small retinal haemorrhages. The diagnosis of iERM is one of exclusion, and it is important to carefully exclude underlying pathology including retinal vascular disease, uveitis and retinal tears.

6 | CLINICAL ERM CLASSIFICATION

Gass[75] first proposed an ERM classification system which became the standard reference for describing the clinical severity of ERM (Figure 3). This has become less relevant with the advent of OCT classification. In clinical practice, the intermediate stage is usually abandoned for simplicity.[3,20]

Grade	Name	Description	Fundus appearance
0	*Cellophane maculopathy* Synonyms: • Cellophane macular reflex • Cellophane maculopathy/retinopathy	Early, translucent form of ERM without distortion of the inner retina.	Figure 3A
1	*Crinkled cellophane maculopathy* Synonyms: • Primary retinal fold • Surface wrinkling maculopathy/retinopathy • Internal limiting membrane shrinkage/ contraction	Intermediate, translucent form of ERM with distortion of the inner retina.	Figure 3B
2	*Macular pucker* Synonyms: • Epiretinal puckering/gliosis • Pre-macular/pre-retinal fibrosis • Idiopathic pre-retinal gliosis • Pre-retinal connective tissue proliferation • Internal retinal fibrosis/fibroplasia	Late, opaque form of ERM with distortion of the inner retina.	Figure 3C
N/A	*Pseudohole*	False appearance of a full thickness macular hole caused by an ERM.	Figure 3D

7 | INVESTIGATIONS

7.1 | Ocular coherence tomography

OCT has become the single most useful ancillary test in the diagnosis of ERM and is more sensitive than clinical examination alone.[76] It has advantages over the descriptive-based classification systems as it not only allows for accurate qualitative description, but also for a quantitative analysis and correlation to visual prognosis.

7.1.1 | Definitions

The shift from traditional slit-lamp biomicroscopy to SD-OCT imaging has led to the need to revise outdated definitions of retinal diseases which may prove difficult to distinguish from one another.

Epiretinal membrane

Hubschman et al[77] define ERM as an irregular, hyper-reflective layer on the ILM commonly associated with retinal wrinkling and hypo-reflective spaces between the ERM and ILM (Figure 4A).

Epiretinal proliferation

Epiretinal proliferation (EP) is a similar yet different clinical entity to ERM, defined by a thick, homogenous, iso-reflective material over the ILM, sometimes covered by a thin hyper-reflective material, without hypo-reflective spaces between it and the ILM (Figure 4B, asterix). Histopathology reveals that EP has a paucity of contractile elements when compared to ERM.[77]

Lamellar macular hole

A LMH is commonly confused with ERM foveoschisis. On SD-OCT, LMH is an irregular foveal contour, with a foveal cavity having undermined edges, and there is the presence of at least one other sign evoking loss of foveal

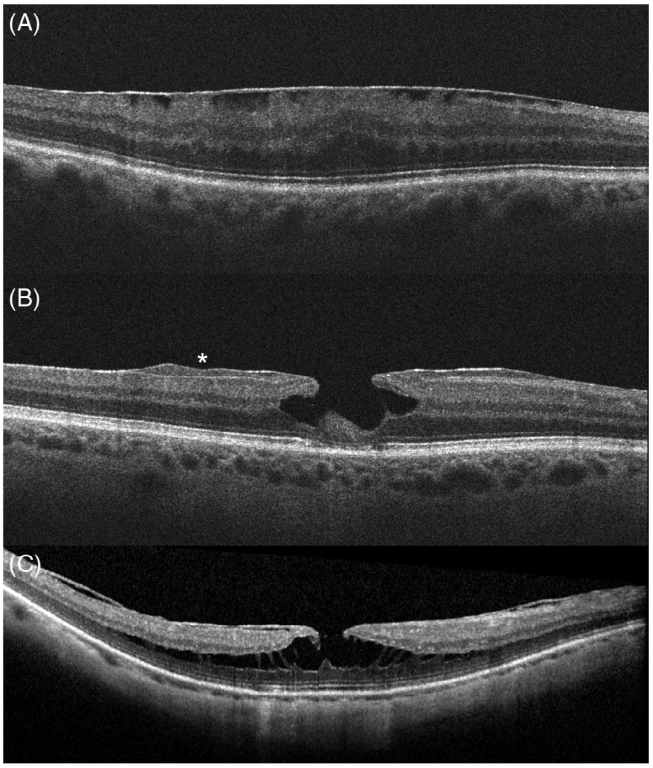

FIGURE 4 Epiretinal membrane and associated definitions. A, Epiretinal membrane. B, Lamellar macular hole with epiretinal proliferation (asterix). C, Foveoschisis

tissue (Figure 4B).[77] LMH may be associated with EP, foveal bump or ellipsoid line disruption.

Foveoschisis

Foveoschisis is a separation of the foveal retinal layers, most commonly the outer nuclear layer (ONL) and outer plexiform layer (Figure 4C).[77] It is likely caused by traction on the retina. An ERM foveoschisis is defined as the presence of both a contractile ERM and foveoschisis at the level of Henle's fibre layer.[77]

Consensus on the definitions for these retinal conditions should reduce diagnostic uncertainty for the clinician and is a dynamic and evolving process as newer technology becomes available.

