Published in final edited form as:

Ophthalmol Retina. 2019 August ; 3(8): 694–702. doi:10.1016/j.oret.2019.03.022.

Characterization of Epiretinal Proliferation in Full-Thickness Macular Holes and Effects on Surgical Outcomes

Esther Lee Kim, M.D.¹, Adam J. Weiner, M.D.², Cindy Ung, M.D.¹, Miin Roh, M.D., Ph.D.^{1,3}, Jay Wang, M.D.¹, Ivan J. Lee, B.S.², Natalie T. Huang, M.D.⁴, Maxwell Stem, M.D.², Mohammad Dahrouj, M.D., Ph.D.¹, Dean Elliott, M.D.¹, Demetrios G. Vavvas, M.D., Ph.D.¹, Lucy H.Y. Young, M.D., Ph.D.¹, George A. Williams, M.D.², Bruce R. Garretson, M.D.², Ivana K. Kim, M.D.¹, Tarek S. Hassan, M.D.², Shizuo Mukai, M.D.¹, Alan J. Ruby, M.D.², Lisa J. Faia, M.D.², Antonio Capone Jr., M.D.², Jason Comander, M.D., Ph.D.¹, Leo A. Kim, M.D., Ph.D.¹, David M. Wu, M.D., Ph.D.¹, Kimberly A. Drenser, M.D., Ph.D.², Maria A. Woodward, M.D., M.S.⁵, Jeremy D. Wolfe, M.D.², Yoshihiro Yonekawa, M.D.^{1,6}

¹Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA

²Associated Retinal Consultants, Oakland University William Beaumont School of Medicine, Royal Oak, MI

³Beetham Eye Institute, Joslin Diabetes Center, Harvard Medical School, Boston, MA

⁴University of Minnesota Department of Ophthalmology and Visual Neurosciences, Minneapolis, MN

⁵Kellogg Eye Center, University of Michigan School of Medicine, Ann Arbor, MI

⁶Boston Children's Hospital, Harvard Medical School, Boston, MA

Abstract

Purpose: Epiretinal proliferation is a distinct clinical entity from epiretinal membrane that is classically associated with lamellar macular holes, but its prevalence and association with full-thickness macular holes (FTMH) have not been well described. We characterize MHEP macular hole associated epiretinal proliferation (MHEP) and its effects on long-term surgical outcomes.

Design: Multi-center, interventional, retrospective case control study.

Subjects: Consecutive eyes that underwent surgery for FTMH with a minimum of 12-months follow-up.

Corresponding author: Yoshihiro Yonekawa, M.D., Massachusetts Eye and Ear Infirmary, Harvard Medical School, 243 Charles St, Boston, MA 02114, Telephone: (617) 573-7900, Fax: (617) 573-3011, yoshihiro_yonekawa@meei.harvard.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Meeting presentations: Retina Society Annual Meeting, Boston, MA, Oct 7, 2017.

Relevant Disclosures: Consultants for Alcon (TSH, YY)

Methods: All eyes underwent pars plana vitrectomy, removal of any epiretinal membranes, and gas tamponade, with or without internal limiting membrane peeling. Spectral domain optical coherence tomography imaging was obtained pre- and post-operatively.

Main Outcome Measures: Improvement in visual acuity and single surgery hole closure rates in eyes with, versus without, MHEP at 12 months.

Results: 725 charts were analyzed, and 113 patients met inclusion criteria. Of 113 eyes with FTMH, 30 (26.5%) had MHEP. Patients with FTMH and MHEP were older ($P < 0.002$), more often male ($P = 0.001$), and with more advanced macular hole stages than those without MHEP ($P = 0.010$). A full posterior vitreous detachment was more common in eyes with MHEP ($P < 0.004$). FTMH with MHEP had significantly less improvement in visual acuity 12-months postoperatively ($P = 0.019$) with higher rates of ellipsoid and external limiting membrane defects ($P < 0.05$) and with a higher rate of failure to close with one surgery compared to FTMH without MHEP (26.7% versus 4.8% [$P = 0.002$]). Peeling the internal limiting membrane was associated with improved rates of hole closure in FTMH with MHEP ($P < 0.001$). Multivariable testing confirmed that the presence of MHEP was an independent risk factor for less visual improvement ($P = 0.031$), single-surgery non-closure ($P = 0.009$), and that ILM peeling improved single-surgery closure rates ($P = 0.026$).

Conclusions: We found that FTMH with MHEP has poorer anatomic and visual outcomes after vitrectomy compared to FTMH without MHEP. ILM peeling was associated with improved closure rates and should be considered when MHEP is detected preoperatively.

Précis:

Macular hole associated epiretinal proliferation (MHEP) is associated with older age, more advanced hole stages, and poorer visual and anatomic surgical outcomes. Internal limiting membrane peeling improved MHEP-associated full-thickness macular hole closure rates.

INTRODUCTION

Success rates for macular hole surgery have steadily improved since Kelly and Wendel first described vitrectomy and posterior hyaloid peeling as a method of surgical treatment.¹ Current standard of care involves vitrectomy, removal of any epiretinal membranes, and gas tamponade, with or without internal limiting membrane peeling. The majority of macular holes can now be closed, but hole-closure rates may still vary, and visual outcomes are not uniform.

