Epiretinal Membranes and Macular Pseudoholes

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Jen-Hsiang Shen, Wei-Chi Wu, and Chi-Chun Lai

1.1 Introduction

1.1.1 Epiretinal Membrane (ERM)

Epiretinal membrane usually occurs in patients over 50 years old and could be seen in 10–30% of the general population over 70 years old. Bilateral involvement is present in 20% of these patients. Eighty percent of these membranes are idiopathic, while about 20% are secondary to previous retinal detachment, vascular, or inflammatory retinal diseases [1–5].

The initial presenting visual acuity is usually fair, and the progression is usually slow [6, 7].

Epiretinal membrane and its pathogenesis had first been reported by Iwanoff in 1865 [8]. However, most of the advances on etiopathogenesis and management took place from the 1980s.

Historically, epiretinal membrane had also been called as primary retinal folds, cellophane maculopathy, surface wrinkling retinopathy, preretinal macular fibrosis, macular pucker, wrinkling of the internal retinal surface, internoretinal fibrosis, and vitreoretinal interface changes [9].

The pathogenesis of ERM was believed to be discontinuity of the internal limiting membrane (ILM). Glial cells may proliferate onto the inner retinal surface. The collagen fibrils of the cortical vitreous may tangle with the proliferation and together form firm vitreoretinal attachment [9–11]. Epiretinal membrane in case with prior retinal break or detachment often had retinal pigmented epithelium (RPE) component and sometimes had pigmented appearance [12–14].

J.-H. Shen
Department of Ophthalmology, Chang-Gung Memorial Hospital, Linkou, Taiwan

W.-C. Wu · C.-C. Lai (✉)
Department of Ophthalmology, Chang-Gung Memorial Hospital, Linkou, Taiwan
College of Medicine, Chang-Gung University, Tauyuan, Taiwan

In 1977, Gass proposed a classification as follows: (1) grade 0 (cellophane maculopathy), in which a translucent epiretinal membrane is not associated with distortion of the inner retina; (2) grade I (crinkled cellophane maculopathy), in which the inner retinal surface is distorted by a thin membrane; and (3) grade II, in which the membrane is thicker, with a distinct grayish appearance, and in which it obscures underlying vessels and causes marked distortion of the retina (Table 1.1) [15].

The management of ERM includes observation and vitreoretinal surgery. Most ERMs are with stable clinical course, but VA deterioration and intolerable metamorphopsia may still occur. Surgery is advised to patients: VA deteriorates under 20/100–20/50 or worse and/or intolerable metamorphopsia [9, 16].

1.1.2 Macular Pseudohole (MPH)

Macular pseudohole (MPH) originates from contraction of epiretinal membrane (ERM), and it is typically round and reddish under biomicroscopy (Fig. 1.1a, b). Patients' initial visual acuity (VA) is often fair, but metamorphopsia may still exist in some patients. MPH could be seen in 8–20% of eyes with ERM [17].

MPH was first described by Arthur W. Allen, Jr., an American ophthalmologist, and John Donald MacIntyre Gass, a Canadian-American ophthalmologist in 1976. They reported four patients having a hole in an epiretinal membrane overlying

Table 1.1 Epiretinal membrane grading proposed by Gass [15]

Grade	Description
0; cellophane maculopathy	Translucent epiretinal membrane is not associated with distortion of the inner retina
I; crinkled cellophane maculopathy	Inner retinal surface is distorted by thin membrane
II	Thicker membrane with a distinct grayish appearance, and in which it obscures underlying vessels and causes marked distortion of the retina

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a
b
Straight edges
c
Stretched edges
d
e

Fig. 1.1 (**a**) This is a right eye fundus from a 66-year-old male patient. This color fundus picture shows central round reddish hole-like structure with contractile epiretinal membrane (ERM). Minimal vessel tortuosity could also be observed on the contractile ERM. (**b**) This is the same fundus of (**a**) under red-free filter. We could observe the more evident contractile folds around macula. (**c**) OCT image from two different patients showed macular pseudoholes with straight edges and stretched edges. (**d**) This was the left eye of a 53-year-old female. She complained of progressively blurred vision in the left eye with insidious onset. Fundoscopy showed yellow-grayish thick ERM with mild distortion of retinal surface and small vessels. Radial retinal folds could all be also appreciated. Red-free photography was not taken during this time point. (**e**) After 2 years of follow-up, the yellow-grayish thick ERM with mild distortion of retinal surface and small vessels. Radial retinal folds could all be also appreciated. The ERM was relatively stable. However, the VA deteriorated from 0.4 to 0.3 in Snellen chart. Red-free photography was not taken during this time point

the macula that mimicked a macular hole. In two patients, the clinical course was stable. One patient progressed to full-thickness macula hole. One patient had spontaneous peeling of epiretinal membrane and hole closure. All of the patients had normal or nearly normal visual acuity at first presentation. Three patients had a slight fluorescence in the base of the hole in fluorescein angiography (FA). The fluorescence is less than in true macular holes and not present in lamellar macular holes [18].

Due to advancement of optical coherence tomography (OCT), the characteristics and morphology of macular pseudohole had been redefined. In 2004, Haouchine et al. assessed 40 MPH cases and summarized a steepened foveal pit combined with thickened foveal edges and a small foveal pit diameter as the features of the MPH. Central foveal thickness was normal or slightly increased (167 ± 42 μm). Mean perifoveal thickness was greater than normal (363 ± 65 μm) [19]. Intraretinal split was considered to be only lamellar macula hole at that stage.

In 2008, Gupta, Sadun, and Sebag demonstrated ERM with multifocal contraction tends to result in retinal edema and intraretinal cystoid space [20]. In 2012, Michalewska et al. were the first to find all subtypes of non-full-thickness macular hole (NFMH) belong to the same entity of maculopathy due to ERM, internal limiting membrane (ILM), or hyaloid contraction [21].

In 2013, Gaudric et al. reviewed 54 eyes with MPH using the Cirrus SD-OCT (Carl Zeiss Meditec, Dublin, California, USA). They found 24 (44%) eyes had vertical foveal pit and straight, smooth edges on the OCT scan corresponding to centripetal contraction of the ERM. Nevertheless, 30 (56%) other eyes exhibited some degree of stretching and cleavage of the foveal pit edge resulting from asymmetrical tangential traction of the ERM between multiple epicenters of contraction. Thus, they proposed some lamellar macular holes (LMH) might be a subcategory of macular pseudohole (MPH).

1.2 Etiopathogenesis

1.2.1 ERM

The pathogenesis of ERM was believed to be discontinuity of the internal limiting membrane (ILM). Glial cells may proliferate onto the inner retinal surface. The collagen fibrils of the cortical vitreous may tangle with the proliferation and together form firm vitreoretinal attachment [9–11].

ERM can occur in eyes with posterior vitreous detachment (PVD) or no PVD yet. In 1977, Foos showed the internal limiting membrane (ILM) is especially thin over larger posterior retinal vessels [22, 23]. In these locations, discontinuity of ILM may occur, and glial cells may proliferate onto the inner retinal surface. The collagen fibrils of the cortical vitreous may tangle with the proliferation and together form firm vitreoretinal attachment [9–11]. Foos also raised that retinal ischemia and inflammation may produce enzymatic destruction of ILM integrity and induce glial proliferation [22, 23].

Michels also summarized the hypothesis in patients with PVD already [9]:

1. Full-thickness retinal breaks with liberation of retinal pigment epithelial (RPE) cells into the vitreous cavity
2. Disruption of the ILM, followed by proliferation of glial cells onto the inner retinal surface
3. Mechanical damage to the optic nerve head, where ILM is attenuated or absent, followed by glial cell proliferation
4. Intraocular hemorrhage or inflammation, or both, that, in turn, introduces other cells capable of proliferation [24, 25]

Epiretinal membrane in case with prior retinal break or detachment often had retinal pigmented epithelium (RPE) component and sometimes had pigmented appearance [12–14]. Several factors have been associated with formation of macular epiretinal membrane after retinal reattachment surgery [9]:

1. Increasing patient age [26]
2. Low preoperative visual acuity [26]
3. Total retinal detachment [27]
4. Preoperative evidence of epiretinal membrane formation elsewhere in the eye [26]
5. Vitreous hemorrhage [28, 29]
6. Drainage of subretinal fluid and multiple perforations [27, 29]
7. Intraoperative complications including vitreous loss [29]

There are two hypothesized sources of contraction: myofibroblasts and contraction of vitreous fibrils [30, 31].

Vascular leakage and intraretinal edema could be seen in cases with thick epiretinal membrane and retinal distortion. FA can detect chronic leakage in about 20% of cases, but these leakages did decrease overtime [9].

In 1981, Kampik and coworkers published the ultrastructural findings in 56 eyes with epiretinal membranes. Myofibroblast-like cells are seen in 91% of these eyes. RPE cells were identified only in eyes with retinal detachment with massive preretinal proliferation (MPP) (11 of 11 cases) or prior retinal detachment (11 of 23 cases). Fibrous astrocytes and fibroblasts were observed in 44 (79%) and 43 (77%) eyes, respectively. In eyes ($n = 23$) with prior retinal detachment, the percentage rose to 83% and 61%, respectively [31].

In 1982, Michels released a series of 74 cases. Forty-six eyes (62%) had prior retinal reattachment surgery. Nine cases (12%) were otherwise healthy eyes with PVD. Two eyes (3%) were considered developmental, while two eyes (3%) were considered acquired type in young patients. Fifteen eyes (20%) had history of uveitis, damage from a penetrating injury, vitreous hemorrhage, or prior photocoagulation or surgery not related to retinal detachment. In the membranes removed, he identified the following components:

1. Pigment epithelial cells
2. Fibrous astrocytes
3. Macrophage
4. Fibrocytes
5. Microfilaments and extracellular collagens

In a more recent report by Yazici et al. in 2011, the majority of ERM remained to be idiopathic in most eyes (43%) [32]. However, it is very difficult to compare these epidemiology studies, because the difference in patient population may influence these results greatly (Table 1.2).