7.1.2 | Classification schemes

Various OCT classification schemes have been proposed, however there is no common consensus or significant evidence to validate one over another.[78-80] Konidaris et al[81] used SD-OCT to develop an ERM classification scheme with nine categories, based on extensive categorisation of the retinal morphology including separating membranes into the presence or absence of a PVD. However, this study was purely anatomical, and like the scheme by Gass is only descriptive. Hwang et al[82] classified ERM morphology into membranes that were attached to or spared the fovea and used multifocal electroretinogram (mfERG) to investigate the effect on retinal function.[83] ERMs which were attached to the fovea and displayed inner retinal thickening were found to have significantly decreased retinal function compared to fovea-sparing membranes. Stevenson et al[20] have suggested a morphological OCT classification system based on whether the fovea is involved or not and whether a PVD is present.

7.1.3 | Govetto et al staging and ectopic inner foveal layers

In 2017, Govetto et al[84] proposed a four-stage ERM classification system using SD-OCT depending on the absence of a foveal pit, presence of ectopic inner foveal layers (EIFLs) and disorganisation of the retinal layers (Figure 5). The authors defined EIFL as the presence of a continuous hypo- or hyper-reflective band extending from the inner nuclear layer (INL) and inner plexiform layer (IPL) across the fovea.[84] The EIFL is speculated to develop after chronic tractional forces from the ERM lead to damage and displacement of retinal architecture with gliosis and Muller cell proliferation.[85] A higher ERM stage using this classification system correlated with poorer VA, greater central foveal thickness (CFT), an increased prevalence of CMO, ellipsoid zone (EZ) disruption, and a reduction in the size of the foveal avascular zone (FAZ).[84]

Other authors have attempted to validate the new ERM staging system by Govetto et al.[84] Doguizi et al[86] evaluated the ERM classification system in 242 consecutive eyes of 121 patients. Consistent with the findings of Govetto et al, VA was found to decrease in an inverse linear relationship the higher the ERM stage. Furthermore, Doguizi et al discovered that significant predictors of VA included the presence and thickness of the EIFL, as well as greater CFT. Alkabes et al[87] have further attempted to validate this new staging system, reporting that the EIFL is a good predictor of metamorphopsia.

7.1.4 | Cotton ball sign and the central bouquet

In the retrospective case series by Tsunoda et al,[88] 30 of 47 eyes with iERM had the cotton ball sign; a round, diffuse, highly reflective region at the centre of the fovea between the EZ and cone outer segment termination (COST) line (Figure 6A). The mean CFT for eyes with the cotton ball sign was significantly thicker than the CFT of eyes without

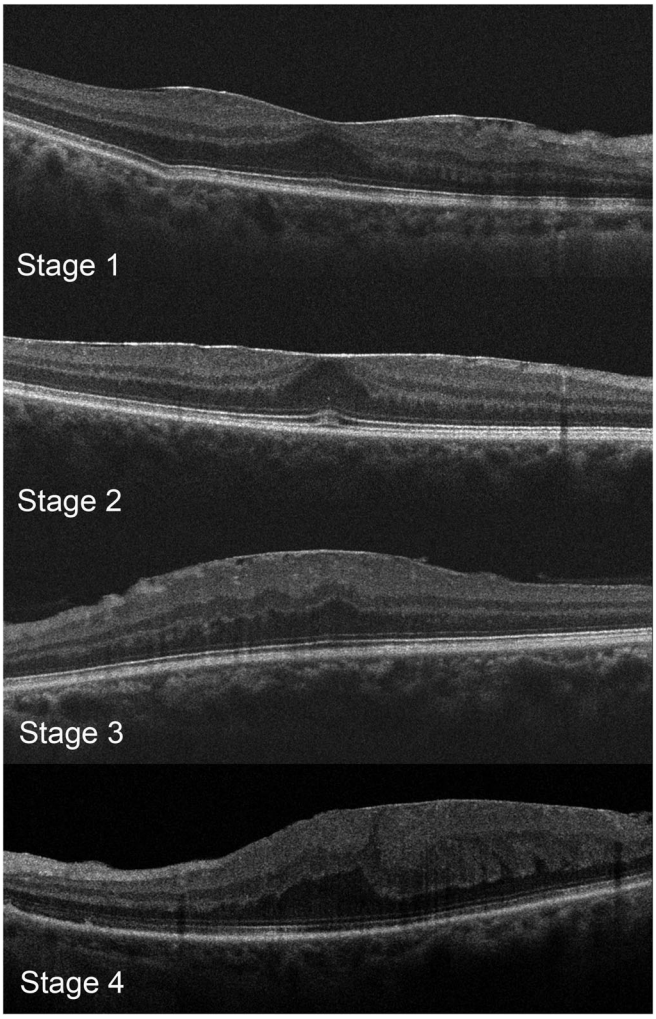

FIGURE 5 Govetto et al[84] optical coherence tomography classification of epiretinal membrane. Stage 1: the foveal pit is present and there are well-defined retinal layers. Stage 2: the foveal pit is absent but there are well-defined retinal layers. Stage 3: the foveal pit is absent, there is the addition of a continuous ectopic inner foveal layer (EIFL) but the retinal layers are still well defined. Stage 4: the foveal pit is absent, there is an EIFL and the retinal layers are disrupted

the cotton ball sign. In half of the cases that underwent surgery, the cotton ball sign disappeared within 6 months and the CFT was significantly thinner than in eyes where the cotton ball sign did not disappear. The authors speculate the chronicity of the traction and development of the cotton ball sign may be a predictor of ERM severity.

