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A Case of Macular Pseudohole Secondary to Epiretinal Membrane

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ABSTRACT

Senile macular holes (MH) in their various incarnations devastate vision, tending to affect elderly women more than men. Early stage macular holes and macular pseudoholes (MPH) minimally impact vision. The two conditions may share a common association with epiretinal membranes (ERM). However, management of the two separate conditions is very different. Selection and timing of management options begins with an accurate differential diagnosis. Differential diagnosis, until recent times, relied on clinical presentation and correlation with fluorescein angiographic evidence. The value of fluorescein angiography in early stage macular holes is limited. Optical coherence tomography (OCT) and its iterations offer a comfortable, non-invasive way to differentiate the two conditions.

CASE REPORT

A 43-year-old African-American female presented as a new patient to our Cornea and Contact Lens Service at The Eye Center of Southern College of Optometry. She wears soft contact lenses. She was ready to renew her correction. The patient experienced an episode of optic neuritis in the right eye in 2006. MRI testing failed to locate plaques consistent with a diagnosis of MS. Her mother has multiple sclerosis. The patient reported longstanding, occasional floaters.

Maximum corrected visual acuities were 6/6 (20/20) OD and 6/7.5 (20/25+2) OS. Pupil responses were equal and without an afferent defect. Color vision testing with pseudoisochromatic plates, Amsler grid testing,

confrontations, and extraocular motilities were normal. Watzke-Allen test was normal in each eye. Anterior segment evaluation revealed clear media and no signs of past or present inflammation.

Posterior pole evaluation was as unremarkable in the right eye. The left eye findings were as seen in Figures 1 and 2. The discs showed no pallor, intact rims, with symmetric cupping in the range of 0.4/0.3 in each eye. The OS vitreous was free of cells or pigment. A well defined epiretinal membrane with an epicenter at 6:00 to the fovea was present. It extended from an area of perivascular sheathing along the inferior temporal arcade, superiorly to circumnavigate the fovea. There were clear tangential tractional forces evident. There were no white or yellowish deposits in the base of the "crater," no undercutting of the rim and no cuff of edema. Red-free filter helped to visualize the extent of the ERM. There was no operculum.

An OCT was performed the same day and the results are presented in Figure 3. The right eye was normal. The scan of the left eye reveals the area corresponding to the epicenter of the ERM thickened the neurosensory retina by almost 50%. The normal architecture was distorted and contracted. The retina was not detached. Cross sectional scans found no operculum, cystic spaces or lamellar holes. The RPE was intact. The overlying vitreal cortex appeared to be adherent in its normal attachments.

A diagnosis of MPH of the left eye was made on the basis of these findings. It was likely that the ERM in the left eye, as well as the perivascular sheathing, were an association with the previous history of optic neuritis. The patient was at risk for MS based on the mother's history and her own.

The fluorescein angiogram appeared normal. Surgical intervention was not indicated due to the absence of tractional complications and the known stability of MPHs over time. The OCT, the angiogram, visual acuities, Watzke-Allen, and Amsler grid findings supported this conclusion.

DISCUSSION

Etiology and Pathogenesis

Aaberg's review of the subject of macular holes instructs us on the proposed etiologies of partial to full thickness

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Fig. 1 Case 1 OS Posterior pole view epiretinal membrane with MPH.



Fig. 2 Case 1 OS close up of MPH and epiretinal membrane. Arrow denotes epicenter of ERM. Note the perivascular sheathing of the vessels.

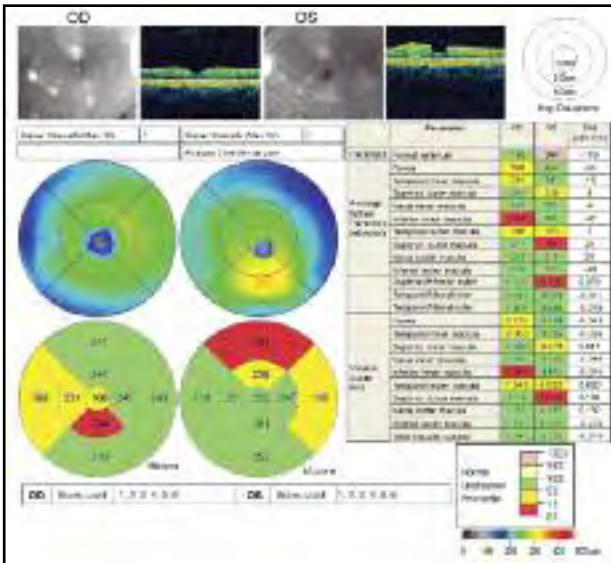


Fig. 3 Case 1 Stratus Optical Coherence Tomograph of both eyes. Note the distorted architecture of the OS fovea, however all retinal layers are intact without operculum.