In summary, the pathogenesis of ERM was believed to be discontinuity of the ILM. Glial cells may proliferate onto the inner retinal surface. The collagen fibrils of the cortical vitreous may tangle with the proliferation and together form firm vitreoretinal attachment. ERM can occur in eyes with posterior vitreous detachment (PVD) or no PVD yet. The grading of ERM still follows the Gass classification as grades 0, I, and II (Table 1.1). The pathology exam showed the component of ERM as pigment epithelial cells, fibrous astrocytes, macrophage, fibrocyte, microfilaments, and extracellular collagens.

1.2.2 MPH

There is currently no published histopathologic report of a macular pseudohole [34]. The pathogenesis of macular hole was initially proposed by Allen and Gass to be the contraction force of epiretinal membrane in 1976 [18]. There are two studies to support this assumption, and they provided more detailed proposals [21, 34] (Table 1.3).

Some pseudoholes have stretched edge or intraretinal cleavage that could not be simply explained by one center of centripetal contraction. Thus, Gaudric et al. studied the en face OCT images of 54 eyes with MPH. They found 24 eyes with straight edges and 30 eyes with stretched edges (Table 1.4 and Fig. 1.2). They found MPH with straight edges often had smooth ERM, contracted around pseudohole, causing radial retinal folds that converged toward the edge of the membrane, revealing the centripetal forces of

Table 1.2 Etiologies of epiretinal membrane

Study	ERM etiology
Michels [9]	Previous retinal detachment in 46 eyes (62%) Idiopathic in 9 eyes (12%) Developmental in 4 eyes (5%) Previous cataract extraction in 3 eyes (4%) Previous uveitis, vitreous hemorrhage, photocoagulation, penetrating injury, other kinds of surgery in 12 eyes (16%)
Poliner et al. [32]	Idiopathic in 61 eyes (69%) Previous retinal detachment in 27 eyes (31%)
Yazici et al. [31]	Idiopathic in 61 eyes (69%) Previous retinal detachment in 27 eyes (31%) Idiopathic in 125 eyes (43%) Diabetic retinopathy in 107 eyes (37%) Retinal vein occlusion in 28 eyes (10%) Uveitis in 12 eyes (4%) Previous retinal detachment in 5 eyes (2%) Other pathologies in 16 eyes (5%)

Table 1.3 Etiopathogenesis of macula pseudoholes (MPH)

Study	Etiopathogenesis
Allen and Gass [18]	Centripetal contraction of ERM
Gaudric et al. [33]	Centripetal force between eccentric epicenters
Michalewska et al. [20]	Hyperreflective linear structure, either epiretinal membrane, thickened internal limiting membrane, or hyaloids could be the common cause of all types of non-full-thickness macular holes (NFMH)

Table 1.4 Type of pseudohole features and epiretinal membrane contraction [34]

Pseudohole feature	ERM contraction
Straight foveal edge ($n = 24$)	Smooth ERM, contracted around pseudohole, causing radial retinal folds that converged toward the edge of the membrane, thus revealing the centripetal forces of contraction ($n = 18$) Complex pattern fold ($n = 4$) Smooth, no visible folds ($n = 2$)
Stretched edge with partial cleavage of inner and outer retina ($n = 30$)	Multiple epicenters of contraction, asymmetric distortion Eversion of foveal edge ($n = 22$) Smooth with few folds ($n = 4$) More or less radial ($n = 4$)

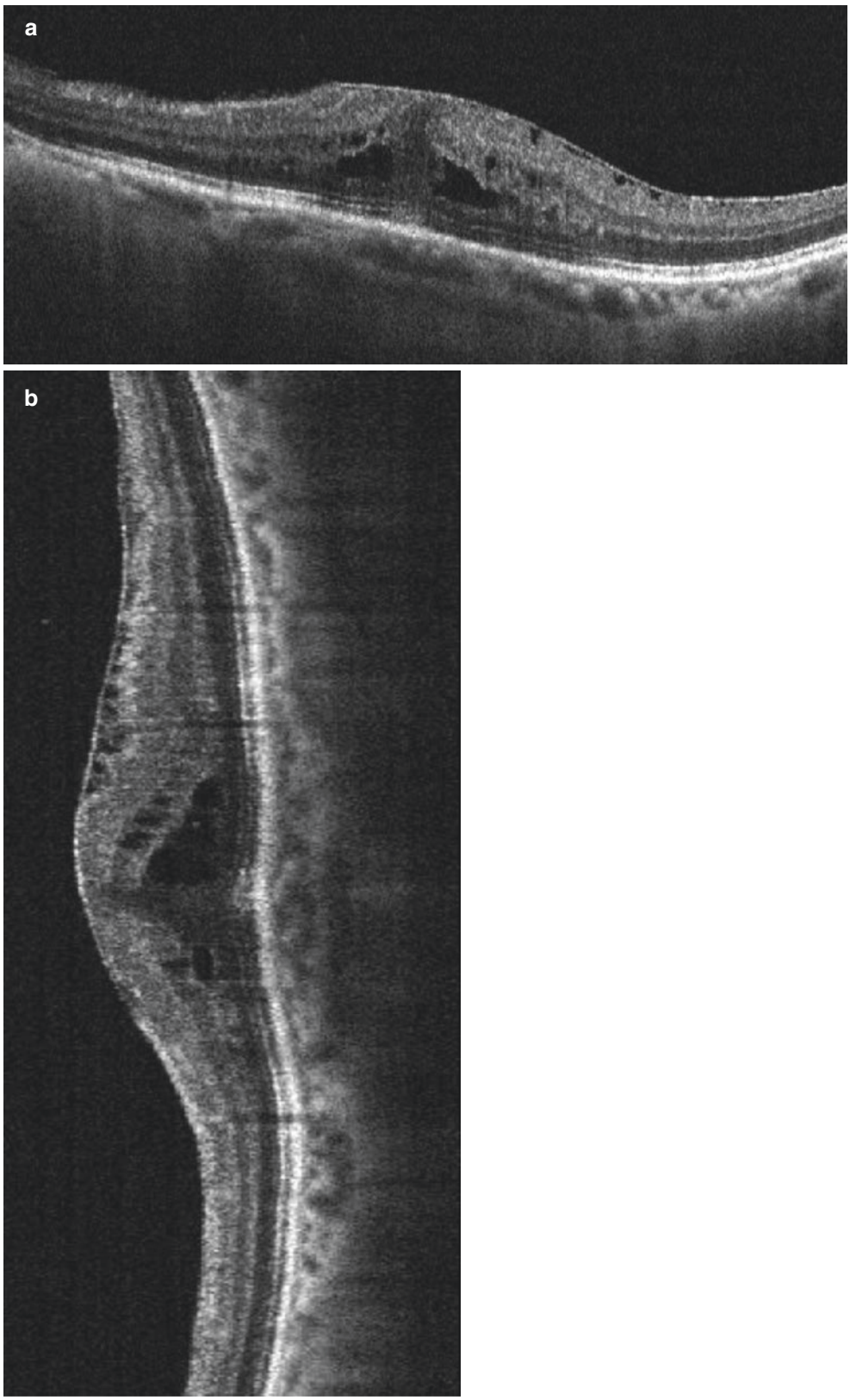

Fig. 1.2 (**a**) High-resolution optical coherence tomography (OCT) showed thickened ERM and central macula edema with intraretinal split, on both horizontal section (**a**) and vertical section (**b**). (**b**) High-resolution optical coherence tomography (OCT) showed thickened ERM and central macula edema with intraretinal split, on both horizontal section (**a**) and vertical section (**b**)

Table 1.5 Characteristics of ERMs on SD-OCT analysis [35]

ERM	Pseudohole eyes (n = 27)
Typical tractional ERM	24
Atypical epiretinal tissue	0
Combined	3

Table 1.6 Proposed stages of macular pseudoholes [36]

Stages	Number	Definition
1	14	No cleavage
2a	13	Localized cleavage not crossing fovea
2b	9	Localized cleavage crossing fovea
3b	14	Diffuse cleavage

contraction. They also noted MPH with stretched edges often had multiple epicenters of contraction and asymmetric distortions [34].

On the other hand, Michalewska et al. championed that not only epiretinal membrane could produce this contraction. They proposed that hyperreflective linear structure-like epiretinal membrane, thickened internal limiting membrane, or hyaloids could be the common cause of all types of non-full-thickness macular holes [21].

Besides these two theories, Schumann et al. analyzed the properties of epiretinal membrane of 27 eyes with MPH in 2015. They confirmed the majority of ERM are typical tractional ERM [35] (Table 1.5).

In 2016, Tomaya et al. proposed three stages of macular pseudoholes: no cleavage (stage 1), localized cleavage (stage 2) that does or does not cross the central fovea (stage 2b and 2a, respectively), and diffuse cleavage (stage 3) (Table 1.6). This reflected different levels of stretching and foveal morphology distortion [36].

1.3 Clinical Features

1.3.1 A Typical Case of ERM

This was the left eye of a 53-year-old female. She complained of progressively blurred vision in the left eye with insidious onset. Fundoscopy showed yellow-grayish thick ERM with mild distortion of retinal surface and small vessels. Radial retinal folds could all also be appreciated (Fig. 1.1d). She had been observed for 2 years and had relative stable clinical course with best-corrected VA deteriorating from 0.4 to 0.3 (Fig. 1.1e). High-resolution optical coherence tomography (OCT) showed thickened ERM and central macula edema with intraretinal split, on both horizontal section (Fig. 1.2a) and vertical section (Fig. 1.2b).

However, due to this worsening, the patient requested for operation. Microincisional sutureless 23G vitrectomy with double peeling with triamcinolone acetonide (TA) staining was performed. Air tamponade with head-positioning for 1 day were also administered. After 1.5 months postoperatively, follow-up OCT showed removal of ERM and ILM on central macula, on both horizontal section (Fig. 1.3a) and vertical section (Fig. 1.3b).

After 2.5 months postoperatively, the intraretinal split subsided and initial restoration of foveal depression could be observed (Fig. 1.4a, b). After 6.5 months postoperatively, the anatomical improvement had been stable (Fig. 1.5a, b).

