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Differentiating Vitreoretinal Interface Pathology with Spectral-domain Optical Coherence Tomography

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Optical coherence tomography (OCT) is an imaging modality that has revolutionized the way the vitreoretinal interface is visualized. Over the past 2 decades, OCT has highlighted the role of vitreomacular adhesions in the development of many vitreoretinal interface pathologies – including vitreomacular traction syndrome (VMTS), epiretinal membranes (ERMs), full-thickness macular holes (FTMHs), lamellar macular holes (LMHs), macular pseudoholes (MPHs), and microholes – that are classically described by their biomicroscopic appearance. OCT imaging studies now provide an anatomical differentiation for these similar but distinct conditions. This issue of *Ophthalmology Rounds* outlines variations of normal and pathological conditions seen at the vitreoretinal interface on spectral-domain (SD) OCT.

Posterior Vitreous Detachments (PVDs)

The evolution of PVDs in healthy eyes helps us to understand the pathogenesis of vitreoretinal interface pathology. Histopathological studies show that more than 60% of subjects over 70 years old have a PVD.[1] Despite its perceived age-related incidence, young patients can have OCT evidence of shallow partial PVD not detected with biomicroscopy; in their study of 209 eyes with biomicroscopy and OCT imaging, Uchino et al[2] detected OCT signs of partial perifoveal PVD in more than 50% of asymptomatic patients under 50 years of age. Based on their findings, they classified the posterior vitreoretinal interface into 5 stages (Table 1).

Longitudinal OCT studies have also assisted in the understanding of the progression of PVDs. Johnson[3] followed patients with partial PVDs using B-scan ultrasonography and time domain (TD) OCT imaging, and found that only 3 of 31 eyes progressed to a complete PVD over an average of 30 months. This suggests that PVD is more of an insidious process that previously thought.

Vitreoretinal adhesion patterns in partial PVDs have been studied with OCT imaging to assess their association with the development of vitreoretinal interface pathology. Gallemore et al[4] observed specific patterns of vitreoretinal adhesions associated with PVDs in eyes with vitreoretinal pathology on TD OCT such as ERM, FTMH, VMT, cystoid macular edema, and diabetic retinopathy. Persistent vitreoretinal adhesions were identified on OCT in 39 of 132 eyes, and also by biomicroscopy in only 11 of these 39 eyes (28%). The researchers noted 2 characteristic patterns of vitreoretinal adhesion: focal (25/39) and multifocal (14/39). Focal adhesions were found in all types of vitreoretinal pathology and occurred near the fovea (Figure 1). Multifocal adhesions were found most commonly in ERMs (71%), likely due to the stronger adhesion these membranes provide at the vitreoretinal interface. The authors concluded that the increased adhesion of the vitreous at the fovea suggests its involvement in the pathophysiology of several macular diseases, including macular holes, macular edema, and VMTS.

Kumagai et al[5] compared the vitreoretinal interface of asymptomatic fellow eyes in patients with unilateral macular holes to asymptomatic fellow eyes of patients with other retinal pathology using spectral domain OCT imaging. They found an increased incidence of foveal deformations associated with vitreoretinal adhesions in the asymptomatic eye of patients with unilateral macular holes and macular pseudoholes, and concluded that patients

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Table 1: Classification of the posterior vitreoretinal interface[2]

Stage	Description
0	No PVD
1	Incomplete perifoveal PVD in up to 3 quadrants
2	Incomplete perifoveal PVD in all 4 quadrants with residual attachment to the fovea and optic disc
3	Incomplete PVD over the posterior pole with residual attachment to the optic disc
4	Complete PVD identified biomicroscopically, but posterior hyaloid face not visible on OCT imaging

PVD = posterior vitreous detachment; OCT = optical coherence tomography

with macular holes have abnormally strong vitreofoveal adhesions.

In a retrospective case series of 43 eyes with various idiopathic vitreomacular diseases but no biomicroscopic evidence of complete PVD, Johnson[3] found that all patients had TD OCT-visualized partial PVDs around the perifoveal macula. It is now clear that visualizing the relationship between the vitreous and the retina is important in understanding the pathogenesis of vitreomacular pathology.