Building on the description of the cotton ball sign, Govetto et al[89] hypothesise that a 100-μm diameter zone they call the "central bouquet" is the most susceptible to tractional damage in ERM and displays the most important pathology. The authors argue that the central bouquet abnormalities may comprise a continuous clinical spectrum caused by force transmission through Müller cells and are manifested on SD-OCT as one of three appearances: the cotton ball sign, acquired vitelliform lesions (Figure 6B) or foveolar detachment (Figure 6C). In a retrospective case series, 58 of 263 eyes with ERM were found to have tractional abnormalities of the central bouquet, the majority (36/58 = 62.1%) of which had the cotton ball sign.[89] The cotton ball sign was associated with better visual acuities, whereas acquired vitelliform lesions were associated with worse visual acuities. Eyes with EIFL were less likely to have central bouquet pathology, for which it may be protective against. Changes to the central bouquet are yet to be incorporated into an ERM classification system.

7.1.5 | Prognostic markers on OCT

The optimal timing of surgical intervention for ERM has been a topic of contentious debate. Objective findings on SD-OCT may be able to provide the evidence for predicting postoperative VA. Numerous studies have reported OCT measurements which correlate to visual prognosis, with attempts at incorporating such biomarkers into newer ERM classification systems. Features on OCT predicting a better prognosis include: absence of EIFL,[90-92] inner retinal irregularity, CMO[93] or acquired vitelliform lesions[89]; preserved integrity of the EZ[83,93,94] and COST[94]; and thinner CFT and preoperative ganglion cell layer-inner plexiform layer (GCL-IPL).[95,96]

Earlier studies demonstrated the importance of the outer retinal layers, particularly the EZ and COST line integrities in predicting postoperative VA.[83,94,97] However, the pathology of ERM involves tangential traction on the inner retinal layers. Therefore, investigation of outer retinal architecture alone is insufficient to predict postoperative prognosis and more recent studies have shifted focus to the inner retina. The area and depth of traction correlate positively with the extent of intraretinal changes and negatively with VA.[98] Retrospective studies of patients undergoing ERM surgery by Govetto et al.[90] Sato et al[91] and Gonzalez-Saldivar et al[92] demonstrated that the presence and thickness of preoperative EIFL had a significantly poorer postoperative visual prognosis than comparator groups without EIFL. These studies suggest that the optimal timeframe for surgery could be before the development of EIFL. There may be a reversibility component to the damage inflicted by ERM, with recovery less likely in eyes with EIFL (ERM stages 3 and 4). Okamoto et al[99] found greater INL thickness in iERM correlated well with preoperative and postoperative metamorphopsia.

A systematic review by Miguel and Legris[96] found a thinner CFT, thinner GCL-IPL and retained integrity of the EZ were all associated with better postoperative VA improvements. Although a thicker preoperative GCL-IPL