Epiretinal proliferation, which is distinct from traditional epiretinal membranes (ERM), has been recently described to accompany lamellar macular holes (LMH).^{1–20} It was first described by Witkin *et al* in 2006 as a thick membrane seen on ultrahigh-resolution optical coherence tomography (OCT).² In contrast to a typical ERM, this “moderately-reflective material filled the space between the inner border of the ERM and the retinal nerve fiber layer [RNFL].” Epiretinal proliferation was seen in association with LMH, full thickness macular hole (FTMH), and ERM. This finding was later re-defined by Pang, Spaide, and Freund in 2014 in conjunction with LMH. The authors termed this finding “lamellar hole-associated epiretinal proliferation” or “LHEP”.³

Epiretinal proliferation versus ERM

Epiretinal proliferation is seen on OCT as a homogenous material of medium reflectivity and varying thickness (Figure 1). On the other hand, ERM is seen as a highly reflective membrane and is uniformly thin (Figure 1). Epiretinal proliferation drapes over the epiretinal surface, tightly following the underlying retinal contour. As a result, it can occur on either, or both, sides of a macular hole. In contrast, there is space between an ERM and the underlying RNFL in many instances. Epiretinal proliferation does not have strong contractile properties, unlike ERMs, which can cause traction and underlying striae of the inner retinal surface as well as tortuosity of the surrounding vasculature.²¹ Intra-operatively, we have found that when peeling the epiretinal tissue, this substance is visible as a sticky, yellowish substance that is more integrated with the intrinsic retinal surface. In 2013, Shiraga *et al* described this in conjunction with LMH as a yellowish-appearing “ERM-containing macular pigment”.⁴ Son *et al* similarly described it as a “yellowish epiretinal tissue” that, after peeling the ILM, persisted as a “floating crown-like yellowish tissue with its base attached to the edge of the [hole] margin,” which they termed the “perifoveal crown phenomenon”.⁵

Recently, epiretinal proliferation has been studied more extensively in association with LMH, but little is known about epiretinal proliferation in association with FTMH (Figure 2).^{6,14} This is necessary to understand, because while intervention for LMH is still controversial, FTMH is undeniably a surgical condition and one of the most common conditions that vitreoretinal surgeons now treat. Therefore, understanding the impact of macular hole associated epiretinal proliferation (MHEP) on FTMH management potentially has large clinical implications. Here we present a multicenter study to determine the clinical relevance and implications of MHEP on surgical outcomes in FTMH.

Materials and Methods

This was a multi-center, interventional, retrospective case control study of consecutive eyes that underwent vitrectomy and membrane peeling for FTMH between January 2013 and January 2016 at one of two institutions: Massachusetts Eye and Ear (MEE), Harvard Medical School in Boston, MA and the Associated Retinal Consultants (ARC), William Beaumont School of Medicine in Royal Oak, MI, for patients who were seen, treated, and followed, only at the main campuses (Boston and Royal Oak). The Institutional Review Boards at MEE and ARC approved the study protocol. The study was compliant with the Health Insurance Portability and Accountability Act of 1996 and was adherent to the tenets of the Declaration of Helsinki.

A list of all surgeries with Current Procedural Technology (CPT) codes of 67041 for vitrectomy with removal of preretinal cellular membrane or 67042 for vitrectomy with removal of retinal internal limiting membrane was generated to screen cases for inclusion into the study. This list was further narrowed down to those surgeries associated with International Classification of Diseases (ICD)-9 billing codes 362.54 for FTMH and/or 362.56 for ERM. Each of these potential surgeries was then individually screened to confirm that they were strictly FTMH or ERM cases that had undergone vitrectomy with membrane peeling without any additional surgical interventions for other pathology (e.g. concomitant

retinal detachment repair). All charts and pre-operative imaging were reviewed by vitreoretinal surgery fellowship-trained physicians (E.K., M.S.) for confirmation of the diagnosis.

Baseline pre-operative variables assessed included the following: age at surgery, gender, laterality of affected eye, lens status, and other ocular co-morbidities, namely the presence or absence of posterior vitreous detachment (PVD), history of retinal tear(s), high myopia ($> -6D$), history of retinal trauma, history of retinal detachment (macula-involving or sparing), age-related macular degeneration (non-neovascular or neovascular), diabetic macular edema, diabetic retinopathy (non-proliferative or proliferative), retinal vein occlusion, anterior uveitis, posterior uveitis, glaucoma, and any prior retinal surgery. Patients were excluded if any significant ocular comorbidities were present, including any prior retinal detachments, intermediate or advanced macular degeneration, diabetic macular edema, diabetic retinopathy, macula-involving retinal vein occlusions as assessed on fluorescein angiography, uveitis, glaucoma, or any prior retinal surgeries.

All patients underwent a pars plana vitrectomy, PVD induction if none was pre-existing, ERM peeling if an ERM was present pre-operatively using forceps, and in the cases of FTMH, air-gas exchange with a tamponade agent. The decision to perform additional ILM peeling was determined by the individual surgeon. Data was collected regarding specifics of the surgery, including vitrectomy gauge, use of indocyanine green (ICG), ILM peeling, use of triamcinolone, use of sub-Tenon's triamcinolone at the conclusion of the case, and choice of gas tamponade agent (air, sulfur hexafluoride [SF_6], or perfluoropropane [C_3F_8]).