Vitreomacular Traction Syndrome (VMTS)

VMTS was described clinically in 1967 by Jaffe[6] as an incomplete PVD with persistent symptomatic traction on the macula and confirmed histologically in 1970 by Reese et al.[7] The important distinction between VMTS and vitreomacular adhesions is that patients with VMTS must be symptomatic, with reduced visual acuity and/or metamorphopsia. In asymptomatic patients, the presence of vitreomacular foveal or perifoveal adhesions are classified as a partial stage 1 or stage 2 PVD in which there is no functional impairment.

In VMTS, the vitreous characteristically remains adherent in a dumbbell-shaped region around the macular and optic nerve, creating persistent anteroposterior tractional forces that can result in visual symptoms and macular complications (Figure 2).[8] VMTS can result in retinal blood vessel avulsion, ERM formation, retinal holes, cystoid macular edema, tractional detachment of the macula, and retinoschisis.[9] VMTS is frequently associated with ERM, a process that is thought to induce thickened and strengthened adhesions of the vitreous cortex to the underlying retina (Figure 3).

Figure 1: Stage 2 Partial PVD. Persistent vitreofoveal adhesion with perifoveal posterior hyaloid detachment. Note the normal foveal contour and intraretinal anatomy.

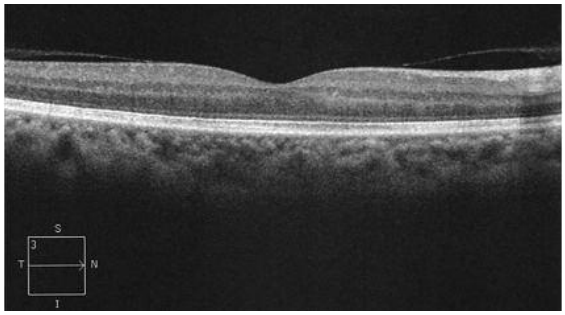
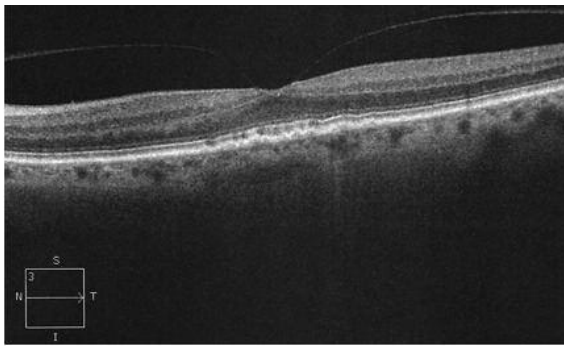


Figure 2: Persistent vitreofoveal adhesion with traction. Persistent attachment of the vitreous at the foveal centre with detached posterior hyaloid from the surrounding perifoveal retina. Note the dumbbell shape to the posterior hyaloid and the loss of normal foveal contour. Retinal pigment epithelium drusen is coincidentally seen in this image.



Epiretinal Membranes (ERMs)

ERMs are proliferative membranes at the vitreoretinal interface. Secondary associations include retinal detachment, retinal tears, macular holes, retinal vascular occlusion, cataract surgery, and laser photocoagulation. Most cases, however, are idiopathic.

Gass suggested a classification for ERM based on biomicroscopic appearance (Table 2).[10] ERM can also be evaluated by OCT imaging. Wilkins et al[11] described 2 patterns of ERM adherence on TD OCT in a study of 186 eyes. Focally attached ERMs, seen in 26% of eyes, could be distinguished from the highly reflective nerve fibre layer by areas of separation (Figure 4). Globally attached membranes occurred more commonly, in 67% of eyes, where the ERM was not visibly separate from the nerve fibre layer on OCT (Figure 5). In those cases, the ERM was detected in 1 of 3 ways: by the foveal contour, where

Figure 3: Vitreomacular traction syndrome. Persistent foveal adhesions with perifoveal vitreous detachment and anteroposterior traction. Note the distortion of the foveal anatomy and the highly reflective epiretinal membrane.