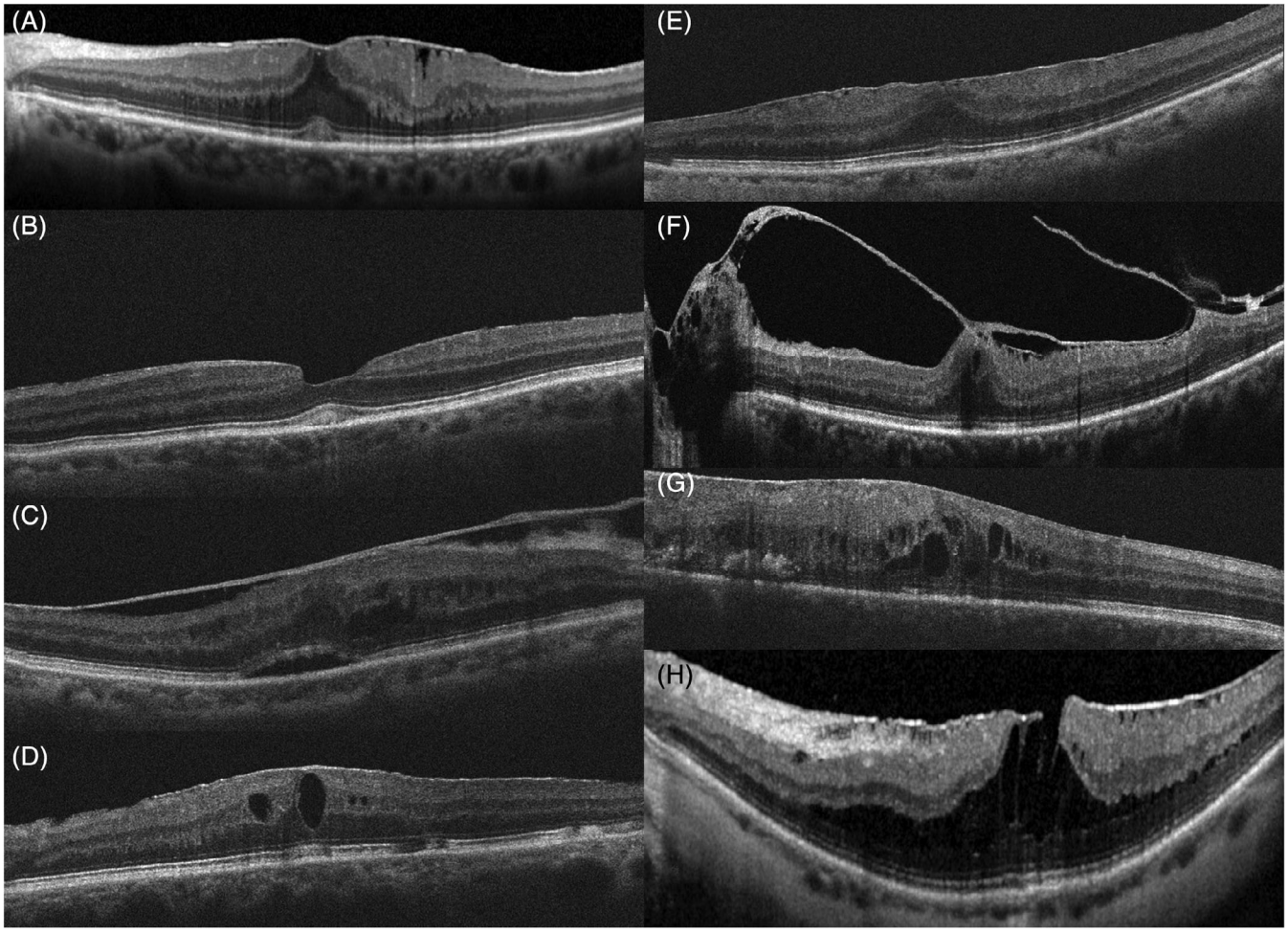

FIGURE 6 Signs associated with idiopathic epiretinal membranes (ERMs) visible on OCT. A, Cotton ball sign (arrow). B, Acquired vitelliform lesion and early lamellar macular hole. C, Subfoveal and intraretinal fluid associated with an ERM and thickened posterior hyaloid face. D, Cystoid macular oedema. E, COST line defect at the fovea. F, Focal traction in an ERM secondary to proliferative diabetic retinopathy. G, Diffusely thick ERM and hyper-reflective foci nasal to the fovea in ERM secondary to proliferative vitreoretinopathy. H, ERM and foveoschisis secondary to high myopia (note the posterior staphyloma and thin choroid)

is associated with worse surgical outcomes, greater postoperative thinning of the GCL-IPL is also associated with poorer vision.[100-102] This may be due to damage from ERM traction and/or iatrogenic ERM peeling.

In 2016, Cho et al[103] proposed the "inner retinal irregularity index", measured by calculating the ratio of the length of the IPL to the RPE within a 3 mm circular zone centred on the fovea. This may be easier to measure than GCL-IPL thickness and significantly correlated with VA preoperatively and 6-months following surgery.

7.1.6 | Morphological OCT changes in secondary ERMs

Most OCT studies have been limited to iERMs. The main morphological difference on SD-OCT between idiopathic and secondary ERM is that secondary ERMs are more likely to have focal points of adhesion to the retina than iERM (Figure 6F).[104] Many studies exclude secondary causes of ERM due to the possibility their effects on VA are confounded by the underlying disease process. Furthermore, a secondary ERM is likely to cause worse symptoms and occur in younger patients, making earlier surgical intervention attractive particularly if the associated aetiology can be treated.[105]

7.2 | Fundus autofluorescence

Fundus autofluorescence can highlight tortuosity of retinal vessels (Figure 7A) and the presence of acquired vitelliform lesions.