After 2 years of follow-up, the macula seemed flat without recurrence of ERM. The VA was stable at 0.4. On the OCT, the retinal layers also showed adequate segmentation. Please note the remnant of ERM on the superior aspect of macula. The ERM did not extend to the parafoveal region. Please also note there were some epiretinal hyperreflectivities on the horizontal section, but these spots did not form contractile ERM (Fig. 1.6a–d).

1.3.2 Examples of Secondary ERM

We demonstrate some cases of secondary ERM here. The first case was the left eye of a 29-year-old female. She suffered from poorly controlled diabetes mellitus. Proliferative diabetic retinopathy with tractional epiretinal membrane and vitreous hemorrhage. The second case was the left eye from a 74-year-old female with prior proliferative diabetic retinopathy with panretinal photocoagulation scars. Tractional membrane over disc and nasal side retina and yellow-grayish contractile macular ERM could be seen. The third case was the left eye from a 74-year-old female with prior proliferative diabetic retinopathy with pan-retinal photocoagulation scars. Tractional membrane over disc and nasal side retina and yellow-grayish contractile macular ERM could be seen. High-resolution OCT showed thickened ERM with attenuation of the foveal pit. No remaining macular ERM could be seen post-operatively. The contractile wrinkling had also been gone (Fig. 1.7).

1.3.3 Presenting Age, VA, and Laterality in ERM

Epiretinal membrane usually occurs in patients over 50 years old and could be seen in 10–30% of the general population over 70 years old. Bilateral involvement is present in 20% of these patients. Eighty percent of these membranes are idiopathic, while about 20% are secondary to previous retinal detachment, vascular, or inflammatory retinal diseases [1, 5] (Table 1.2). The initial presenting visual acuity is usually fair, 20/50, or better, and the progression is usually slow [5–7].

In 1982, Sidd et al. published a series of 98 eyes in 89 patients, with 83 more than 50 years old. Sixty eyes (60/98,

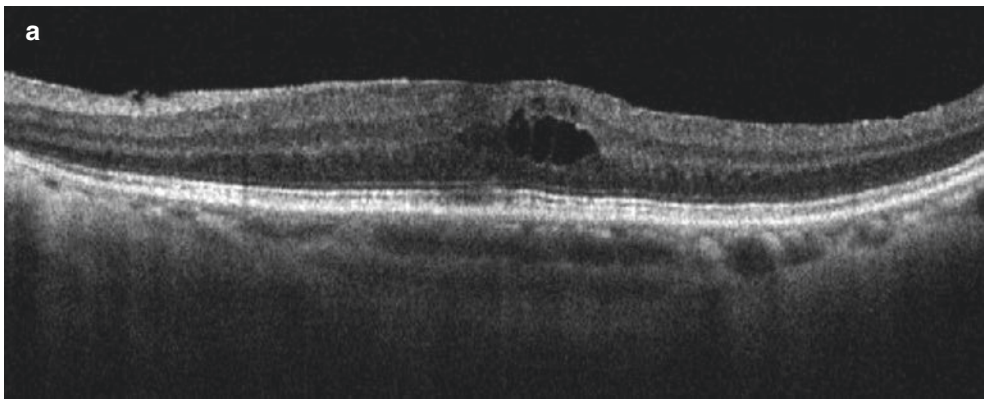

Fig. 1.3 (**a**) After 1.5 months postoperatively, follow-up OCT showed removal of ERM and ILM on central macula, on both horizontal section (**a**) and vertical section (**b**). The central foveal thickness decreased markedly, and the intraretinal splitting lessened. Please also note very thin ILM still evident on the side close to optic nerve head. We preferably perform limited ILM peeling in our cases. (**b**) After 1.5 months postoperatively, follow-up OCT showed removal of ERM and ILM on central macula, on both horizontal section and vertical section. The central foveal thickness decreased markedly, and the intraretinal splitting lessened. Please also note very thin ILM inferiorly and residual ERM-ILM superiorly. We preferably perform limited ILM peeling only in our cases

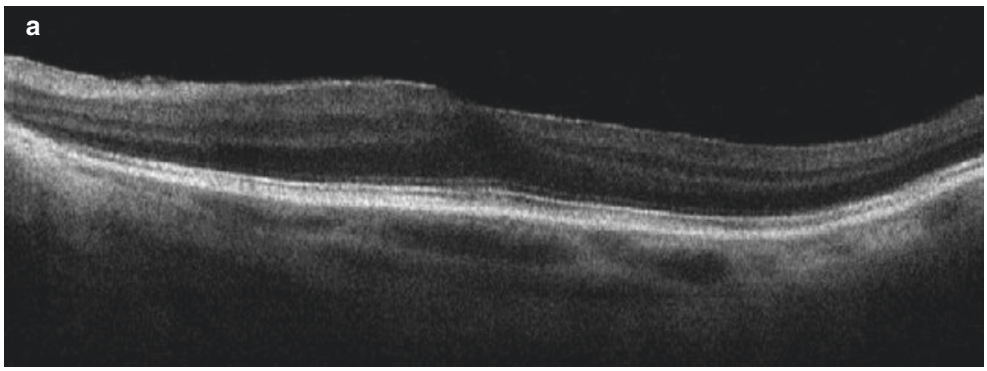

Fig. 1.4 (**a**) After 2.5 months postoperatively, the intraretinal split subsided, and initial restoration of foveal depression could be observed. (**b**) After 2.5 months postoperatively, the intraretinal split subsided, and initial restoration of foveal depression could be observed

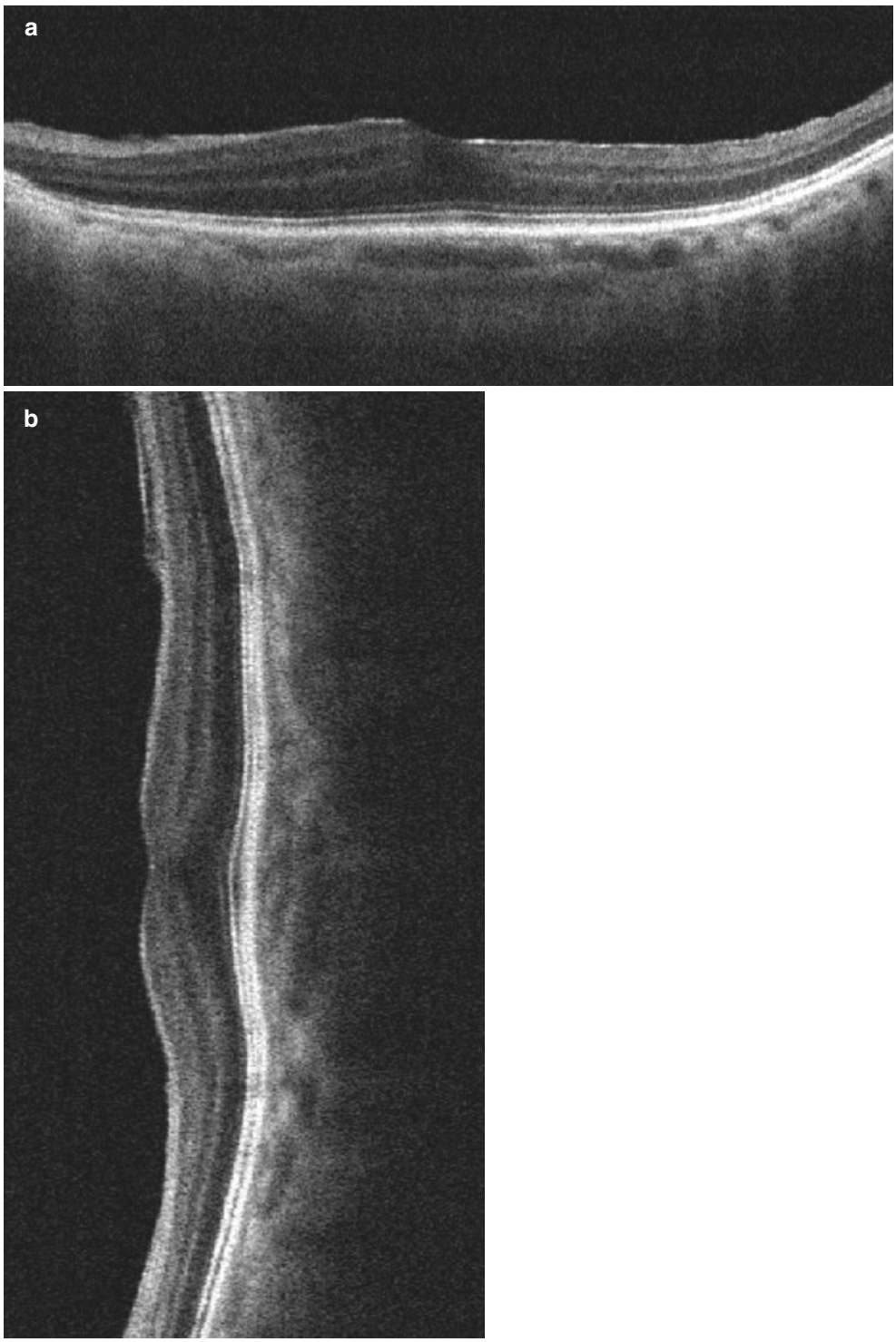

Fig. 1.5 (**a**) After 6.5 months postoperatively, the anatomical improvement had been stable. There was no more foveal cystic change, and the segmentation of retinal layers was well-defined. (**b**) After 6.5 months postoperatively, the anatomical improvement had been stable. There was no more foveal cystic change, and the segmentation of retinal layers was well-defined

61%) had initial presenting VA 6/12 (20/40) or better. Nine patients had initial bilateral epiretinal membrane, and a second eye became involved in one initially unilateral patient during the follow-up period. Sixteen of 74 eyes (21%) had fluorescein leakage into the macula [7].