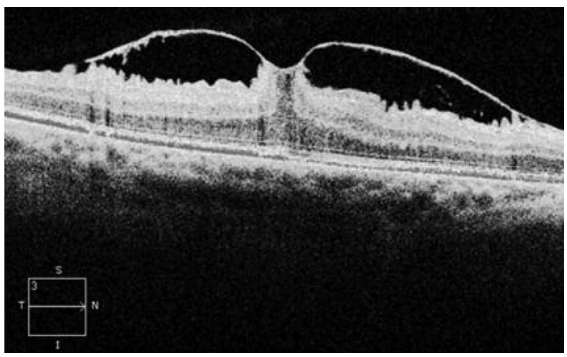


Table 2: Classification of epiretinal membranes[10]

Grade	Description
0	Translucent membrane without retinal distortion
1	Translucent membrane with irregular folds in the inner retina
2	Opaque membrane with vascular or retinal distortion in all layers

pseudoholes were present (32/125); by contrast in reflectivity between the membrane and the retina (65/125); or by the presence of a tuft (92/125). These globally adherent ERMs were more easily documented on biomicroscopy than on TD OCT. More recent literature using SD OCT suggests that ultrahigh resolution imaging is better at identifying ERMs than TD imaging, with 15% (8/52 eyes) of ERMs identified by SD OCT not appreciated on TD OCT imaging.[12]

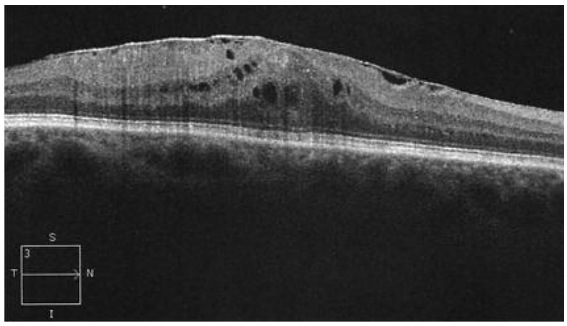
Despite restoration of the macular anatomy after ERM surgery, some patients do not experience good functional outcomes. Recent literature using SD OCT suggests that this may be related to microstructural abnormalities seen in the outer retina. In a prospective case series of 41 patients undergoing pars plana vitrectomy with ERM peeling, preoperative disruption of the inner segment/outer segment (IS/OS) photoreceptor line was associated with worse postoperative visual recovery. Similar studies have confirmed the importance of outer retinal microstructure in the visual recovery of patients undergoing membrane peeling for ERM (Figure 5B).[13]

Macular Holes

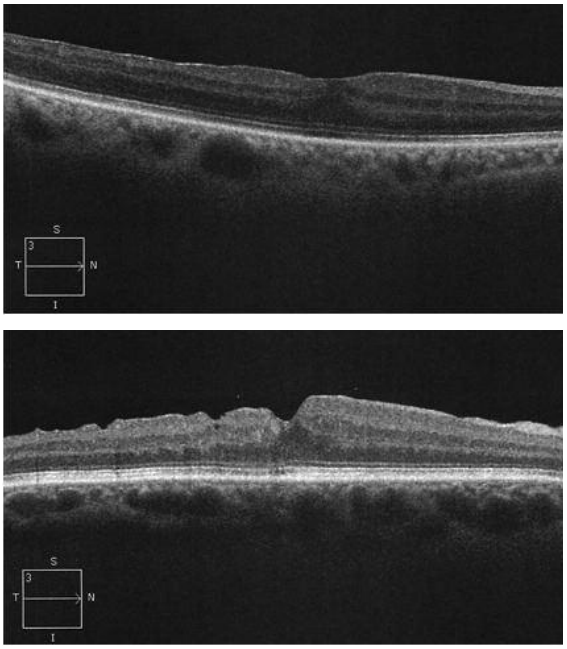
A macular hole is a full-thickness loss of retinal tissue in the central fovea. The majority of macular holes are idiopathic. More infrequently, macular holes occur secondary to other causes such as blunt trauma, traction (eg, epiretinal membrane or VMTS), or after rupture of the inner wall of a cyst in cystoid macular edema. In high myopes with staphylomas, macular holes can progress to rhegmatogenous retinal detachment.

The classification of macular holes was described by Johnson and Gass[15] in 1988 based on observations in 158 eyes with idiopathic macular holes. Gass also described 2 similar vitreoretinal abnormalities: lamellar macular holes and macular pseudoholes. In 2003, Atweel and Ip[16] proposed a modified classification of stage I macular holes based on OCT imaging. These 2 classification schemes are presented in Table 3.