At each clinic visit, all subjects underwent a comprehensive ophthalmologic evaluation that included measurement of best pinhole-corrected visual acuity (BCVA), tonometry, slit lamp examination, dilated fundus examination, and spectral-domain optical coherence tomography (SD-OCT) imaging. Snellen chart visual acuity was converted to logarithm of minimal angle of resolution (logMAR) units for statistical analysis. Post-operative data were collected at 12 months. Other exclusion criteria included less than 12-months follow-up, and incomplete imaging at post-operative visits. The primary outcomes were single-surgery hole closure and visual acuity at 12 months.

SD-OCT

SD-OCT imaging was acquired with either the Spectralis (Heidelberg Engineering, Heidelberg, Germany) or Cirrus HD-OCT (Carl Zeiss Meditec, Oberkochen, Germany). OCT imaging was reviewed by three ophthalmology-trained observers (A.W., C.U., J.W.), and all diagnoses and OCT measurements were confirmed by two vitreoretinal surgery fellowship-trained graders (E.K., M.S.). The Spectralis or Cirrus review software caliper tool was used to obtain all measurements manually. Based on the pre-operative B-scan image involving the foveal center, observers noted the following findings: presence or absence of MHEP, whether or not the MHEP involved the fovea, total MHEP width at the widest point, MHEP maximal thickness, central foveal thickness, presence or absence of vitreomacular adhesion (VMA) or vitreomacular traction (VMT) and their respective widths, presence or absence of ERM, posterior hyaloid status, external limiting membrane (ELM) defect involving the fovea, ellipsoid zone (EZ) defect involving the fovea, RPE defect involving the

fovea, central macular thickness, and macular volume. Graders also measured the narrowest hole diameter as well as the presence of cuffs of macular edema (ME). Macular hole staging was based primary on the posterior hyaloid status: 0= VMA, 1= impending PVD with partial thickness hole, 2= <400µm hole width with VMT, 3= 400µm hole width with VMT, 4= vitreofoveal separation (with or without an operculum over the FTMH), and 5= complete PVD (Weiss ring present).

Data were analyzed using SPSS 22 (SPSS, Inc., Chicago, IL). Continuous variables are presented as mean and standard deviation (SD), whereas categorical variables are presented as absolute values (n) and relative frequency (%). In order to identify possible factors affecting the post-operative change in BCVA after pars plana vitrectomy, multivariable linear regression was performed after adjusting for age, gender, clinical features, and objective measures identified in the univariable analysis. To explore potential factors associated with the need for a second surgery in the setting of persistent or recurrent macular holes, multivariable binary logistic regression was performed after adjusting for age, gender, clinical features, and objective measures identified in the univariable analysis. Regression coefficients and odds ratio were reported with 95% confidence intervals (CIs). A two-tailed *P* value of < 0.05 was considered statistically significant.

RESULTS

A total of 725 charts were analyzed and 113 eyes of 113 patients met the criteria for inclusion into the study (Table 1). This included surgeries performed by 15 different surgeons at two institutions. The mean age at surgery for all patients was 65.8 ± 10.2 years old (range 13–86). 77 of 113 patients (68.1%) were female. A majority of patients were Caucasian, specifically 86 of 113 (76.1%), followed by African American, comprising 11 of the total 113 patients (9.7%). The right eye was involved in 62 of 113 cases (54.9%). Heidelberg OCTs were performed in 67 eyes (59.3%), and the rest were with Cirrus OCTs (40.7%). The mean follow-up duration was 23.4 months.

Baseline Pre-Operative Characteristics

Out of 113 patients with FTMH, 30 (26.5%) had MHEP while the remaining 83 did not (Table 2). The average age of patients without MHEP was 64.3 ± 10.7 years old, while the average age of those with MHEP was 69.9 ± 7.3 years old ($P = 0.002$). 19 of 83 patients without MHEP (22.9%) were male compared with 17 of 30 patients with MHEP (56.7%) ($P = 0.001$). A majority of patients were Caucasian in both groups. Six of the 113 FTMH arose from secondary causes (i.e. trauma), while the remainder were primary or idiopathic in etiology. None of the secondary FTMH were associated with the presence of MHEP. There was a statistically-significant difference in FTMH stage between those eyes with MHEP and those without, such that a greater percentage of MHEP-associated FTMH had more advanced stages compared with those FTMH without MHEP ($P = 0.01$). Similarly, when assessing the posterior hyaloid status on pre-operative OCT, the posterior hyaloid was more often detached from the posterior pole in FTMH with MHEP than in FTMH without MHEP ($P = 0.004$). In addition, ERM was more commonly associated with the presence of MHEP than the absence of MHEP at 33.3% versus 26.5%, respectively ($P < 0.001$). Heidelberg

OCTs were performed in 14 of the 30 MHEP eyes (46.7%) and Cirrus OCTs in the remaining 16 eyes (53.3%) ($P = 0.078$).

We looked at several features on the pre-operative OCT, including macular volume, central macular thickness, presence of EZ defect, presence of ELM defect, and presence of RPE defects at the fovea. Of all these findings, only the pre-operative macular volume was found to be significantly different, such that FTMH with MHEP had significantly thicker macular volumes than FTMH without MHEP (10.2 versus 9.2, respectively) ($P < 0.001$).

Surgical Outcomes

No differences in surgical techniques were found between FTMH with MHEP and without MHEP: pars plana vitrectomy gauge ($P = 0.569$), use of ICG ($P = 0.135$), use of intra-operative triamcinolone ($P = 0.504$), rate of ILM peeling ($P = 0.271$), and choice of tamponade agent ($P = 0.578$) (Table 3).