In 1988, Appiah, Hirose, and Kado reviewed 395 eyes in 324 eyes with idiopathic premacular gliosis. The mean age of onset in these patients was 64.6 years old. Initial visual acuity was 20/40 or better in 214 eyes (54.2%), 20/50 to 20/100 in 136 eyes (34.4%), and poorer than 20/100 in 45 eyes (11.4%).

Fig. 1.6 (**a**) After 2 years of follow-up, the macula seemed flat without recurrence of ERM. There was also no retinal folding. (**b**) After 2 years of follow-up, the macula seemed flat without recurrence of ERM. There was also no retinal folding. (**c**, **d**) After 2 years of follow-up, the macula seemed flat without recurrence of ERM. On the OCT, the retinal layers also showed adequate segmentation. Please note the remnant of ERM on the superior aspect of macula. The ERM did not extend to the parafoveal region. Please also note there were some epiretinal hyperreflectivities on the horizontal section, but these spots did not form contractile ERM

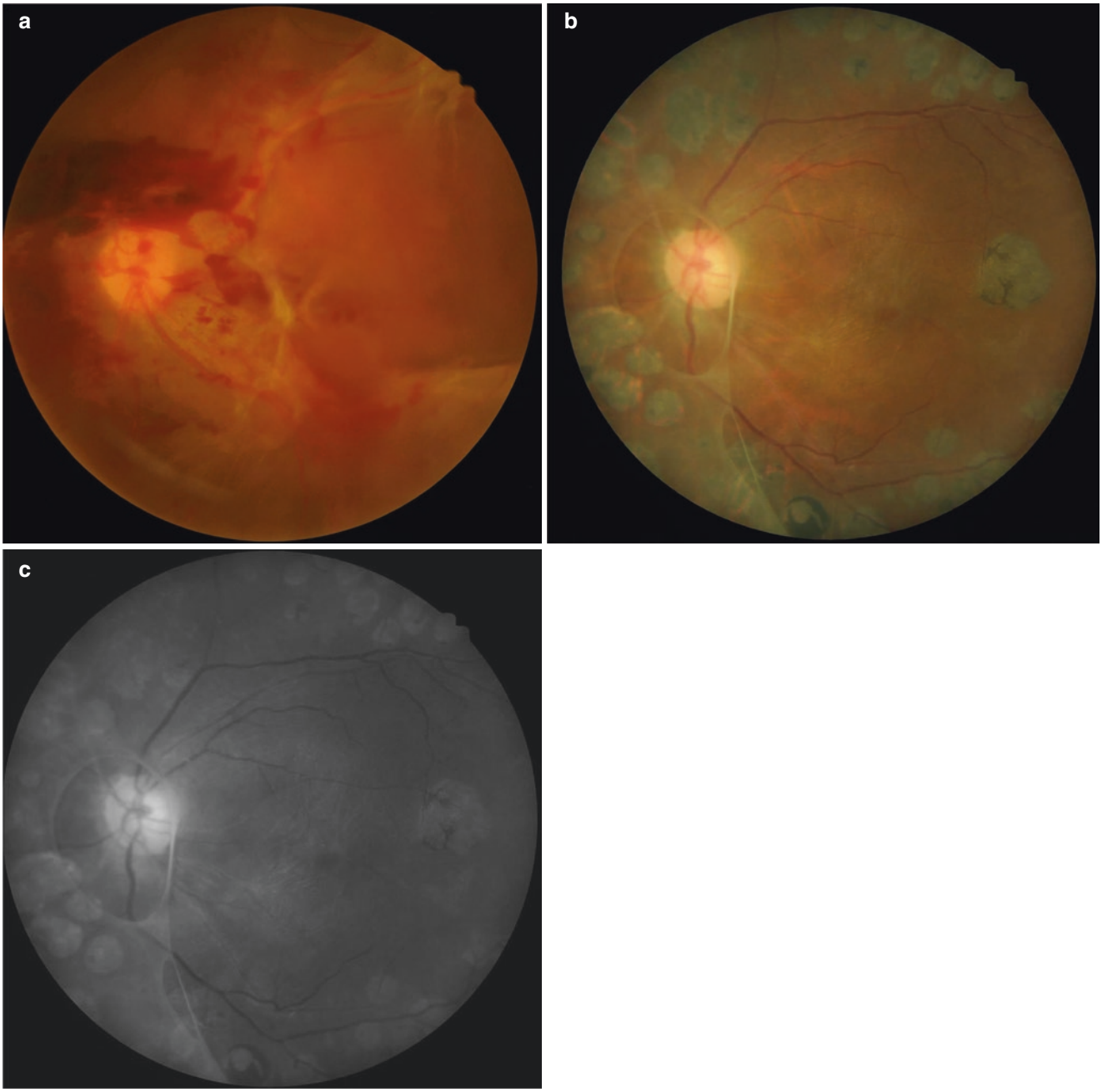

Fig. 1.7 (**a**) This was a left eye of a 29-year-old female. She suffered from poorly controlled diabetes mellitus. Proliferative diabetic retinopathy with tractional epiretinal membrane and vitreous hemorrhage could be seen in this fundus color photo. The postoperative photo was not available for this patient. (**b**) This was a left eye from a 74-year-old female with prior proliferative diabetic retinopathy with pan-retinal photocoagulation scars. Tractional membrane over disc and nasal side retina and yellow-grayish contractile macular ERM could be seen. (**c**) This was a left eye from a 74-year-old female with prior proliferative diabetic retinopathy with pan-retinal photocoagulation scars. Tractional membrane over disc and nasal side retina and yellow-grayish contractile macular ERM could be seen. Please note the contractile wrinkling of macular ERM being more evident under this red-free fundus photo. (**d**, **e**) High-resolution OCT showed thickened ERM with attenuation of the foveal pit. (**f**) One month after the vitrectomy and double membrane peeling. The macular tractional ERM and ILM were peeled off. No remaining macular ERM could be seen postoperatively. (**g**) One month after the vitrectomy and double membrane peeling. The macular tractional ERM and ILM were peeled off. No remaining macular ERM could be seen postoperatively. The contractile wrinkling had also been gone in this red-free photography. (**h**, **i**) One month after the vitrectomy and membrane peeling, there was mild restoration of the foveal contour. This patient was referred back to original ophthalmologist after this examination

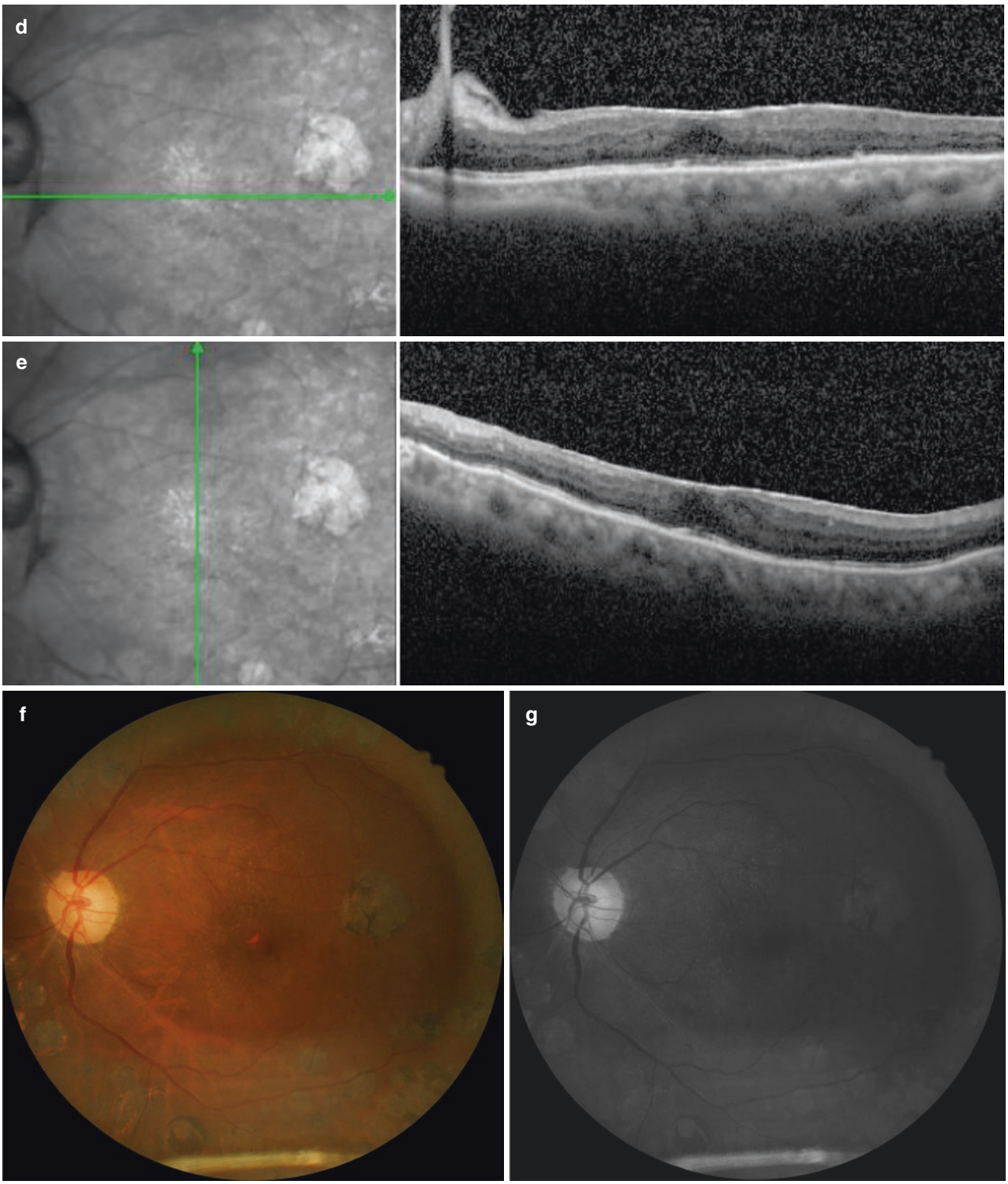

Fig. 1.7 (continued)