Primary Vascular Diseases	Secondary Inflammatory Conditions
Hypertension	TB periphlebitis
CRAO	Syphilis
BRAO	Harada's disease
CRVO	Behcet's syndrome
BRVO	Coat's disease
	Non-specific chorioretinitis
	Pseudophakic CME

holes. Understanding the evidence presented gives additional insight into the development of pseudomacular holes. His review divides pathogenesis of MH formation into those caused by 1) trauma theory 2) cystoid degeneration 3) vitreous theory.¹

Trauma induced holes originate from the primary mechanical tearing or secondary delayed cystoid changes. These changes may occur proximal to the time of the trauma or even months later.¹

Cystoid macular degeneration originates from primary vascular conditions and secondary inflammatory conditions (Table I).¹ Arguments emphasize the roles of

ischemia and inflammatory mechanisms. Treatments based on these etiological models develop as discussions continue regarding their relative merits. We see topical non-steroidal anti-inflammatory agents proving their worth in conditions such as pseudophakic cystoid macular edema.² The Standard Care vs. Corticosteroid for Retinal Vein Occlusion (SCORE) Study is currently underway as a multicenter study funded by the National Eye Institute. It attempts to evaluate the efficacy of intravitreal injections of triamcinolone for cystoid macular edema. Other NEI studies compare the treatment efficacy of macular edema with an anti-VEGF agent against triamcinolone in combination with photocoagulation for diabetic macular edema or photocoagulation alone.³⁻⁶

Vitreomacular traction caused by the mechanical traction of the vitreous body itself at its points of attachment to the macula or a tangential traction caused by cellular proliferation in the subhyaloid space has been shown to contribute to the development of senile macular holes, lamellar cysts and pseudoholes.^{1, 7-10}

Table II Review of classification of macular hole formation after Gass^{11,12}

Stage	Biomicroscopic Findings	Anatomic Interpretation (1988)	Anatomic Interpretation (1995)
1-A (impending hole)	Central yellow spot, loss of foveolar depression, no PVS	Serous foveolar detachment	Same
1-B (impending or occult hole)	Yellow ring with bridging interface, loss of foveolar depression, no PVS	Serous foveolar detachment with lateral displacement of xanthophyll	Same for small ring. For larger ring cannot detect transition from impending to occult hole.
2	Eccentric defect inside edge of yellow ring	Early hole, eccentric	Hole in contracted prefoveolar vitreous bridging round retinal hole, no loss of foveolar retina
	Central round defect with rim of elevated retina <ul style="list-style-type: none"> • With prefoveolar opacity • Without prefoveolar opacity 	Hole with operculum Hole, no PVD from disc and macula	Hole with pseudo-operculum Same
3	Central round $\geq 400 \mu\text{m}$ diameter defect, no Weiss Ring, rim of elevated retina <ul style="list-style-type: none"> • With prefoveolar opacity • Without prefoveolar opacity 	With operculum Without operculum	Hole with pseudo-operculum, no PVD Same
4	Central round defect, rim of elevated retina, Weiss ring <ul style="list-style-type: none"> • With prefoveolar opacity • Without prefoveolar opacity 	Hole and PVD of disc and macula Hole and PVD of disc and macula	Hole with pseudo-operculum and PVD of disc and macula Same

Gass first expounded on the vitreoretinal changes associated with early stage idiopathic senile MH formation and pathogenesis in 1988. The classification systems developed by Gass became the accepted standard.^{10,11} His work gave impetus to the use of membrane peels, partial membrane peels and posterior segmentation of the prefoveal vitreous cortex, as well as calling for collaboration on an efficacy study.¹⁰ The classification schema was updated by Gass in 1995 (Table II).¹¹ The advent of OCT opens the door for a further revision of the classification system. Optical coherence tomography provides the potential to correlate the biomicroscopic appearances with 10 μm accuracy and further elucidate on the natural history of the histological changes in MH formation.^{12, 13}