There was no difference in mean pre-operative BCVA between FTMH eyes without MHEP (0.69 logMAR or 20/98 Snellen equivalent) and with MHEP (0.61 logMAR or 20/81 Snellen equivalent) ($P = 0.214$) (Table 4). The overall BCVA at 12 months post-operatively was not significantly different between FTMH without MHEP (0.33 logMAR or 20/43) and with MHEP (0.42 logMAR or 20/53 Snellen equivalent). However, the positive change in BCVA, or improvement in BCVA, was found to be statistically less in FTMH eyes with MHEP, with an average 0.19 ± 0.24 logMAR gain compared with 0.36 ± 0.35 logMAR in eyes without MHEP ($P = 0.019$). Among the 30 FTMH with MHEP, those whose holes were closed at 12 months post-operatively had an average VA of 0.34 logMAR, or 20/44 Snellen equivalent, compared with 0.92 logMAR, or 20/166 Snellen equivalent, in those holes which remained open ($P < 0.0001$).

Furthermore, the need for repeat vitrectomy and membrane peeling due to failure of hole closure with the first surgery was significantly more common in FTMH with MHEP (7 of 30 eyes, or 23.3 %) versus FTMH without MHEP (4 of 83 eyes, or 4.8%) ($P = 0.007$). Overall, re-operation with vitrectomy and further membrane peeling was performed at an average of 5.5 ± 6.7 months, or a median of 3.5 months, after the initial surgery for all FTMHs that failed initial surgery. Specifically, among FTMH without MHEP, re-operation was performed at an average of 1.8 months after the initial surgery compared with 7.4 months in FTMH eyes with MHEP.

Comparing OCT images at 12-months post-operatively, FTMH with MHEP had significantly higher rates of foveal EZ defects (83.3% versus 42.2%, $P = 0.001$) and ELM defects (60% versus 27.7%, $P = 0.001$) than FTMH without MHEP (Table 4). There was no difference in macular volume ($P = 0.078$), central macular thickness ($P = 0.866$), and foveal RPE defects ($P = 0.180$).

Statistical analysis was performed to identify which variables were associated with a change in BCVA after surgery (Table 5). On univariable analysis, age, gender, myopia, posterior hyaloid status, presence of ERM, presence of pre-operative CME, pre-operative EZ defect involving the fovea, pre-operative RPE defect involving the fovea, macular hole stage,

macular volume on OCT, ILM peeling intra-operatively, gas tamponade agent, and need for repeat vitrectomy and membrane peel were all not found to be associated with the change in BCVA post-operatively. However, the presence of MHEP was found to be associated with significantly less improvement in BCVA ($P=0.019$), and a better pre-operative BCVA was associated with a greater post-operative improvement in BCVA ($P<0.001$). Multivariable analysis showed that the presence of MHEP was indeed associated with less improvement in BCVA ($P=0.046$), even after controlling for hole closure, and better pre-operative BCVA led to greater post-operative improvement in BCVA ($P<0.001$). In addition, the pre-operative presence of RPE defects involving the fovea was found to be associated with less improvement in BCVA ($P=0.019$).

A similar analysis was performed to identify which variables may be associated with failure of hole closure and/or the need for secondary vitrectomy and membrane peeling (Table 6). Univariable analysis suggested that the presence of MHEP ($P=0.007$), absence of ILM peel intraoperatively ($P=0.004$), and need for longer-acting tamponade agent ($P=0.02$) were all associated with the need for repeat vitrectomy and membrane peeling due to lack of hole closure. However, multivariable analysis showed that only the presence of MHEP ($P=0.009$) and the absence of ILM peeling ($P=0.026$) were associated with the need for secondary surgery due to failed hole closure.

DISCUSSION

Since it was first described by Pang *et al* as LHEP in 2014,³ epiretinal proliferation has been explored by many investigators in association with LMH. However, this is the first large-scale and detailed study examining the characteristics and effects of epiretinal proliferation in FTMH and the potential surgical implications, including its association with hole closure rates after surgical repair. We found that MHEP was present in 26.5% of eyes with FTMH that underwent vitrectomy. Previously reported rates of MHEP in FTMH include 8%,³ 9.6%,⁷ and 17.7%.⁶ The rates of 8% and 9.6% were generated upon reviewing all FTMH in general, whereas 17.7% was found in reviewing the rate of MHEP only in FTMH eyes that had undergone vitrectomy surgery for macular hole repair, which is more consistent with our cohort and thus more similar to our rate of 26.5%.

Our study found that MHEP was significantly more common in older (69.9 years versus 64.3 years old), male patients (56.7% versus 22.9%) with a detached posterior hyaloid (53.5% with complete PVD versus 22.9%) and more advanced macular hole stages than in FTMH eyes without MHEP. The only quantitative difference that we identified on pre-operative SD-OCT was a greater macular volume in FTMH with MHEP.

With respect to visual outcomes after vitrectomy, the presence of MHEP was found to be associated with significantly less improvement in BCVA at 12-months post-operatively (0.19 logMAR versus 0.36 logMAR, $P=0.019$). On the 12-month post-operative OCT, FTMH with MHEP had significantly higher rates of ELM and EZ defects than FTMH without MHEP, which presumably are the primary causes for the worse visual outcomes. Whether these are effects from changes induced to the retina by MHEP, additional surgical manipulation that may be required during the surgery to address MHEP, or the fact that

MHEP-associated FTMH were associated with more advanced hole stages are unknown. Factors which led to a greater improvement in BCVA overall were a better pre-operative BCVA and the absence of RPE defects on pre-operative OCT, so these factors should be examined carefully and patients counseled accordingly.