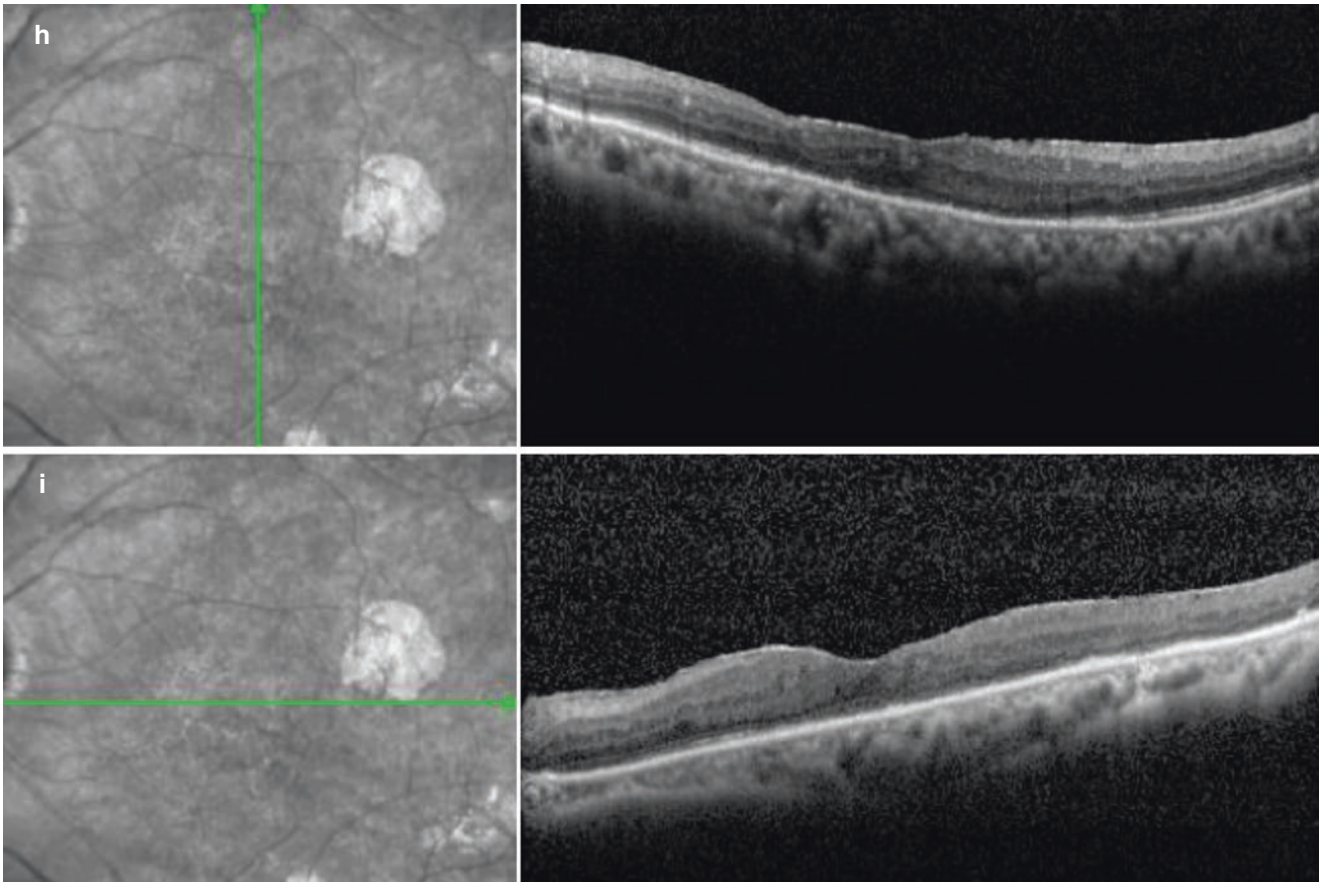

Fig. 1.7 (continued)

In a more recent nature-course observation, Hejsek et al. followed 53 eyes in 49 patients (average 21.3 months). No statistically significant anatomical or functional impairment was observed. BCVA remained constant in 29 eyes (54.7%), improvement by 1 or more lines (ETDRS) was observed in 12 eyes (22.6%), and impairment by 1 or more lines (ETDRS) was found in 12 eyes (22.6%). Only three eyes (5.6%) were worse by more than 1 line (ETDRS). This study further confirmed that the majority of eyes with idiopathic epiretinal membranes are functionally stable [16].

1.3.4 Status of Posterior Vitreous Detachment (PVD) in ERM

Most eyes with ERM, both idiopathic and secondary, have PVD, ranging from 84% to 98% from literature.

In 1975, Wise reviewed 137 eyes with idiopathic membranes involving the macula and found PVD 118 (86%) eyes [37].

In 1982, Sidd and coworkers published a series of 89 patients. Sixty-four eyes had been recorded for PVD status, and 59 eyes (92%) had PVD [7].

In 1988, Appiah et al. reviewed the vitreous status of 357 eyes. Partial or complete PVD was seen in 303 (84.9%) eyes. Forty-three (14.2%) of these 303 eyes had PVD with vitreous adhesion to the macula.

In a more recent series by Yazici et al., 125 eyes with idiopathic ERM and 168 eyes with secondary ERM were reviewed. PVD was seen in 98% of idiopathic ERM and 96% of secondary ERM [32].

1.3.5 Summary of Clinical Features in ERM

Epiretinal membrane usually occurs in patients over 50 years old and could be seen in 10–30% of the general population over 70 years old. Bilateral involvement is present in 20% of these patients. Eighty percent of these membranes are idiopathic, while about 20% are secondary to previous retinal detachment, vascular, or inflammatory retinal diseases. The initial presenting visual acuity is usually fair, 20/50, or better, and the progression is usually slow. Most eyes with ERM, both idiopathic and secondary, have PVD, ranging from 84% to 98% from literature.

MPH could be seen in 8–20% of eyes with ERM.

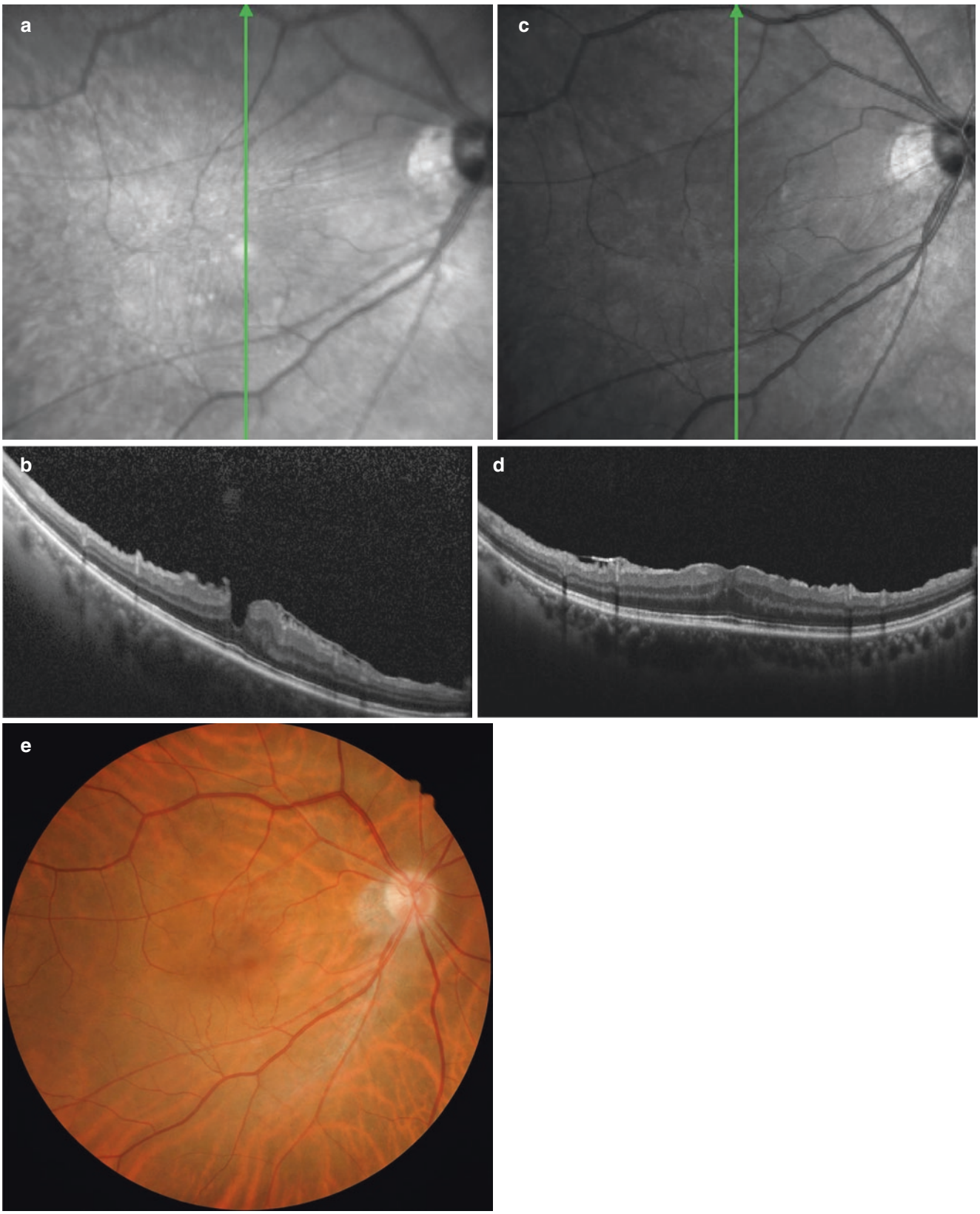
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Fig. 1.8 (**a**) This shows the vertical section of an eye with macular pseudohole under high-resolution spectral domain optical coherence tomography (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany). Please also note the centripetal contraction folds clearly shown. (**b**) This section shows the classic steepened foveal edge with increased foveal thickness under the centripetal traction from epiretinal membrane (ERM) high-resolution spectral domain OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany). (**c**) This shows the vertical section of the same eye with macular pseudohole, 1 year after 23-gauge vitrectomy, epiretinal membrane and internal limiting membrane peeling, air tamponade, and prone positioning, under high-resolution spectral domain OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany). Note the closure of the macular pseudohole. (**d**) This shows the vertical section of the same eye with macular pseudohole, 1 year after 23-gauge vitrectomy, epiretinal membrane and internal limiting membrane peeling, air tamponade, and prone positioning, under high-resolution spectral domain OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany). Please note the closure of the macular pseudohole and moderate restoration and normal foveal structure. (**e**) This color fundus shows the same eye with macular pseudohole, 1 year after 23-gauge vitrectomy, epiretinal membrane and internal limiting membrane peeling, air tamponade, and prone positioning. Please note the closure of the macular pseudohole and disappearance of epiretinal membrane and contractile folds