Notwithstanding the considerable knowledge gained about the natural history of macular holes, it remained until 1998 to see the first published retrospective study of the natural history of pseudomacular holes.¹⁴ Forty-nine eyes with epiretinal membranes and macular pseudoholes were evaluated. Whereas macular holes present with a median Snellen visual acuity of 6/60 (20/200),¹¹ pseudomacular holes were found to have a median Snellen visual acuity that was considerably better at 6/9 (20/30).¹⁴ Macular holes seldom progress to Snellen acuities worse than 6/120 (20/400).¹¹ Pseudoholes demonstrated stability in visual acuity over more than 12 months of

review, with 83% of eyes having final acuity equal to entrance acuity. Interestingly, 74% of the eyes studied experienced a change in macular appearance.¹⁴

Vitreoretinal interactions play a major role in understanding the development of macular holes. Understanding pseudohole formation requires an equal appreciation for the role of epiretinal membrane formation in their creation. Histopathological studies of epiretinal membranes provide insight into their cellular morphology but not their pathogenesis.¹⁵ Participants in ERM formation include macrophage, Müller cells, glial cells, astrocytes, fibrocytes, myofibroblasts, descendents of RPE cells, and metaplastic collagen production.^{7,8,15,16}

One plausible explanation for their development describes the membrane forming prior to posterior vitreous separation. The attachment of the posterior vitreous face around the foveola allows the membrane to form around this area creating the pseudohole as if a firewall was present. Other explanations include tractional forces from the vitreous causing a “dehiscence” of the central crater or that the central area may be less visible due to a “hypoplastic” nature.¹⁴

Diagnostic and Clinical Features

Since approximately 48% of patients with impending macular holes undergoing vitrectomy may regain visual acuity of 6/12 (20/40) or better, application of the

Table III Key features in differentiating pseudomacular holes (PMH) from macular holes (MH). ^{1,13}		
Diagnostic Features	PMH	MH*
Epiretinal membrane	+	+
Median Snellen acuity	6/9 (20/30)	6/60 (20/200)
Cuff of detachment	-	+
Fine yellow deposits in base	-	+
Amsler grid	±	±
Watzke-Allen	28%	100%
Fluorescein angiography	Early fluorescence	Increased choroidal fluorescence
Size	397 µm	Solar eclipse holes - smallest traumatic - largest senile holes - 750 µm
OCT	Intact neurosensory retina with surrounding preretinal thickening and traction	Separation of neurosensory retina layers into cystic spaces, loss down to RPE, overlying operculum

*Full thickness holes

classification schema devised by Gass and accurate differential diagnosis is critical.¹¹ In fact, one study of 14 eyes revealed accurate diagnosis occurred in only 43% of eyes with epiretinal membranes and pseudohole.¹⁷

Clinically, both conditions may present with accompanying epiretinal membrane.^{1,14,17} Differentiation on the basis of visual acuity as previously mentioned is most helpful. There is overlap in cases of lamellar cysts and impending hole formation, confounding matters.^{1,11} Key features of the differential diagnosis are displayed in Table III.

Holes vary in appearance depending on the stage of development presented. They may appear as a change in foveolar light reflex with tenting of the vitreous circumferentially, small tears in the internal limiting membrane, convexity of the inner retinal layers, to loss of the inner retinal layers down to the photoreceptor outer segments, and finally down to the retinal pigmented epithelium. The margins of full thickness holes go from sloping in early stages to undercutting in later stages with surround cuffs of edema from subretinal fluid accumulation.^{1,10,11} White to yellow deposits may be observed along the surface of the exposed RPE and may vary in amount and location over time.^{1,10,11} Amsler grid findings vary as do Watzke-Allen results and the visibility of a 50 µm spot aiming beam from a laser. Patient reports vary from apparent breaks in the line or absence of visibility of the laser spot in full thickness holes to pinching of the line and spot visible in small cysts, depending on the stage.^{1,11-14,18-20} Both are sensitive tests for macular defects but not specific enough to render

a differential diagnosis in and of themselves, with the exception of full thickness holes. Interestingly, both Amsler grid results and aiming beam visibility improved in 71% to 86% of postoperative macular hole treatments. This is consistent with improvement in acuities in many cases.¹⁹ Fluorescein angiographic appearances reveal little changes in early cystic stage or with lamellar holes, but show increased hyperfluorescence in full thickness holes as the choroid becomes more visible due to a breakdown in the RPE.^{1,10,11,14,18-22}