Figure 4: Epiretinal membrane (ERM), focally attached. Areas of clear separation of ERM from underlying retina nerve fibre layer, and loss of foveal depression with cystoid macular edema. Note shadow artifacts obscuring outer retinal layers.



Figures 5A, B: ERM, globally attached. Hyperreflective membrane lining inner retina with irregular surface and loss of foveal contour. 5A shows mild ERM, while 5B illustrates more pronounced ERM with cystoid macular edema. Note disruption in the IS/OS junction in 5B.



Impending macular holes and pseudocysts

Early stages of macular hole formation have been characterized as macular cysts,[17] macular thinning,[18] impending macular holes,[19] and foveal pseudocysts.[20]

Stage 1A and 1B

Further to his observation of a yellow spot in the foveola of patients, Gass theorized that these individuals had a localized foveal detachment with preservation of the inner retinal layers, and described this as an impending macular hole, or stage 1A (Figure 6). Recent OCT imaging of these cases suggests that a foveal splitting, not detachment, occurs with a "pseudocyst" visible on OCT often prior to clinical findings of the yellow spot (Table 3).[16] Gass further hypothesized that progression of the yellow spot to a yellow ring (Stage 1B) occurred from centrifugal displacement of the outer retinal layer and a dehiscence at the umbo but with preservation of the innermost retinal structure from bridging vitreous cortex (Figure 7).[21]

The term "pseudocyst" was coined because the cystoid space seen on OCT, first imaged in 1995,[16] has no true cyst wall and occurs secondary to a tractional splitting of the retina.[22] A pseudocyst is a precursor to macular holes in which the posterior hyaloid is partially

Table 3: Classification of macular holes

Grade	Biomicroscopic description[15]	OCT description[20]
1A	Localized foveal detachment	Localized splitting of foveal retina creating a pseudocyst
1B	Centrifugal displacement of the outer retinal layer with preservation of the innermost retinal structure	Enlargement of the pseudocyst and extension into the outer retina with an intact inner retinal roof
2	Small full-thickness macular defect <400 µm	Full-thickness macular defect <400 µm 2A: with continued attachment to the flap of the retina 2B: with operculation
3	Full-thickness macular defect >400 µm with perifoveal hyaloid attached	Full-thickness macular defect >400 µm with locally detached perifoveal hyaloid face, visualized anterior to the hole
4	Full-thickness macular defect >400 µm with complete PVD	Full-thickness macular defect >400 µm with complete PVD, not visible on OCT imaging

detached over the posterior pole but still adherent to the fovea with splitting of the underlying retina. Haouchine et al[22] reported a prospective case series of 22 eyes with pseudocysts diagnosed on OCT imaging. In all cases, a partially detached posterior hyaloid was seen over the posterior pole remaining adherent to the foveal centre. The authors noted a characteristic biconvex shape to the posterior hyaloid, suggesting that anteroposterior tractional forces are being transmitted to the underlying retina, creating the pseudocyst. Foveal pseudocysts may progress to form FTMHs or LMHs. The unroofing of a stage 1A pseudocyst results in an

Figure 6: Stage 1A pseudocyst, impending macular hole. Pseudocyst in the inner retina with intact roof and outer retinal layers. Persistent vitreofoveal adhesion with detached perifoveal hyaloid membrane is visible.

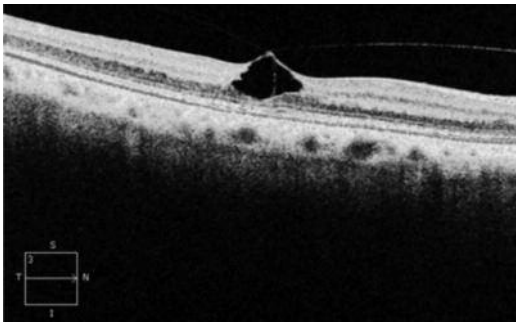
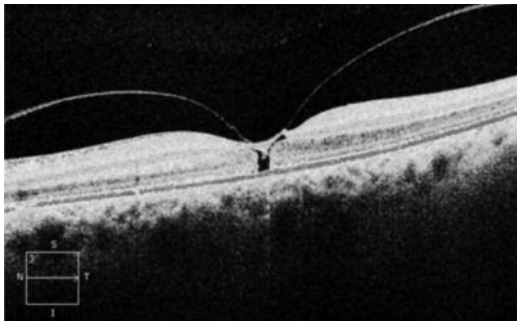