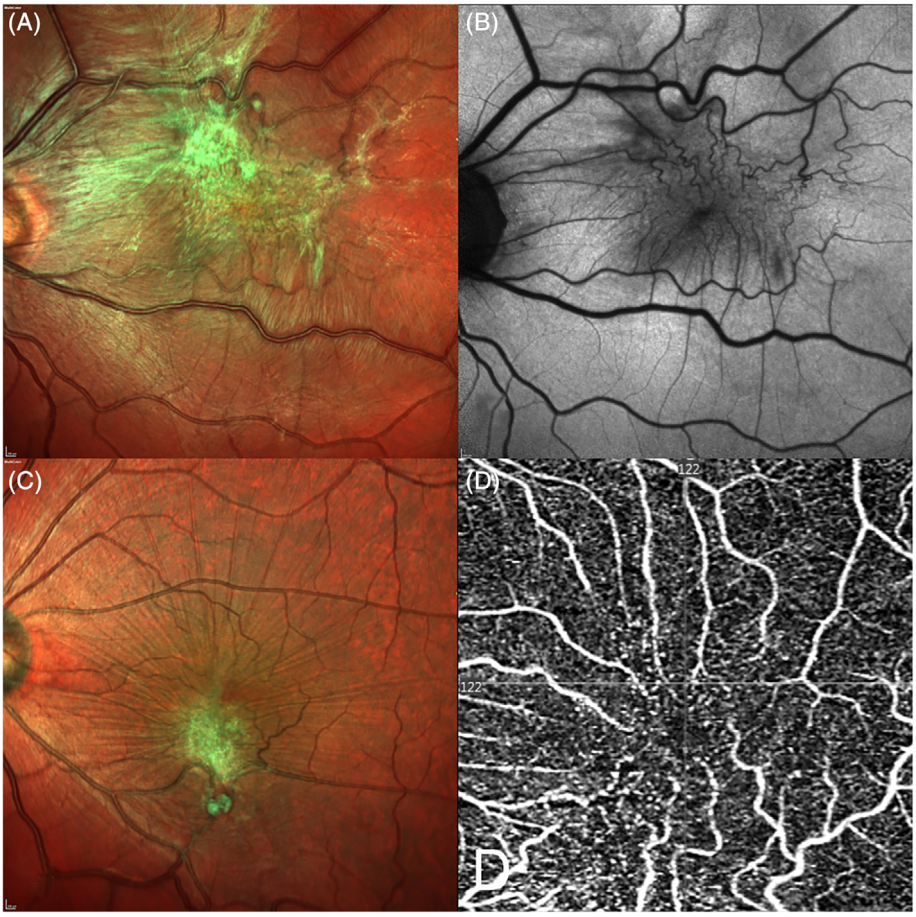

FIGURE 7 Imaging of retinal vasculature changes associated with epiretinal membrane. A, Multicolour imaging of an ERM. Fundus autofluorescence (B) highlights tortuosity of the retinal vessels. C, An ERM shows constriction and inferior dragging of the foveal avascular zone on OCT-angiography (D)

7.3 | Angiography: fluorescein and OCT-angiography

Fluorescein or OCT-Angiography (OCT-A) may be required preoperatively to identify underlying secondary causes of an ERM such as retinal vascular disease (eg, diabetic retinopathy or retinal vein occlusion), retinal vasculitis or vascular tumours (eg, retinal capillary haemangioblastoma or vasoproliferative tumour). Conversely, ERMs can alter or damage macular capillaries by exerting tangential and vertical forces on the retina. Analysis of ERMs with OCT-A has shown a reduction (Figure 7B) or disappearance of the FAZ due to stretching and displacement of vessels in both the superficial (SCP) and deep capillary plexuses (DCP).[84,106] Unlike fovea plana and foveal hypoplasia in which the FAZ may also be absent, ERMs do not have macular-foveal capillaries that cross the fovea. Following ERM peeling, there is a reduction in the vessel density of the SCP but increase in the parafoveal vessel density of the DCP.[107] This re-organisation of the macular capillary plexuses correlates with postoperative VA[108] and microperimetry results.[109]

7.4 | Microperimetry

Microperimetry allows the assessment of functional impairment from ERMs which may explain patients' reported visual discomfort when they might otherwise be undetectable by best-corrected visual acuity (BCVA) or visual fields. A reduction in the mean retinal sensitivity on microperimetry correlates with thickening of the ONL from iERMs.[110] One study found that improvements in postoperative metamorphopsia, measured by preferential hyperacuity perimetry, correlated with improvements in BCVA and CFT but were also predicted by preoperative metamorphopsia, CFT and EZ integrity at baseline.[111] Some studies have suggested that additional ILM peeling may reduce retinal sensitivity and cause micro-scotomas correlated with the site of surgical grasping of the ILM.[112,113]

7.5 | Electroretinography

In iERMs, a reduction in mfERG responses has been demonstrated not only in the fovea but also in the

perifovea.[83,114-119] Lower responses on mfERG (especially P1 amplitude densities in the central ring) are correlated with greater central subfield thickness (especially inner retinal thickness) and BCVA.[120] Although double peeling in ERM surgery may be associated with micro-scotomas on microperimetry, it has been shown to improve electroretinogram (ERG) responses.[114,119,121-123] This includes an increase in density of mfERG responses,[114] improved amplitudes of pattern ERG (p50 and N95) and reduced P50 implicit times,[118] suggesting improved retinal ganglionic macular function. A delay in P1 implicit times predicts poor visual recovery following ERM peeling.[83] However, the limited accessibility and extensive time required to perform ERG make this investigation impractical for routine use in most clinical settings.

7.6 | Adaptive optics scanning laser ophthalmoscopy

Adaptive optics scanning laser ophthalmoscopy has been used by researchers to examine the retina in patients with ERM. Macrofolds, microfolds (5-10 μm) and hyper-reflective microstructures of the vitreomacular interface have been seen to resolve or redistribute after surgical ERM peeling.[124] These hyper-reflective microstructures have been observed in other retinal and even neurological conditions, raising the possibility that they represent reactive gliosis in the inner retinal layers.[125-129]

7.7 | Deep learning

A few studies have utilised computer software to develop deep learning algorithms to identify ERMs with high sensitivity (98.7%) and specificity (98%).[130,131] In these studies, the authors were able to "teach" software to differentiate between the SD-OCT characteristics of normal eyes and eyes with ERM, without the need of an ophthalmologist or interpretation. Deep learning has already been developed with good results for diabetic retinopathy in the past using retinal fundus photography.[130,132] In the future it is likely that deep learning will have a larger role in identifying causes of secondary ERMs and predicting surgical outcomes.