1.3.6 A Typical Case of MPH

This is a right eye from a 66 years old male patient. Epiretinal membrane with contractile wrinkling could be observed under color fundus and red-free photo (Fig. 1.1a, b). Under high-resolution spectral domain optical coherence tomography (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) (Fig. 1.8a, b), classic steepened foveal edge with increased foveal thickness under the centripetal traction from epiretinal membrane (ERM) is shown. The preoperative visual acuity (VA) was 0.6 (0.22 logMAR). One year after small-gauge vitrectomy, epiretinal membrane and internal limiting membrane peeling, air tamponade, and prone positioning, the pseudohole is closed with moderate restoration of normal foveal structure (Fig. 1.8c–e). The postoperative VA was 0.7 (0.15 logMAR).

1.3.7 Presenting Age, Visual Acuity, and Fluorescein Angiography in MPH

In 1992, Fish et al. reviewed 14 eyes with epimacular membrane and pseudohole. The mean age of patients was 61.6 years, and median visual acuity was 20/30. Mean horizontal and vertical diameters of the pseudoholes were 384 μm and 410 μm, respectively. FA showed three eyes with increased tortuosity or abnormal straightening of the perifoveal vessels; three eyes with a foveal window defect; and three eyes with late leakage from the perifoveal vessels [38].

The visual function of MPH eyes was often fair but varied from reports. In 1999, Massin et al. had case-control comparison of 50 eyes with idiopathic ERMs only and ERMs combined with pseudohole. The median preoperative visual acuity (VA) was the same as 20/63 (range, 20/32–20/860). In 1997, Tsujikawa et al. observed 49 eyes diagnosed with macular pseudoholes or impending macular holes. The median VA was 20/25 (range, 20/15–20/100). Only one eye showed a relative scotoma in perimetry, compared with 100% in full-thickness macular hole [39]. In 2008, Chen and Lee reviewed 92 eyes of macular lamellar defects, comprised of MPH, LMH, and foveal pseudocyst (FP). The MPH had the best VA of 0.1 (SD = 0.15) logMAR (equivalent to 20/25 Snellen acuity) compared with that of the LMH group (0.28 (SD = 0.25) logMAR; p = 0.005) and the FP group 0.30 (SD = 0.26; p = 0.01) [40]. In 2012, Michalewska and colleague reviewed 21 eyes with MPH, and the mean VA was 0.58. After excluding eyes with photoreceptor defects, the mean VA was 0.54 [21].

1.3.8 Status of PVD in MPH

The status of posterior vitreous detachment had been shown in one report. Schumann et al. had a series of 23 MPH underwent vitrectomy. They found eight (35%) eyes with vitreous attached, five (22%) eyes with vitreous partially detached, and ten (43%) eyes with complete PVD [35].

1.3.9 Detailed MPH Characteristic Discovery Under OCT Advances

The detailed characteristics of MPH had been revealed as OCT technology advanced. In 2004, Haouchine et al. observed 40 eyes with MPH. They summarized MPH as a steepened foveal pit combined with thickened foveal edges and a small foveal pit diameter. Central foveal thickness was normal or slightly increased (167 ± 42 μm). Mean perifoveal thickness was greater than normal (363 ± 65 μm) [19]. Intraretinal split was considered as hallmark for lamellar macula hole at then. Also, photoreceptor layer was considered as intact [41].

However, Gupta, Sadun, and Sebag demonstrated ERM with multifocal contraction tends to result in intraretinal cystoid space, in 2008. In 2013, Gaudric et al. reviewed 54 eyes with MPH using the Cirrus SD-OCT (Carl Zeiss Meditec,

Dublin, California, USA). They found 24 (44%) eyes had vertical foveal pit and straight, smooth edges on the OCT scan corresponding to centripetal contraction of the ERM. Nevertheless, 30 (56%) other eyes exhibited some degree of stretching and cleavage of the foveal pit edge resulting from asymmetrical tangential traction of the ERM between multiple epicenters of contraction. Thus, they proposed some lamellar macular hole (LMH) might be a subcategory of macular pseudohole (MPH).

Gaudric and colleagues further elaborated the ERM contraction by the en face OCT image. In the group with straight foveal edges, 18 of 24 (75%) eyes had a characteristic pattern of a smooth ERM, contracted around the pseudohole, causing radial retinal folds that converged toward the edge of the membrane, thus revealing the centripetal forces of contraction generated by the membrane. Four other eyes had a more complex pattern of folds, and in the two remaining eyes, the membrane was smooth with no visible folds. In the group with stretched edges combined with a partial cleavage between the inner and outer retina, 22 of 30 (73%) eyes displayed a characteristic pattern of multiple epicenters of contraction at the peripheral edge of the membrane, which resulted in an asymmetric distortion of the fovea and explained the eversion of the foveal edge on OCT scans. In four eyes, the ERM was smooth, with few retinal folds, and in the four other eyes, the folds were more or less radial. There was no significant difference in gender, age, posterior vitreous detachment (PVD), VA, central macular thickness (CMT), and central foveal pit thickness between two groups [34].

In 2015, Schumann et al. proved photoreceptor and external limiting membrane (ELM) damage from 39 eyes with MPH. Among the 39 eyes, 27 eyes had examination by high-resolution spectral domain OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany). They stratified ERM to "typical tractional ERM" and "atypical epiretinal tissue." Defect of inner and outer segment (IS/OS) and ELM was seen in 11% of MPH eyes. The median best-corrected visual acuity (BCVA) was 0.30 logMAR. Metamorphopsia was complained in 59% (n = 23) of the patients, and 59% (n = 23) had vitrectomy during follow-up.

They found a lower BCVA in the disrupted IS/OS and ELM group; and there was no significant difference in the intact IS/OS and ELM group and disrupted IS/OS-only group. In the nonoperated eyes (31 LMH and 16 MPH eyes), there is no BCVA difference in the subgroups. They did not reveal the independent result of MPH eyes in this analysis.

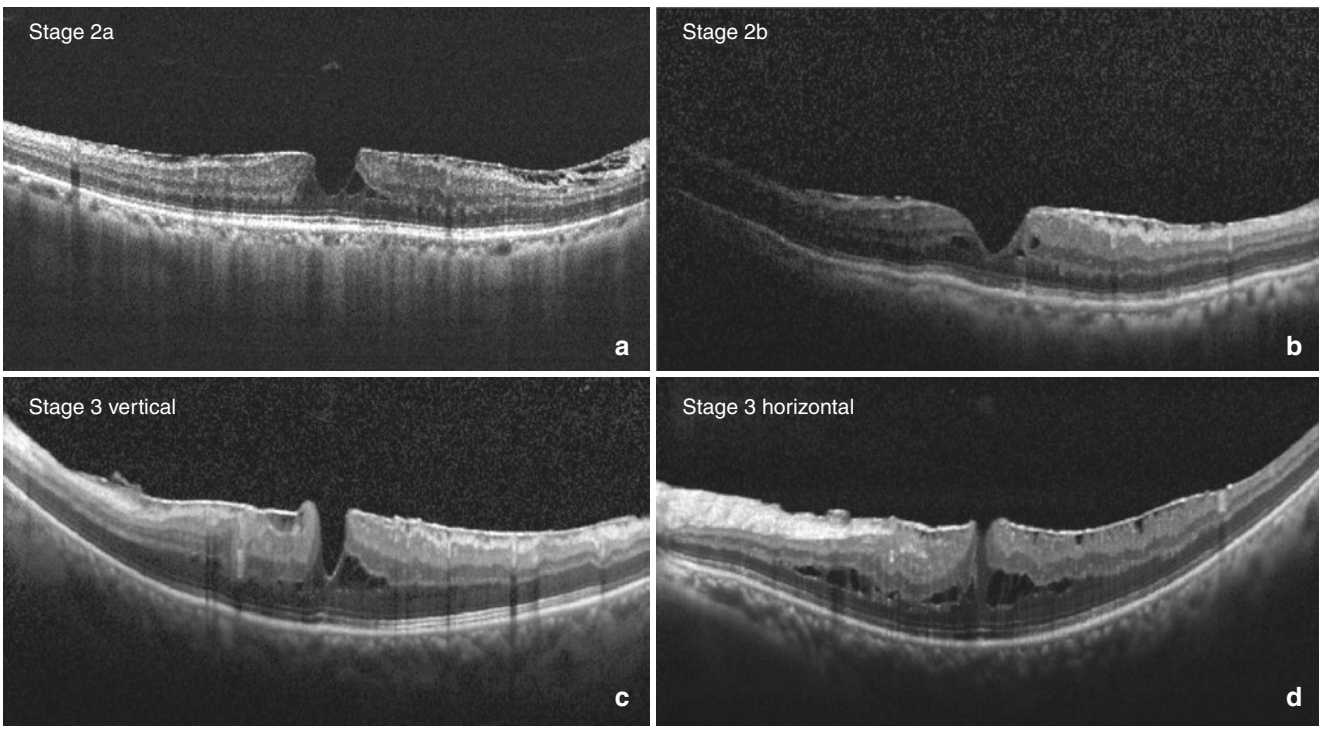

Fig. 1.9 (**a**) This optical coherence tomography section showed localized cleavage on only one side of the foveal edge. This is a stage 2a macular pseudohole according to Toyama's report in 2016. (**b**) This optical coherence tomography section showed localized cleavage crossing both sides of the foveal edge. This is a stage 2b macular pseudohole according to Toyama's report in 2016. (**c**, **d**) This optical coherence tomography section showed diffuse cleavage crossing both sides of the foveal edge. This is a stage 3 macular pseudohole according to Toyama's report in 2016. Please note that the diffuse cleavage might only be seen on some sections, usually not shown in all section. The same condition is also demonstrated in Toyama's paper

On the contrary, Toyama and colleague did not observe any disruption in the ellipsoid zone and ELM in 50 eyes with MPH [36].