MHEP was also independently associated with failure of the macular hole to close with vitrectomy, requiring repeated surgery compared to FTMH without MHEP. Specifically, only 4.8% (4 of 83) FTMH without MHEP required repeat surgery compared with 23.3% (7 of 30) FTMH with MHEP. One of the most clinically significant findings from this study was that intraoperative ILM peeling at the time of initial surgery was found to significantly improve the rate of hole-closure in eyes with MHEP. Of the 30 eyes with FTMH and MHEP, the rate of failure to close the hole with the first surgery was an astounding 42.9% (6 of 14) in eyes that did not undergo ILM peeling versus just 6.3% (1 of 16) in eyes that did undergo ILM peeling ($P = 0.031$). Of note, the one FTMH that did not close in spite of ILM peeling was large (831 micrometers) with a fully detached posterior hyaloid. ILM peeling is therefore recommended in patients with FTMH accompanied by MHEP.

Finally, we found that MHEP was associated with more advanced FTMH stages. This raises the question of whether the presence of MHEP leads to more advanced stages or whether more advanced FTMH stages lead to MHEP. As a majority of non-MHEP cases were also advanced (64 of 83, or 77.1%, were stage 4 or 5 holes), this suggests that the former case may be possible. Furthermore, it would be interesting to ascertain the natural course of MHEP and whether it is associated with hole chronicity, given its greater association with more advanced FTMH. Future prospective studies will be needed to assess this.

At the time of submitting this manuscript, only two other published studies have examined surgical outcomes of FTMH with and without MHEP.^{6,14} Ubukata *et al* evaluated post-operative results at six months.⁶ Fewer variables and imaging parameters were examined, but they also did find that patients with FTMH and MHEP were older. However, the authors found no differences in gender between the two groups. At six-months post-operatively, FTMH with MHEP had significantly worse visual acuity than FTMH without MHEP and had a greater rate of EZ and ELM defects on OCT, which is similar to the results of the present study. In a second study, Lai *et al* conducted a non-comparative small case series with FTMH and MHEP.¹⁴ Interestingly, the authors noted that permanent or transient spontaneous hole closure occurred in 69.2% (9 of 13) of FTMH with MHEP. Serial pre-operative OCTs were not evaluated in our current study, but their results are intuitively in contrast with our results, which show that FTMH with MHEP have significantly lower rates of hole closure, even with surgical intervention. Four of their nine cases did not require surgery, three eyes showed subsequent reopening after spontaneous hole closure requiring surgery, one case reopened after the initial surgery with spontaneous closure observed several months later, and the final case had a persistent hole after the initial surgery which then spontaneously closed one year after surgery. The authors also reported that an intact EZ line was present in only 23% of eyes at one-year follow-up, which is similar to the results in the present study. Further studies would be required to assess the natural history of these eyes.

Epiretinal proliferation has been proposed to derive from a variety of origins, including retinal glial cells (Müller cells),¹⁷ vitreous components (based on ultrastructural characteristics of fibroblasts and hyalocytes),²⁰ and epithelial cells, specifically RPE cell proliferation with migration through EZ defects.⁵ The yellow pigment seen intraoperatively has been speculated to derive from carotenoids that originate from the macular xanthophyll pigments present at the fovea.¹⁶ Our data suggests that removing ILM in all cases of FTMH with MHEP significantly improves the closure rate, suggesting that this tissue may facilitate continued traction at the hole edges that prevent hole closure rather than facilitate its reconstitution.

There are several limitations to the current manuscript, in addition to the inherent biases of a retrospective study. First, a reading center with blinded graders would be ideal for any study involving image analysis but would require additional resources that were not available for this particular study. Second, although all patients underwent SD-OCT imaging, both Cirrus and Heidelberg OCT machines were used. The units differ in the software algorithms and can lead to subtle differences in retinal thickness measurements. However, the same units were used for each patient throughout the study so the longitudinal pre-operative and post-operative relative comparisons are not affected, and there were similar numbers of the two units that were utilized between the two arms for the cross-sectional preoperative descriptive analyses. Third, this is a multicenter, multi-surgeon study, and surgical approaches were not standardized. However, the same surgeons performed surgery in both arms, with or without MHEP, and several aspects of the surgery such as vitrectomy gauge, gas choice, ILM peeling, among others, were investigated. Finally, although this study focuses on FTMH, other macular pathology such as LMH and ERM may have different visual, anatomic, and surgical implications in the presence of MHEP.

In conclusion, MHEP is not an uncommon finding in FTMH, and its presence was associated with lower improvement in BCVA post-operatively, less outer retinal reconstitution, and lower closure rates. An important finding was that ILM peeling was associated with improved surgical outcomes in eyes with MHEP. Detecting the presence of MHEP on pre-operative OCT may be useful in guiding the surgical approach and discussing a relatively guarded visual prognosis in these patients. Future prospective and controlled studies of MHEP in FTMH may be warranted to provide deeper insight into this clinically relevant finding, in order to further improve outcomes.