8 | MANAGEMENT

8.1 | Conservative management

The current mainstay of treatment options is limited to watchful waiting or surgery. ERM is a chronic, slowly progressive disease where the majority of patients will not require intervention.[129] It was reported in the BMES[5] that over a 5-year follow-up period most eyes with ERM did not progress in severity, one-quarter regressed or resolved, and only 1 in 10 progressed from a cellophane macular reflex to pre-retinal fibrosis. The presence of a LMH often implies stability and these do not usually require surgery unless there is progressive retinal thickening associated with visual decline.[133]

8.2 | Medical management

There is currently no medical management for ERM, although macular oedema associated with some secondary causes of ERM (diabetic retinopathy, retinal vein occlusion and uveitis) may be responsive to intravitreal anti-VEGF (vascular endothelial growth factor), steroids or non-steroidal agents. Vitreopharmacolysis is an area of research exploring the utility of biological enzymes to dissolve the ERM. Intravitreal ocriplasmin has been investigated for use in VMT associated with ERM, but not for resolution of the membrane.[129] In phase III clinical trials using ocriplasmin in subjects with VMT, there was a subset of patients who also had ERM, but the effects of ocriplasmin were uncertain given the small sample.[134]

8.3 | Surgery for ERMs

Vitreoretinal surgery for ERM is usually performed when there is vision loss or symptoms affecting activities of daily living.[129] The optimal timing of surgery to prevent irreversible damage is currently unknown, however as discussed this may be prior to the development of an EIFL seen on SD-OCT imaging. The aim of surgery is to remove the membrane and release retinal traction. The ILM is suspected to serve as a scaffold for cellular proliferation and it has become common practice to also remove this with an ERM/ILM double peel. Peeling the ILM ensures more complete removal of the ERM.[135] The rate of recurrence of ERM is significantly less with double peeling of the ERM/ILM compared to ERM peeling alone, reducing the need for repeat surgery.[136] Despite this, peeling of the ILM is associated with inner retinal dimpling, greater micro-scotomas and does not appear to improve VA outcomes.[135-137] For this reason, some authors have advocated double peeling only for recurrent ERMs.[138] Phacovitrectomy is routinely preferred by some surgeons, as it avoids the need for a future second cataract surgical procedure, is cost and resource efficient and has been shown to have a good safety profile.[139]

Sutureless, transconjunctival, three-port pars plana Micro Incision (23-, 25-, or 27- gauge) Vitrectomy Surgery (MIVS) is now the standard of care for ERM peeling. Although some studies have not shown a benefit of a particular vitrectomy gauge,[140] others have shown a benefit of 27- over 25-gauge in terms of earlier recovery of VA and reduction in CRT.[141] Following core vitrectomy, a PVD is induced with the vitreous cutter in the rare case where it is not already present. Peripheral vitrectomy is then completed.

Chromovitrectomy refers to the use of vital dyes to stain transparent membranes, facilitating visualisation and removal during vitrectomy surgery.[129] Common dyes used are triamcinolone acetonide which stains the vitreous, trypan blue (TB) which stains the ERM and brilliant blue G (BBG) and indocyanine green (ICG), which preferentially stains the ILM.[142] Combined formulations of TB and BBG are available for dual ERM/ILM peeling. Although TB can stain the lens capsule, development of denser formulations with the addition of polyethylene glycol obviates the need for a partial fluid-air exchange prior to injection. The time for an adequate stain with TB and/or BBG is between 1 and 3 minutes before it is removed by washing. The popularity of ICG has been limited due to retinotoxicity in higher concentrations.[142]

Peeling of the ERM and/or ILM is usually performed under a higher magnification lens. Forceps (ILM, end-grasping or asymmetrical) are the most common tools for ERM peeling, with a "pinch and peel" technique used to initiate the peel.[143] A circular peel of the macula extending to the vascular arcades is completed with a capsulorhexis-like technique. Other tools that can be used to start the peel include diamond dusted scrapers, flex loops, micro-vitreoretinal blades and needle picks.[144] Scissors can be used in situations where the ERM is highly adherent to the retina.

At the completion of membrane peeling, scleral indentation is performed to inspect the peripheral retina for tears. The sclerostomy cannulae are removed and integrity of the wounds inspected—sutures are not routinely required for MIVS.