In the same report, Toyama et al. further categorized the foveal edge to three stages of stretch cleavage between outer plexiform layer and the outer nuclear layer. The stages are as follows: no cleavage (stage 1), localized cleavage (stage 2) that does or does not cross the central fovea (stage 2b and 2a, respectively), and diffuse cleavage (stage 3). We used our patient's OCT to demonstrate these stages (Figs. 1.8b and 1.9a–d).

The number of patients categorized into each stage was 14 (28.0%), 13 (26.0%), 9 (18.0%), and 14 (28.0%) for stages 1, 2a, 2b, and 3, respectively. Temporal (12.3%) or nasal (11.1%) cleavage was more common than inferior (8.0%) or superior (9.3%) cleavage [36].

There was a significant difference in VA between the stages 2a and 2b ($p = 0.0099$ by multiple regression model). Therefore, the patients were categorized into two groups, the no/mild cleavage group (stage 1/2a) and the extensive cleavage group (stage 2b/3). They also found age, gender, and phakic status were not significant in affecting VA [36].

1.3.10 How to Differentiate Between Lamellar Macular Hole (LMH) and MPH

On biomicroscopy, the diagnosis of MPH is based on the presence of a well-delineated round or oval image of the macula with definite ERM with retinal folds. The diagnosis of LMH is described as a round- or petal-shaped reddish lesion with flat, sharply circumscribed edges. The center sometimes slightly depressed. Paler thin tracts could occasionally be seen. However, in 2004, Haouchine and coworkers had shown considerable misdiagnosis when confirmed by OCT. Among the 40 eyes diagnosed as MPH on OCT, 35 were also diagnosed as MPH, and two were diagnosed as LMH on biomicroscopy. Among the 29 cases diagnosed as LMH on OCT, 14 were diagnosed as MPH and eight as LMH on biomicroscopy [19] (Fig. 1.10a).

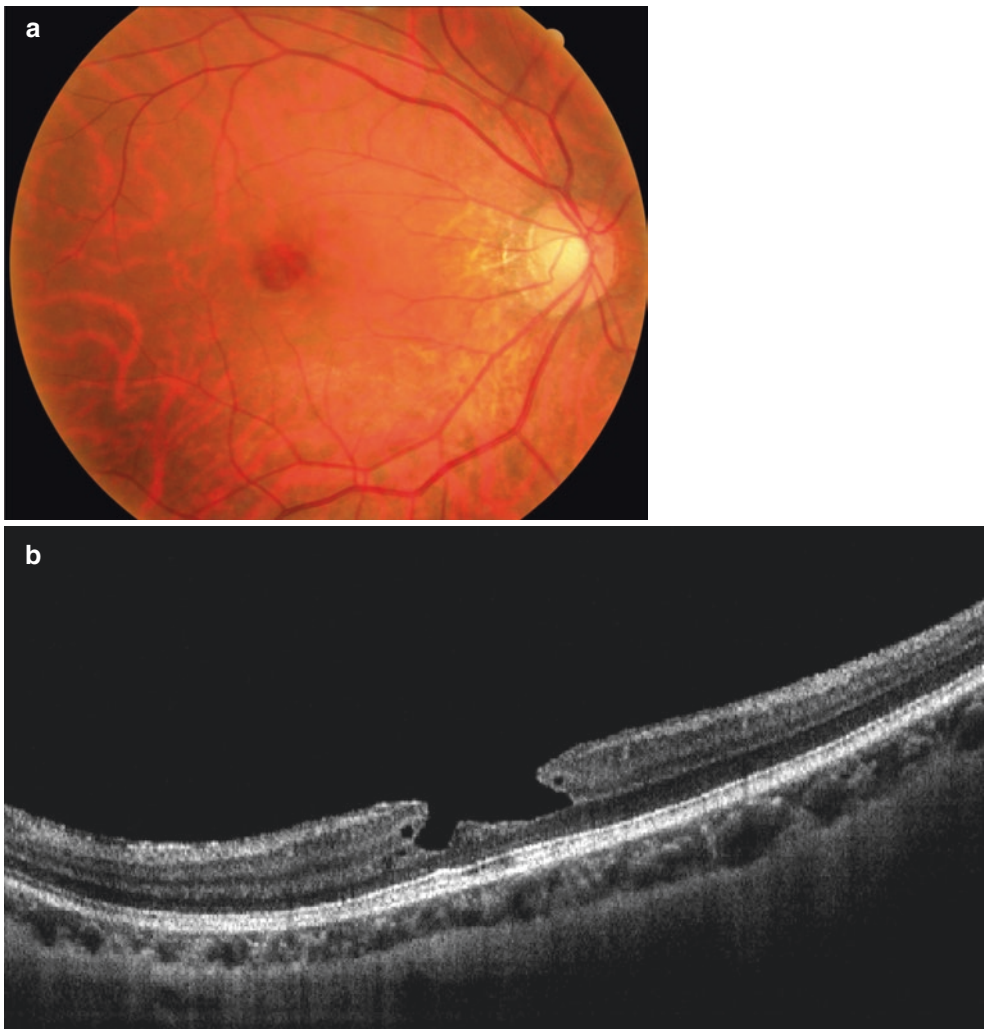

Fig. 1.10 (**a**) This is a right eye fundus photo of a 36-year-old female. Round and also mild petal-shaped reddish lesion with flat, sharply circumscribed edges could be appreciated. The center also seems slightly depressed. This represents a typical case of lamellar macular hole (LMH). (**b**) This is the OCT image of the right eye of the 36-year-old female shown in Fig. 1.9a. Please note that all the four criteria described by Haouchine et al. could be seen: (1) thin irregular foveal floor, (2) split foveal edges, (3) near-normal perifoveal retinal thickness, and (4) central foveolar thickness thinner than normal

They published their observation of 71 eyes from 70 patients. Characteristic of OCT in LMH was defined as the following and now being well adapted [19] (Fig. 1.10b).

1. Thin irregular foveal floor
2. Split foveal edges
3. Near-normal perifoveal retinal thickness
4. Central foveolar thickness thinner than normal

These criteria defined by Haouchine et al. are still widely used today. We may use these criteria to differentiate LMH from MPH.

1.3.11 Summary of Clinical Features in MPH

The mean age of patient was 61.6 years. The VA was generally fair, but with various median VA reported from 20/63 to 20/25. Metamorphopsia was complained in 59% of the patients. Mean horizontal and vertical diameters of the pseudoholes were 384 μm and 410 μm, respectively. Thirty-five percent of the eyes had vitreous attached. Twenty-two percent of the eyes had vitreous partially detached; and 43% of the eyes had complete PVD.

MPH generally has steepened foveal pit combined with thickened foveal edges and a small foveal pit diameter. Central foveal thickness was normal or slightly increased. Mean perifoveal thickness was greater than normal. With the advance of OCT, MPH could be classified into groups with straight edges and stretched edges. In the group with straight foveal edges, most eyes had a characteristic pattern of a smooth ERM. In the group with stretched edges combined with a partial cleavage, most eyes displayed a characteristic pattern of multiple epicenters of ERM contraction. There is a lower BCVA in the disrupted IS/OS and ELM group; and there was no significant difference in the intact IS/OS and ELM group and disrupted IS/OS only group.

Three stages of stretch cleavage had been defined as no cleavage (stage 1), localized cleavage (stage 2) that does or does not cross the central fovea (stage 2b and 2a, respectively), and diffuse cleavage (stage 3). There was a significant difference in VA between the stages 2a and 2b.

1.4 Management

The management of epiretinal membrane (ERM) includes observation and vitreoretinal surgery. Surgery is advised to patients [9, 16]:

1. VA deteriorates under 20/100–20/50 or worse.
2. Intolerable metamorphopsia.

The management of macular pseudohole (MPH) includes observation and vitreoretinal surgery. Surgery is advised to patients:

1. Visual acuity decreases more than two Snellen lines during the follow-up.
2. Initial visual acuity below 0.6, disturbing to the patient.
3. Visual acuity is better than 0.6, but disturbing metamorphopsia [21].

1.4.1 Observation in ERM and MPH

Generally speaking, the majority of patients had relatively stable clinical course [6, 7, 16]. Therefore, observation is suggested unless the criteria of surgery are met.

In 1982, Sidd et al. published their observation in 98 eyes with epiretinal membrane. Seventy-two eyes completed follow-up, with mean of 31.1 months. The fundus remained grossly unchanged in 65 eyes (90%). Fifty-one eyes (71%) had final VA deterioration within one line. Decrease in retinal wrinkling and VA improvement of two lines or more occurred in only two patients (2%) [7].

In 1988, Appiah, Hirose, and Kado reviewed 395 eyes in 324 eyes with idiopathic premacular gliosis, in which 214 eyes completed follow-up, with mean follow-up period of 33.6 months. One hundred and six (49.5%) of the 214 eyes maintained within 1 line of initial VA, 28 (13.1%) were more than 1 line better, and 80 (37.4%) were poorer [6].

In rare cases, epiretinal membrane will spontaneously peel off from the retina, and VA improvement may be observed [42].

In a more recent nature-course observation, Hejsek et al. followed 53 eyes in 49 patients (average 21.3 months). No statistically significant anatomical or functional impairment was observed. BCVA remained constant in 29 eyes (54.7%), improvement by 1 or more lines (ETDRS) was observed in 12 eyes (22.6%), and impairment by 1 or more lines (ETDRS) was found in 12 eyes (22.6%). Only three eyes (5.6%) were worse by more than 1 line (ETDRS). This study further confirmed that the majority of eyes with idiopathic epiretinal membranes are functionally stable [16].