Financial support:

Children's Ophthalmology Foundation (YY), Mukai Research Fund (Mass Eye & Ear, SM), Yonekawa Research Fund (Mass Eye & Ear, YY), National Eye Institute (EY0235096) (MW), Iraty Award for Retinal Research and K08EY02399301 (DW)

REFERENCES

1. Theodossiadis PG, Grigoropoulos VG, Emfietzoglou I, et al. Evolution of lamellar macular hole studied by optical coherence tomography. *Graefes Arch Clin Exp Ophthalmol* 2009;247:13–20. [PubMed: 18766367]

2. Witkin AJ, Ko TH, Fujimoto JG, et al. Redefining lamellar holes and the vitreomacular interface: an ultrahigh-resolution optical coherence tomography study. *Ophthalmology* 2006;113:388–397. [PubMed: 16513456]
3. Pang CE, Spaide RF, Freund KB. Epiretinal proliferation seen in association with lamellar macular holes: a distinct clinical entity. *Retina* 2014;34:1513–1523. [PubMed: 24732699]
4. Shiraga F, Takasu I, Fukuda K, et al. Modified vitreous surgery for symptomatic lamellar macular hole with epiretinal membrane containing macular pigment. *Retina* 2013;33:1263–1269. [PubMed: 23594723]
5. Son G, Lee JS, Lee S, Sohn J. Epiretinal Proliferation Associated with Macular Hole and Intraoperative Perifoveal Crown Phenomenon. *Korean J Ophthalmol* 2016;30:399–409. [PubMed: 27980358]
6. Ubukata Y, Imai H, Otsuka K, et al. The Comparison of the Surgical Outcome for the Full-Thickness Macular Hole with/without Lamellar Hole-Associated Epiretinal Proliferation. *J Ophthalmol* 2017;2017:9640756. [PubMed: 29387485]
7. Itoh Y, Levison AL, Kaiser PK, et al. Prevalence and characteristics of hyporeflective preretinal tissue in vitreomacular interface disorders. *Br J Ophthalmol* 2016;100:399–404. [PubMed: 26206790]
8. Choi WS, Merlau DJ, Chang S. Vitrectomy for macular disorders associated with lamellar macular hole epiretinal proliferation. *Retina* 2017;38:664–669.
9. Schumann RG, Compera D, Schaumberger MM, et al. Epiretinal membrane characteristics correlate with photoreceptor layer defects in lamellar macular holes and macular pseudoholes. *Retina* 2015;35:727–735. [PubMed: 25341885]
10. Compera D, Schumann RG, Cereda MG, et al. Progression of lamellar hole-associated epiretinal proliferation and retinal changes during long-term follow-up. *Br J Ophthalmol* 2018;102:84–90. [PubMed: 28546149]
11. Compera D, Entchev E, Haritoglou C, et al. Lamellar Hole-Associated Epiretinal Proliferation in Comparison to Epiretinal Membranes of Macular Pseudoholes. *Am J Ophthalmol* 2015;160:373–384. [PubMed: 25982970]
12. dell’Omo R, Virgili G, Rizzo S, et al. Role of Lamellar Hole-Associated Epiretinal Proliferation in Lamellar Macular Holes. *Am J Ophthalmol* 2017;175:16–29. [PubMed: 27889502]
13. Ko J, Kim GA, Lee SC, et al. Surgical outcomes of lamellar macular holes with and without lamellar hole-associated epiretinal proliferation. *Acta Ophthalmol* 2017;95:e221–e226. [PubMed: 27647708]
14. Lai T-T, Chen S-N, Yang C-M. Epiretinal proliferation in lamellar macular holes and full-thickness macular holes: clinical and surgical findings. *Graefes Arch Clin Exp Ophthalmol* 2016;254:629–638. [PubMed: 26311257]
15. Marques MF, Rodrigues S, Raimundo M, et al. Epiretinal Proliferations Associated with Lamellar Macular Holes: Clinical and Surgical Implications. *Ophthalmologica* 2018;240:8–13. [PubMed: 29590656]
16. Obana A, Sasano H, Okazaki S, et al. Evidence of Carotenoid in Surgically Removed Lamellar Hole-Associated Epiretinal Proliferation. *Invest Ophthalmol Vis Sci* 2017;58:5157–5163. [PubMed: 29049715]
17. Pang CE, Maberley DA, Freund KB, et al. Lamellar hole-associated epiretinal proliferation: A Clinicopathologic Correlation. *Retina* 2016;36:1408–1412. [PubMed: 27164549]
18. Pang CE, Spaide RF, Freund KB. Comparing functional and morphologic characteristics of lamellar macular holes with and without lamellar hole-associated epiretinal proliferation. *Retina* 2015;35:720–726. [PubMed: 25521439]
19. Sun J-P, Chen S-N, Chuang C-C, et al. Surgical treatment of lamellar macular hole secondary to epiretinal membrane. *Graefes Arch Clin Exp Ophthalmol* 2013;251:2681–2688. [PubMed: 23680863]
20. Compera D, Entchev E, Haritoglou C, et al. Correlative Microscopy of Lamellar Hole-Associated Epiretinal Proliferation. *J Ophthalmol* 2015;2015:450212. [PubMed: 26425350]

21. Hirano M, Morizane Y, Kimura S, et al. Assessment of Lamellar Macular Hole and Macular Pseudohole With a Combination of En Face and Radial B-scan Optical Coherence Tomography Imaging. *Am J Ophthalmol* 2018;188:29–40. [PubMed: 29360459]

Figure 1.

a) Epiretinal proliferation is seen on optical coherence tomography as a homogenous material of medium reflectivity and varying thickness. b) Epiretinal membrane is seen as a highly reflective membrane and is uniformly thin.