8.4 | Management of secondary ERMs

Surgical removal of secondary ERM is the same as that for iERM, though the underlying aetiology also must be addressed to prevent recurrence. This may include: retinal laser or cryotherapy for a retinal tear, retinopexy and intravitreal tamponade for a retinal detachment, panretinal photocoagulation for PDR, sector laser photocoagulation for neovascularisation secondary to a retinal vein occlusion, intravitreal anti-VEGF therapy for choroidal neovascularisation and periocular or intravitreal steroid for uveitis. Secondary ERMs tend to occur in younger patients, with more optic disc and extramacular involvement, worse initial and postoperative VA but greater visual improvement than iERMs.[145]

8.5 | Surgical complications and postoperative OCT changes

Generic complications of vitrectomy surgery include cataract, endophthalmitis, haemorrhage, hypotony and retinal detachment.[146] In addition, OCT imaging has provided insights into post-surgical retinal damage which can occur, particularly with ERM/ILM double peeling. However, there is little evidence that postoperative changes on SD-OCT are linked to poorer VA or even changes on microperimetry.[95]

8.5.1 | Swelling of the arcuate nerve fibre layer (SANFL)

The earliest postoperative change on SD-OCT is swelling of the arcuate nerve fibre layer (SANFL). This transient feature lasts up to 3 months[147] and is seen as a hyperreflectant swelling of the retinal nerve fibre layer (RNFL) in the papillomacular bundle on SD-OCT, with hypo-reflectance on infrared imaging and hypoautofluorescence.[148] It is thought to result from peeling of the ILM, either by direct surgical trauma to the RNFL or damage to the Muller cell endplates.[148] Early SANFL has been correlated with late focal RNFL thinning of the temporal macula up to 1 year following surgery.[148]

8.5.2 | Dissociated optic nerve fibre layer (DONFL)/concentric macular dark spots/ inner retinal dimpling

Almost half of patients who undergo ERM peeling demonstrate postoperative dark arcuate striae along the RNFL visible with blue light filters (Figure 8E). First described as "dissociated optic nerve fibre layer" (DONFL) by Tadayoni et al,[149] it was subsequently named "inner retinal dimpling" by Spaide,[150] who identified concentric macular dark spots of the inner retinal surface, best seen on volume-rendered B-scan SD-OCT (Figure 8F). One hypothesis is that it represents regeneration of traumatised Müller cell processes.[150] Some authors claim it may actually represent a successful peel rather than a complication.[147]