Generally speaking, the majority of patients with MPH had relatively stable clinical course [18, 21]. Therefore, observation is suggested unless the criteria of surgery are met.

In 1976, Allen and Gass witnessed one in four pseudoholes that progressed to full-thickness macular hole [18].

In 2012, Michalewska et al. published an observation of 125 eyes (116 patients) with non-full-thickness macular hole (NFMH), including 21 eyes with macular pseudohole (MPH), during 2006–2009. None of the MPH progressed to full-thickness macula hole (FTMH) [21].

1.4.2 Vitreoretinal Surgery in ERM

In 1978, Machemer reported the first pars plana vitrectomy for visually distorting epiretinal membrane removal [43].

Shea, Michels and Gilbert, and Margheiro and coworkers were the pioneers to report fair results after epiretinal membrane peeling in eyes with prior retinal detachments. They reported VA improvement in 88–90% of the cases [44–47]. However, the postoperative VA is usually between 20/30 and 20/100 [43, 47, 48].

1.4.2.1 Indication for Surgery in ERM

In 1982, Michels supported that surgery be considered in eyes with visual acuity of 20/100 or less, because final VA in successful cases often ranges between 20/30 and 20/70 at then [9].

In a more recent review by Hejsek et al. in 2017, they suggested vitrectomy in:

1. VA deteriorates under 20/50 or worse.
2. Intolerable metamorphopsia.

However, no recommendation has yet been established on the exact timing of the surgery [16].

1.4.2.2 ERM Peeling in ERM

In 1996, Shimada et al. compared ERM peeling by one of the three following methods: without staining in 46 eyes, triamcinolone acetonide (TA) staining in 42, and brilliant blue G (BBG) staining in 54. They found in the BBG group, 61% (33/54) achieved double peeling during the initial ERM peeling [49].

1.4.2.3 ILM Peeling in ERM

In 1996, Shimada et al. conducted internal limiting membrane (ILM) peeling using brilliant blue G (BBG). They also compared 104 eyes with single peeling and 142 eyes with double peeling and found the VA improvement was similar. However, the recurrence rate was much lower in the double peeling group [49].

In 2003, Park et al. collected 22 eyes (55%) with single peeling and 20 eyes (45%) with double peeling. VA improved or was unchanged in 79% in single peeling group and 100% in double peeling group. VA improved five or more lines in 25% in single peeling group and 30% in double peeling group [50].

In 2012, Chuang et al. followed 104 eyes from 104 patients that underwent double peeling. They compared no staining ($n = 61$), triamcinolone acetonide (TA) ($n = 20$), and indocyanine green (ICG) ($n = 23$). The improvement of VA and central foveal thickness (CFT) were similar. However, the recurrence was 13.1% in the no staining group, compared with TA- or ICG-assisted group ($p = 0.011$) [51].

In 2017, Chang et al. published extensive review and meta-analysis including 11 retrospective studies and one randomized controlled trial involving 756 eyes. They found that the postoperative BCVA within 12 months was significantly better in the non-ILM peeling group ($p = 0.0460$). However, the double peeling group achieved significantly better postoperative BCVA after 18 months ($p = 0.0049$). Single peeling group exhibited a higher reduction in postoperative CRT ($p = 0.0020$) and a higher recurrence rate of ERM ($p = 0.0048$) than the double peeling group. However, the rate of improvement in BCVA and postoperative CRTs were similar in these two groups [52].

1.4.2.4 Postoperative VA Improvement in ERM

In 1982, Michels published a series of 74 eyes. Sixty-two eyes (84%) had VA improvement of two or more lines. The rest 12 eyes (16%) had unchanged VA. He raise predicting factors as (1) age of the patient, (2) preexisting damage to the macula before occurrence of the epiretinal membrane, (3) severity of macular distortion because of the membrane or secondary changes or both in the retina or pigment epithelium, (4) length of time the membrane had been present, and (5) ease or difficulty of removal of the membrane.

He had shown the group with duration longer than 12 months had inferior VA than those less than 6 months. He also showed that in group with previous RD, those with macula spared had better final VA. In total, however, only 5 (7%) of the 74 eye operated achieved VA of 20/20.

Twenty-one (28%) eyes reached final VA of 20/40 or better, and 37 (50%) eyes had final VA ranged from 20/50 to 20/100. Thus, he suggested surgery be considered in eyes with visual acuity of 20/100 or less [9].

For eyes with recurrence, Grewing and Mester reported 42 recurrences (12%) from 350 eyes vitrectomized for epiretinal membrane. They found VA improvement was still significant albeit the existence of recurrent epiretinal membrane. Eight (19%) of these 42 eyes had second vitrectomy, but their final VA is not different from the 32 eyes without second vitrectomy. Also, eyes with or without recurrence had similar VA improvement [53].

1.4.2.5 Recurrence Rate in ERM

Surgical removal of epiretinal membranes has infrequent recurrence. In 1981, Michels reported only 2 recurrences in 50 cases [48].

In 1996, Grewing and Mester reported 42 recurrences (12%) from 350 eyes vitrectomized for epiretinal membrane. Type of membrane (thick or thin) nor completeness of membrane removal did not affect recurrence rate [53].

In 2003, Park et al. reported a recurrence or persistent contraction to ILM in 21% of single peeling group. They found none of these in double peeling group [50].

In 2009, Shimada et al. reported 104 eyes that underwent single ERM peeling, and 17 eyes (16.3%) had recurrence. They also reported no recurrence in 142 eyes that underwent double ERM and ILM peeling [49].

In summary, the recurrence rate is significantly lowering in the double peeling group.

1.4.3 Vitreoretinal Surgery in MPH

Not all of the MPH eyes need vitreoretinal surgery unless they show signs of progressive loss of vision or increased visual symptoms such as metamorphopsia. Surgery of MPH typically requires ERM removal, and incidentally the internal limiting membrane (ILM), to improve the macular profile [34].

In 1999, Massin and colleagues reported the postoperative results for 50 eyes with pseudohole and a paired series of idiopathic ERMs without pseudohole operated on during the same period. All patients underwent standard three-port pars plana core vitrectomy and ERM peeling. For the patients with pseudohole, median preoperative visual acuity was 20/63 (range, 20/32–20/860), and median postoperative visual acuity was 20/40 (range, 20/20–20/860). Vision improved by 2 or more lines in 31 (62%) of 50 eyes. Forty eyes (80%) reached visual acuity of 20/50 or more. Pseudohole persisted in 22 eyes (44%) 3 months after surgery and in 15 eyes (30%) at 6 months. There was no difference in visual acuity, whether or not the pseudohole persisted [54].

In 2013, Gaudric et al. published a series of 33 patients, 14 eyes with straight foveal edges and 19 eyes with stretched edges, who underwent core vitrectomy and ERM removal. Trypan blue staining, followed by ILM peeling, was performed in 23 of the 33 patients. Short-acting gas tamponade (20% SF_6 air) was used only in four cases (two in each group) because of the intraoperative retinal tear. Mean macular thickness decreased equally in the two groups, and postoperative thickness was similar (363.8 μm vs. 345.3 μm; $p < 0.12$). The macular profile improved in all patients, with the disappearance or attenuation of the verticalization of the foveal edges. Of the 19 patients with stretched and cleaved edges, the cleavage completely disappeared in 14 patients, was attenuated in three patients, and remained unchanged in the two remaining patients. En face OCT images showed, in all patients, an alteration of the macular surface known as the dissociated optic nerve fiber layer, commonly seen after ILM peeling. The mean VA of the 33 eyes that underwent surgery improved from 0.44 logMAR (Snellen equivalent, 20/50) before surgery to 0.28 logMAR (Snellen equivalent, 20/40) after surgery ($p = 0.001$). There was no significant difference between the two groups in preoperative or postoperative VA ($p = 0.44$ and $p = 0.65$, respectively) and no difference in visual gain [34].

In 2015, Schumann et al. reviewed 39 eyes with MPH, and 59% of eyes ($n = 23$) had vitrectomy during follow-up. For the operated eyes, the preoperative BCVA was 0.40 logMAR (mean ± SD, 0.46 ± 0.26 logMAR). The postoperative BCVA was 0.10 logMAR (mean ± SD, 0.22 ± 0.21 logMAR). It was not superior using gas tamponade and prone positioning. They also published a mixed postoperative data comprised of 17 LMH eyes and 23 MPH eyes. They found a lower BCVA in the disrupted IS/OS and ELM group; and there was so significant difference in the intact IS/OS and ELM group and disrupted IS/OS-only group. In the nonoperated eyes (31 LMH and 16 MPH eyes), there is no BCVA difference in the subgroups. They did not reveal the independent result of MPH eyes in this analysis [35].

In 2015, Hirota et al. reported 31 eyes with a macular pseudohole underwent vitrectomy with internal limiting membrane removal. The BCVA improved significantly, and the length of the interdigitation zone (IZ) band defect decreased significantly after the surgery. Length of the IZ band defect is associated with preoperative and postoperative BCVA ($p < 0.001$ for all). The BCVA was not significantly correlated with the length of the ellipsoid zone, external limiting membrane band defect (ELM), and the central foveal thickness [55].

In 2016, Toyama and coworkers publish a series of 50 eyes with MPH, in which 36 eyes were evaluated by SD-OCT postoperatively. Lamellar cleavage subsided in 32 (88.9%) eyes [36].

To sum up, surgery is advised in patients whose visual acuity decreases more than two Snellen lines during the follow-up, initial visual acuity below 0.6, or disturbing metamorphopsia. With or without air/gas tamponade and prone positioning, the results are comparable. The anatomical improvement could be seen in the majority of patients, ranging from 70% to 90%, of operated eyes [36, 52]. Based on group analysis, VA would improve in both straight and smooth edges. Worse postoperative VA could be seen in eyes with disrupted IS/OS and interdigitation zone defect.

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