Figure 2. Epiretinal proliferation seen in association with a full-thickness macular hole on optical coherence tomography. It drapes over the epiretinal surface, snugly following the underlying retinal contour, and occurs on both sides of the hole.

Table 1. Baseline demographics of all eyes included in the study. MHEP= macular hole associated epiretinal proliferation

Demographics	Value (n=113)
Age (years), mean (SD)	65.8 (10.2)
Follow-up period (months), mean	23.4
Sex, no. (%)	
Male	36 (31.9)
Female	77 (68.1)
Race/ethnicity, no. (%)	
White	86 (76.1)
African-American	11 (9.7)
Asian	5 (4.4)
Hispanic	1 (0.9)
Other	2(1.8)
Unknown	8(7.1)
Affected eye, no. (%)	
Right	62 (54.9)
Left	51 (45.1)
Pre-operative visual acuity (logMAR), mean (SD); range	0.67 (0.32); 0.1–2.0
Lens status, no. (%)	
Phakic	79 (69.9)
Pseudophakic	34 (30.1)
Aphakic	0 (0)
MHEP present	
Yes, no. (%)	30 (26.5)
No, no. (%)	83 (73.5)

Table 2.

Baseline pre-operative characteristics for eyes with full-thickness macular holes based on the presence or absence of macular hole associated epiretinal proliferation (MHEP). ERM= epiretinal membrane, CME= cystoid macular edema, OCT= optical coherence tomography. *Macular hole stages: 0= vitreomacular adhesion, 1= impending posterior vitreous detachment (PVD), 2= <400mm hole width with vitreomacular traction (VMT), 3= >400mm hole width with VMT, 4= vitreofoveal separation, and 5= complete PVD (Weiss ring present). P-values < 0.05 are highlighted in bold.

Pre-Operative Variables	- MHEP (n=83)	+ MHEP (n=30)	P-value
Age (years), mean (SD)	64.3 (10.7)	69.9 (7.3)	0.002
Sex, male, no. (%)	19 (22.9)	17 (56.7)	0.001
Race, Caucasian, no. (%)	60 (72.2)	26 (86.7)	0.620
Presence of ERM, no. (%)	22 (26.5)	10 (33.3)	<0.001
Presence of CME, no. (%)	5 (6.0)	1 (3.3)	1.000
Myopia (<-6D spherical equivalent), no. (%)	4 (4.8)	1 (3.3)	1.000
Drusen, no. (%)	2 (2.4)	3 (10)	0.507
Posterior hyaloid status on OCT, no. (%)			
Attached at macula	4 (4.8)	2 (6.7)	0.004
Partially attached at macula	18 (21.7)	1 (3.3)	
Off macula	42 (50.6)	19 (22.9)	
Off disc			
Macular hole stage, no. (%) [*]			
stage 0	1 (1.2)	2 (6.7)	0.01
stage 1	1 (1.2)	0 (0)	
stage 2	12 (14.5)	1 (3.3)	
stage 3	5 (6.0)	0 (0)	
stage 4	45 (54.2)	11 (36.7)	
stage 5	19 (22.9)	16 (53.3)	

Table 3.

Intra-operative variables for eyes with full-thickness macular holes based on the presence or absence of macular hole associated epiretinal proliferation (MHEP). ICG= indocyanine green, ILM= internal limiting membrane

Operative Variables	- MHEP (n=83)	+ MHEP (n=30)	P-value
Pars plana vitrectomy gauge (23/25/27), <i>no.</i>	41/39/3	15/15/0	0.569
Use of ICG staining, <i>no. (%)</i>	50/83 (60.2)	13/30 (43.3)	0.135
Use of Kenalog/Triesence staining, <i>no. (%)</i>	25/83 (30.1)	11/30 (36.7)	0.504
ILM peeling, <i>no. (%)</i>	55/83 (66.3)	16/30 (53.3)	0.271
Tamponade agent (air/SF6/C3F8), <i>no.</i>	1/43/39	0/13/17	0.578

Table 4.

Surgical outcomes comparing pre-operative (pre-op) and post-operative (post-op) visual acuity, hole closure rates, and optical coherence tomography (OCT) findings for eyes with full-thickness macular holes based on the presence or absence of macular hole associated epiretinal proliferation (MHEP). BCVA= best pinhole-corrected visual acuity, ELM= external limiting membrane, EZ= ellipsoid zone, RPE= retinal pigment epithelium. P-values < 0.05 are highlighted in bold.