Figure 7: Stage 1B pseudocyst, impending macular hole: Full-thickness pseudocyst with roof of cyst in place and vitreofoveal adhesion of the posterior hyaloid with perifoveal vitreous detachment. Note the biconvex shape to the posterior hyaloid face.



LMH. The unroofing of a stage 1B pseudocyst results in an FTMH.

Stage 2 FTMHs

Unroofing of a pseudocyst, or impending macular hole, results in a stage 2 FTMH. Occasionally, a pseudo-operculum is seen overlying the small defect (<400 µm). OCT imaging reveals that the roof of the pseudocyst can remain partially attached to the perifoveal retina with traction exerted by persistent vitreous attachments (Figure 8).

Stage 3 and 4 FTMHs

Gass hypothesized that vitreofoveal traction during PVD causes enlargement of the full-thickness defect to >400 µm and the development of a stage 3 FTMH.[19] OCT imaging shows thickened perifoveal retina with intraretinal cystoid spaces (Figure 9). Stage 3 FTMHs may have a cuff of perifoveal subretinal fluid that usually remains localized. Ataweel and Ip[16] suggest that the perifoveal hyaloid face is often visualized anterior to the hole on OCT imaging, in contrast to the Gass classification where the posterior hyaloid is attached in the perifoveal region.

Figure 8: Stage 2A full-thickness macular hole (FTMH). Unroofed stage 1B pseudocyst reveals a full-thickness defect with the inner flap attached and held in traction by persistent vitreofoveal adhesions. Note the perifoveal intraretinal cysts with lateral schisis and ERM.

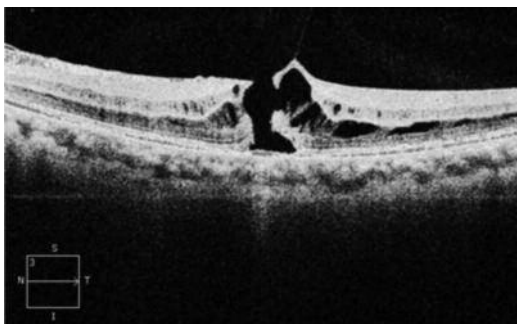
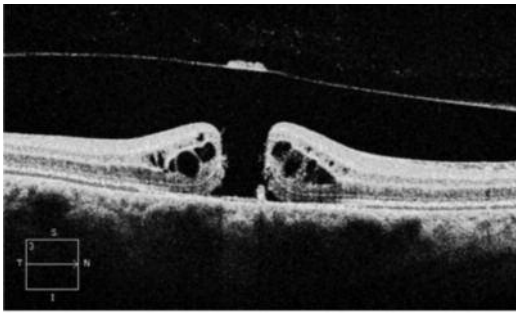


Figure 9: Stage 3 FTMH with operculum. FTMH, perifoveal retinal thickening with intraretinal cystoid spaces, and operculum in a visibly detached posterior hyaloid.



The FTMH evolves to stage 4 with complete detachment of the posterior hyaloid, confirmed with biomicroscopy or ultrasonography. The vitreous face is not evident on OCT imaging in stage 4 FTMH.

Precursors to macular holes: Stage 0

In 2004, a study by Chan et al[23] outlined patterns of vitreofoveal insertion of the posterior hyaloid in the fellow eyes of 94 patients with idiopathic macular holes using TD OCT imaging, with a mean follow-up of 41 months. They found a significant association between oblique insertion of the posterior hyaloid into a normal appearing retina and the development of a macular hole. Patients with this vitreofoveal abnormality had a 6-fold increased risk of developing a macular hole (5/12; 41.7%) compared with those without the abnormal hyaloid insertion (3/67; 4.5%). They suggest that these configurations be considered stage 0 macular holes.