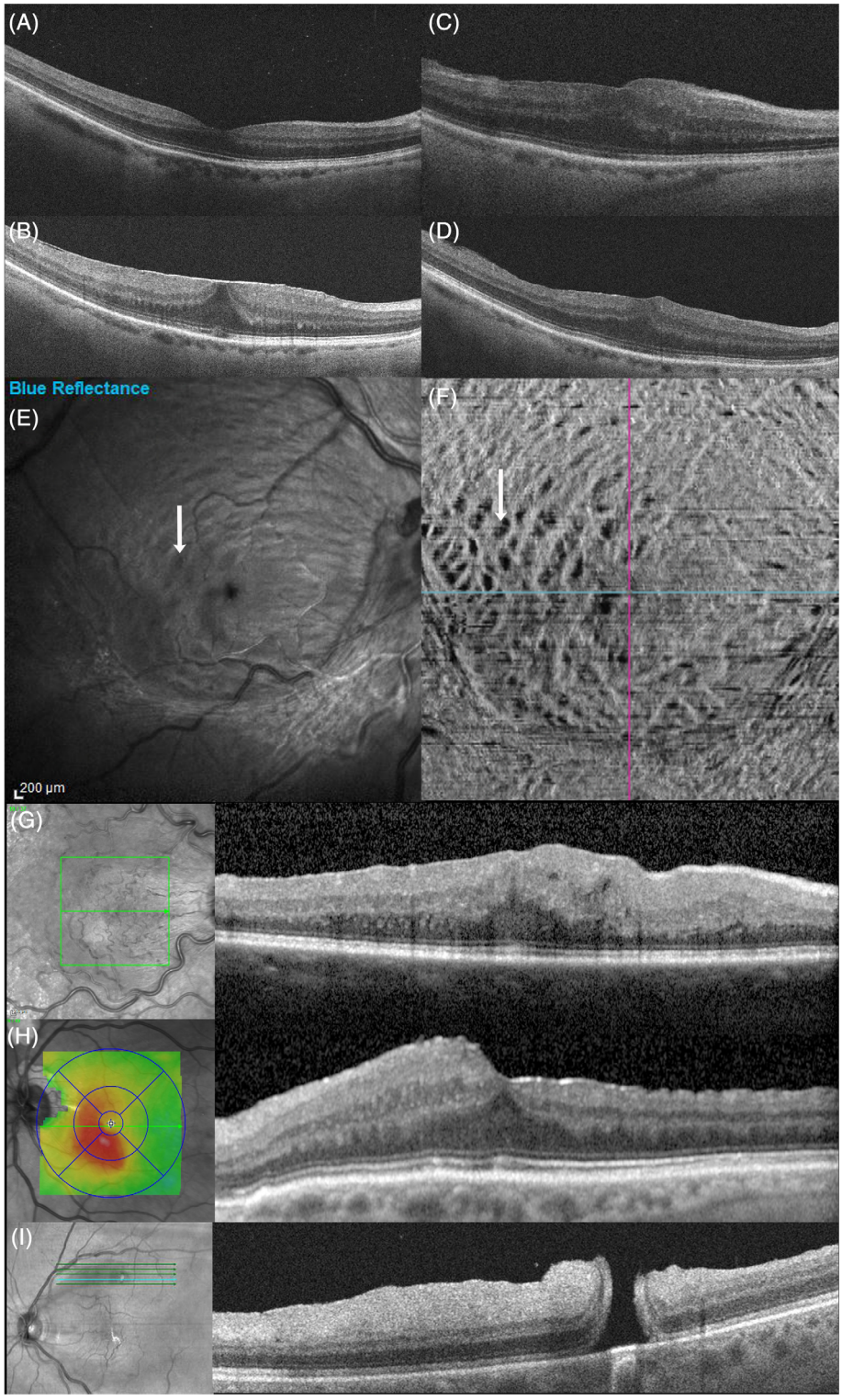

FIGURE 8 Evolution of an ERM and post-peeling OCT complications. A, A 63-year-old Caucasian female presents with a right posterior vitreous detachment. Vitreous cells are visible (VA 6/12). B, Three-years later a stage 2 ERM has developed (6/15). C, A further 2 years later vitrectomy and epiretinal membrane peeling surgery is performed. On the first postoperative day the retina is thickened, most prominently nasal to the fovea (VA 6/18). D, Two-months postoperatively the retinal oedema is settling (VA 6/7.5). E, Inner retinal dimpling ("dissociated optic nerve fibre layer") following ERM peeling is be visualised with blue light filters or F, en face OCT (arrows). G, Microcystic macular oedema following ERM peeling. H, A 74-year-old Caucasian male 5-years following left ERM peel. Note the thickening nasal to and thinning temporal to the fovea. I, Full thickness paramacular hole presumably induced by a deep grab during ERM peeling. Images E and F courtesy of Dr Netan Choudhry

8.5.3 | Microcystic Macular Oedema (MMO)

INL microcystic macular oedema (MMO) can precede ERM surgery but is more common after combined ERM/ILM peeling.[151] It is visible on OCT (Figure 8G) but angiographically silent.[151] The nasal quadrant is most commonly affected[152] and the INL is thickened but the GCL thinned.[151] Some,[152] but not all[151] studies have identified poorer visual outcomes with MMO, particularly when present in the central and temporal quadrants.[152] One hypothesis for MMO is that it is a non-vascular retrograde maculopathy caused by ganglion cell loss affecting Müller cell water pumping function.

8.5.4 | Nasal displacement of the fovea and temporal retinal thinning

Retinal displacement of the fovea towards the optic disc after surgery has been described on SD-OCT, likely due to an imbalance of nasal and temporal biomechanical forces after the release of ERM traction.[153] Stretching and thinning of the retina mostly occur temporal to the fovea, and the nasal subfield initially thickens (Figure 8H).[153] Greater thinning of the GCL is associated with greater retinal displacement.[153]

8.5.5 | Full thickness paracentral macular holes

Full thickness paracentral MHs are rare but have been observed after combined ERM/ILM removal (Figure 8I). The MHs are thought to be iatrogenic as they mostly occur at the point of peel initiation or at the edge of the peeled ILM.[154] They are usually asymptomatic, have good visual prognosis unless close to the fovea and do not usually require treatment.[154]

8.6 | Postoperative visual outcomes

Surgery for ERM is a relatively safe and efficacious procedure with good visual outcomes.[139]

Patients with better preoperative VA have a better final postoperative VA but there is a greater improvement in patients with poorer preoperative VA.[155] Postoperative VAs are similar with either a single or double peel and the VA is on average an improvement of two lines for either method.[129,135-137] In the absence of an improvement of VA, many patients also report relief from metamorphopsia which can be more debilitating than decreased VA.[156]

Postoperative OCT evaluation of the retina has revealed improvement in retinal architecture including a gradual re-establishment of foveal profile, flattening of epiretinal disruption, reduction of inner retinal layer distortions and partial re-composition of outer retinal layers.[157] Postoperative VA has also been documented to improve for up to 3 years, likely due to a progressive resolution of intraretinal oedema and restoration of retinal architecture.[157,158]

8.7 | Future directions

Deep learning has the potential to help refine visual prognosis and identify patients who would benefit most from surgery. Vitreopharmacolysis is an area of research that has the potential to identify enzymes capable of dissolving an ERM.[129,134] Three-dimensional heads-up displays have been used for macular surgery, but are yet to show any clinical benefits to the patient over use of a standard operating microscope.[159] Intraoperative OCT may help identify residual membranes in 12% of cases and confirm complete membrane peeling contrary to surgeons impressions in 9% of cases.[160] Vitrectomy may become a robotic operator-dependent field of surgery. Tremor-cancelling and force-sensing micro-forceps are robotic features which are anticipated to improve microsurgery in the future for better surgical outcomes.[161] Hands-free microsurgery may overcome the limitations of human physical skill, adequate visualisation and mental fatigue.[161]

9 | CONCLUSION

Our understanding of ERM pathophysiology has been greatly improved by histopathological studies and retinal imaging advances, in particular OCT. Despite this, difficulties in finding a perfect pathogenic model that explains all clinical scenarios likely suggests a heterogeneous group of diseases. An improved ability to identify prognostic biomarkers on OCT, combined with deep learning and improved surgical techniques will continue to improve visual outcomes, with medical interventions and robotics offering the possibility of earlier intervention.

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CONFLICT OF INTEREST

None declared.

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