Surgical Outcomes			
	- MHEP (n=83)	+ MHEP (n=30)	P-value
Pre-op BCVA (logMAR), <i>mean (SD)</i>	0.69 (0.32)	0.61 (0.26)	0.214
Post-op BCVA (logMAR), <i>mean (SD)</i>	0.33 (0.28)	0.42 (0.29)	0.142
Positive improvement in BCVA, <i>mean (SD)</i>	0.36 (0.35)	0.19 (0.24)	0.019
Need for second vitrectomy + membrane peel, <i>no. (%)</i>	4 (4.8)	7 (23.3)	0.007
Pre- and Post-Operative OCT Findings			
	- MHEP (n=83)	+ MHEP (n=30)	P-value
Pre-op macular hole narrowest diameter ($^{\circ}$ m), <i>mean (SD)</i>	347.6 (189.0)	325.9 (198.8)	0.697
Pre-op macular volume, <i>mean (SD)</i>	9.2 (1.0)	10.2 (1.0)	<0.001
Pre-op central macular thickness ($^{\circ}$ m), <i>mean (SD)</i>	379.7 (68.0)	385.0 (80.9)	0.751
Pre-op ELM defect, <i>no. (%)</i>	82 (98.8)	30 (100)	1.000
Pre-op EZ defect, <i>no. (%)</i>	82 (98.8)	30 (100)	1.000
Pre-op RPE defect, <i>no. (%)</i>	34 (41.0)	9 (30)	0.381
Post-op macular volume, <i>mean (SD)</i>	9.0 (2.1)	9.5 (1.3)	0.078
Post-op central thickness ($^{\circ}$ m), <i>mean (SD)</i>	274.2 (42.3)	276.1 (56.5)	0.866
Post-op ELM defect, <i>no. (%)</i>	18 (21.7)	18 (60)	<0.001
Post-op EZ defect, <i>no. (%)</i>	35 (42.2)	25 (83.3)	<0.001
Post-op RPE defect, <i>no. (%)</i>	7 (8.4)	5 (16.7)	0.180

Table 5.

Univariable and multivariable linear regression analysis of selected variables associated with a change in best pinhole-corrected visual acuity (BCVA) after surgery for full-thickness macular holes. Multivariable analysis refers to results adjusted for age, gender, and clinical factors identified through univariable analysis ($p < 0.2$). ERM= epiretinal membrane, CME= cystoid macular edema, MHEP= macular hole associated epiretinal proliferation, EZ= ellipsoid zone, PVE= posterior vitreous detachment, RPE= retinal pigment epithelium, ILM= internal limiting membrane. *CI= confidence interval. P-values < 0.05 are highlighted in bold.

Risk factors	Univariable analysis		Multivariable analysis	
	Regression coefficient (95% CI)*	P-value	Regression coefficient (95% CI)	P-value
Age	0.002 (−0.004, 0.008)	0.585	0.001 (−0.005, 0.006)	0.836
Gender	−0.017 (−0.149, 0.115)	0.795	−0.075 (−0.188, 0.037)	0.189
Myopia ($\leq -6D$, $> -6D$)	0.200 (−0.097, 0.496)	0.185	0.01 (−0.249, 0.269)	0.939
PVD (no, yes)	0.075 (−0.07, 0.221)	0.307		
Associated ERM (no, yes)	−0.011 (−0.140, 0.117)	0.860		
Associated CME (no, yes)	0.061 (−0.213, 0.335)	0.658		
Associated MHEP (no, yes)	−0.163 (−0.299, −0.027)	0.019	−0.128 (−0.254, −0.002)	0.046
Pre-op macular volume	−0.029 (−0.078, 0.020)	0.240		
Pre-op EZ defect (no, yes)	−0.595 (−1.242, 0.052)	0.071	−0.465 (−0.993, 0.063)	0.084
Pre-op RPE defect (no, yes)	0.098 (−0.027, 0.223)	0.123	0.159 (0.027, 0.291)	0.019
Pre-op BCVA	0.647 (0.438, 0.810)	<0.001	0.638 (0.464, 0.812)	<0.001
Macular hole stage	−0.020 (−0.074, 0.033)	0.456		
Intra-operative ILM peel (no, yes)	0.097 (−0.028, 0.223)	0.128	−0.103 (−0.240, 0.034)	0.141
Tamponade agent (SF ₆ , C ₃ F ₈)	−0.031 (−0.155, 0.093)	0.624		
Need for second surgery (no, yes)	−0.149 (−0.355, 0.056)	0.153	−0.29 (−0.214, 0.156)	0.756

Univariable and multivariable logistic regression analysis of selected variables associated with the need for repeat vitrectomy and membrane peeling for full-thickness macular holes. Multivariable analysis refers to results adjusted for age, gender, and clinical factors identified through univariable analysis ($p < 0.2$) ERM= epiretinal membrane, MHEP= macular hole associated epiretinal membrane, ILM= internal limiting membrane, PVD=posterior vitreous detachment. *CI= confidence interval. P-values < 0.05 are highlighted in bold.

Table 6.

Risk factors	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI*)	P-value	Odds ratio (95% CI*)	P-value
Age	0.962 (0.916, 1.011)	0.127	0.933 (0.863, 1.009)	0.081
Gender (male, female)	0.524 (0.149, 1.846)	0.315	0.822 (0.154, 4.396)	0.818
Myopia ($< -6D$, $\geq -6D$)	2.450 (0.249, 24.09)	0.442		
PVD (no, yes)	1.288 (0.316, 5.254)	0.724		
Associated ERM (no, yes)	1.441 (0.411, 5.051)	0.568		
Associated MHEP (no, yes)	6.011 (1.616, 22.351)	0.007	10.568 (1.491, 74.918)	0.009
Macular hole stage	1.772 (0.784, 4.00)	0.169	1.083 (0.482, 2.434)	0.846
Intra-operative ILM peel (no, yes)	0.046 (0.006, 0.372)	0.004	0.79 (0.008, 0.740)	0.026
Tamponade agent (SF ₆ , C ₃ F ₈)	11.957 (1.475, 96.91)	0.02	4.250 (0.35, 51.65)	0.256