Partial-thickness Macular Holes: Macular Lamellar Holes and Pseudoholes

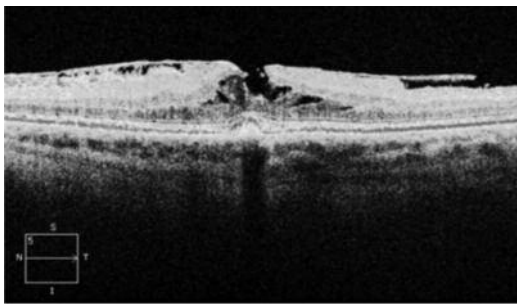
Macular lamellar holes and pseudoholes share the common clinical feature of a round and reddish appearance in the macula. Lamellar holes and pseudoholes are difficult to identify and differentiate biomicroscopically. Reports of only 28%-37% of lamellar holes diagnosed on OCT are also detected clinically.[24]

Gass and Norton[25] first described lamellar holes in 1969 as an abortive process of a FTMH where outer retinal tissue is preserved. Gass[26] presented a possible pathogenesis for lamellar holes in a 1975 clinicopathological case report of a patient who developed a lamellar macular hole after chronic aphakic cystoid macular edema. Since then, the process has been described as one that occurs as a complication of macular edema where a cyst in the retina is unroofed of the inner retinal tissue.

Witkin et al[27] outlined OCT criteria for diagnosing lamellar holes after retrospectively looking at 1205 OCTs of the same number of eyes, of which 19 had lamellar holes. They suggest 4 basic OCT criteria to diagnose lamellar holes (Figure 10):

- Irregular foveal contour
- Break in the inner fovea
- Dehiscence of the inner retina from the outer retina at the fovea
- Absence of a full-thickness defect

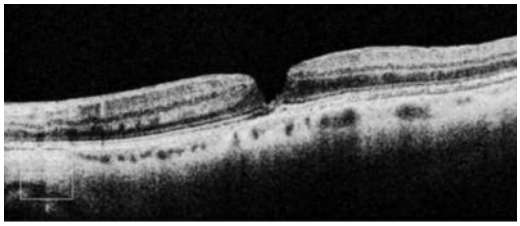
Figure 10: Partial thickness macular hole: lamellar hole. Foveal-edge splitting with mild retinoschisis and partial-thickness central defect. Epiretinal membrane, classically a feature of pseudoholes, is now found on spectral-domain OCT in most lamellar holes.



MPHs, described by Allen and Gass in 1976 in 4 patients,[28] were labeled "mimickers" of macular holes with no true retinal defect. The unique feature in these eyes was their association with contraction of a perifoveal ERM (Figure 11). However, OCT imaging reveals that ERMs are also commonly seen in association with LMH. Haouchine[24] found that 62% of eyes with LMH had an associated ERM seen on TD OCT. Witkin et al[27] found that 80% of eyes with LMH had an associated ERM seen on SD OCT. Michalewska et al[29] retrospectively studied 10 239 consecutive SD OCTs to select for non-FTMHs, including MPHs and LMHs, and found 100% of 125 eyes had coexisting ERM.

Results from OCT studies now suggest an overlap in the definition and pathogenesis of LMH and MPH.[24,29] Michalewski et al reported 2 cases of patients with MPHs and associated ERMs followed with SD OCT who progressed to LMHs. More recently, the same authors suggest a reclassification of non-FTMHs into 4 subtypes: pseudoholes,

Figure 11: Partial-thickness macular defect: pseudohole. ERM with steepened foveal contour suggestive of a pseudohole. Reduced foveolar retinal thickness is usually a feature of a lamellar hole.



paralamellar macular holes, pseudoholes with lamellar defects, and LMHs.[30] They hypothesize that these are all different appearances of a progressive disease.

Summary

OCT is an essential tool in the evaluation of the vitreoretinal interface that has modified the way we define the normal process of PVD and many vitreoretinal pathologies. These conditions include VMTS, ERM, FTMH, LMH, and MPH. OCT imaging studies will continue to clarify not only the appropriate classification for these conditions but also their pathogenesis and management. SD OCT imaging will likely provide prognostic information on visual recovery for patients with vitreoretinal diseases and microstructural outer retinal abnormalities.

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