Key features in recognizing pseudoholes include typically better visual acuity with the exceptions of comparisons against impending macular holes or cysts, lack of changes in the foveolar reflex as seen in early stage holes, absence of operculums of neurosensory retina, absence of deposits as seen in full thickness holes, and no cuff of edema.¹⁷ Angiographic evidence in a study by Fish and associates found generally normal to few instances of hyperfluorescent window defects in the area of the pseudohole.¹⁷ The study examined 14 eyes all with epiretinal membranes. They found 27% had abnormal tortuosity or straightening of the perifoveal vessels, 27% had late leakage in the macula, and 27% had foveal window defects. These are findings similar to those seen in stage 1 and stage 2 macular holes.¹⁷ Klein and associates found early hyperfluorescence coinciding with choroidal filling that appeared to be a transmission defect. They postulate that it may be due to the centripetal tractional forces of the coexisting ERM, and that this is not unlike the transmission defects seen in full thickness holes.²¹

Is there a more specific diagnostic test that can overcome the 43% diagnostic accuracy rate in diagnosing pseudoholes?¹⁷ Surgical interventions in early stage macular holes offer great potential benefits to the patient but not without considerable risks. OCT testing offers a tremendous advantage in response to this question.^{12,13} Other technologies such as scanning laser ophthalmoscopic perimetry are further pushing the limits forward.²¹

Wilkins and associates examined 186 eyes with ERM and found that OCT provided quantitative data on the structural assessment and adherence of the membranes preoperatively and postoperatively. They found that it may be "useful" in characterizing the prognosis for these patients. They also found OCT distinguished MPH from the more challenging lamellar cysts, lamellar holes and the less challenging full thickness holes.²²

Further, since visual acuity correlates better with retinal thickness than fluorescein leakage, important prognostic indicators for postoperative recovery are given. Clearly OCT provides an advantage over fluorescein angiography in the equivocal cases.²⁴⁻²⁶ The decision to pursue surgery on a given patient rests with a complex analysis of data and its presentation to the patient. Optical coherence tomography provides a major leap forward in aiding in that decision making.

MANAGEMENT

Treatment of MH varies depending on surgeon preference, classification stage and the idiosyncrasies of a particular case. Options used have included trans pars plana vitrectomy with decision of cortical and ERM elements, endolaser, transforming growth factor-B₂, autologous serum, and cyanoacrylate adhesives.^{27,28}

All surgeries create additional risks. These risks appear higher for MH patients than for ERM peels alone. Vitrectomy and membrane peeling for MH in one study generated posterior complications in 23% of 98 patients. In rank order of incidence they included peripheral retinal breaks (3%), hole enlargement (2%), RPE loss under the hole (1%), phototoxicity (1%), and endophthalmitis (1%).²⁷ This mirrors other authors' findings of improved quality of life despite cataracts and hole reopening.²⁸⁻³⁰

Prevention of reopening of the hole when an ERM improved from 85% to 94% with concomitant removal of the internal limiting membrane.³¹ Optical coherence tomography improves the understanding of the histopathology of macular holes, particularly in early stages, and its treatment.¹³ High resolution imaging offers an even greater capacity to understand pathogenesis, timing of surgical intervention, monitoring of outcomes, and assessment of any damage sustained.²⁹

A retrospective study of 50 trans pars plana vitrectomy with membrane peel for MPH found that 62% of the eyes treated experienced a gain of two or more lines of visual acuity. There was not a statistically significant

difference ($p = 0.34$) in the eyes treated with ERM + MPH and those eyes treated with only an ERM alone. Eighty percent of the ERM + MPH and 72% of the ERM group achieved 6/15 (20/50) or better.³⁴

CONCLUSION

MPH and MH share many common considerations, such as accompanying ERM presence. Differentiating MPH from early stage lamellar cysts and holes is confounding. The literature review demonstrates that even experienced retinal specialists frequently confuse the two. The advent of OCT and other scanning laser ophthalmoscopes are revolutionizing our approach to making a differential diagnosis. Complications from surgical interventions are not uncommon and may pose a greater threat than the MPH itself since visual acuity remains stable over the long term in both MPH and late stage MH.

This case provides an example of where this type of decision making has been facilitated by the use of OCT. As is true with many of these types of technologies, the best is yet to come in the evolution in resolution. □

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