Title:

Mixed pathophysiologies of lamellar macular holes and related diseases: a multimodal optical coherence tomography-based study

Abbreviated title:

Mixed types of LMH and related diseases

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Keywords:

en-face imaging, epiretinal membrane, epiretinal membrane foveoschisis, lamellar macular hole, metamorphopsia, mixed type, optical coherence tomography, retinal fold, retinal traction

Summary statement:

This study investigates the mixed pathophysiologies in lamellar macular holes (LMH) and related diseases. Analyzing 126 eyes, it found that 34.1% had mixed pathophysiologies, showing a correlation between retinal traction and metamorphopsia in the LMH-related mixed group. The study underscores the importance of multidirectional OCT in diagnosing these diseases accurately.

ABSTRACT

Purpose: To investigate the characteristics of mixed pathophysiologies in lamellar macular holes (LMH) and related diseases using multimodal optical coherence tomography (OCT).

Methods: Overall, 126 eyes diagnosed with LMH, epiretinal membrane foveoschisis (ERM-FS), or macular pseudohole (MPH) using the horizontal B-scan image according to the definition proposed by Hubschman *et al*. in 2020 were analyzed using multimodal OCT imaging including horizontal and vertical 5-line B-scan, radial scan, and macular three-dimensional volume scan images. If at least two diagnostic criteria for LMH, ERM-FS, or MPH were satisfied in these scans, the patient was diagnosed as having a "mixed type." Retinal traction force was quantitatively evaluated by measuring the maximum depth of the retinal folds (MDRF) using en-face images.

Results: Mixed types constituted 34.1% of the cases. The LMH-related mixed group demonstrated intermediate characteristics between the ERM-FS/MPH and true LMH groups in terms of retinal traction and LMH-specific features and had a significant positive correlation between the MDRF and mean M-CHARTS scores ($P = 0.034$).

Conclusion: A thorough OCT analysis is necessary to accurately diagnose LMH and related diseases. A significant positive correlation was observed between the MDRF and the degree of metamorphopsia in the LMH-related mixed group.

INTRODUCTION

Lamellar macular hole (LMH) is a common macular disease characterized by retinal tissue loss, causing decreased visual acuity and metamorphopsia.[1–3] No diagnostic criteria have been established since the first report by Gass.[4] However, a consensus definition based on optical coherence tomography (OCT) was proposed by Hubschman *et al.* in 2020.[5] This definition clarified the diagnostic criteria for three diseases: LMH, previously known as degenerative LMH,[6] epiretinal membrane foveoschisis (ERM-FS), previously known as tractional LMH,[6] and macular pseudohole (MPH).

According to previous reports, there are “mixed” lesions, such as LMH with ERM,[5] and LMH may occur as a result of retinal traction caused by ERM.[7] Moreover, we have previously studied retinal traction in LMH and related diseases diagnosed according to the consensus definition. Our findings revealed that parafoveal retinal folds caused by ERM were present in 26.9% of LMH cases.[2] OCT images revealed that cases of mixed pathophysiologies with overlapping features of different diseases may be present. However, the frequency and characteristics of these cases remain unclear.

Therefore, we aimed to categorize LMH, ERM-FS, and MPH cases based on a detailed examination of OCT and characterize the pathophysiologies of each category.

METHODS

Study design and participants

In this retrospective observational study, we reviewed the medical records of 119 consecutive patients (126 eyes) who visited the Okayama University Hospital between August 2015 and February 2023 and were diagnosed with LMH, ERM-FS, or MPH according to the definition proposed by Hubschman *et al*. using a horizontal B-scan image.[5] Patients with high myopia (spherical equivalent ≤-6 diopters or axial length ≥26.0 mm), diabetic maculopathy, age-related macular degeneration, retinal vein occlusion, or active uveitis were excluded. All investigative procedures were conducted in accordance with tenets of the Declaration of Helsinki. The study was approved by the Ethics Committee of Okayama University Hospital, Okayama, Japan (reference number: K2205-010). Written informed consent was obtained from all participants.

Ophthalmologic examinations

All patients underwent comprehensive ophthalmologic examinations, including best-corrected visual acuity (BCVA) testing with refraction using a 5-m Landolt C acuity chart and indirect and contact lens slit-lamp biomicroscopy. Metamorphopsia was quantified using M-CHARTS (Inami, Tokyo, Japan), an inspection sheet comprising a straight line and 19 dotted lines with dot intervals ranging from 0.2 to 2.0 degrees of visual angle. The M-CHARTS score is defined as the visual angle of the dotted line that is no longer perceived as distorted. [8–10] The test was conducted in both horizontal and vertical directions, and the mean M-CHARTS score was calculated by averaging the horizontal and vertical M-CHARTS scores. The axial length was measured using an optical biometer (OA-2000; Tomey, Nagoya, Japan).

Categorization of mixed-type cases based on OCT analysis

All OCT procedures were performed using swept-source OCT (Triton; Topcon Corporation, Tokyo, Japan). In all cases, horizontal and vertical 5-line B-scan images (12 mm long, 0.25-mm intervals) and macular three-dimensional volume scan images over a 7 × 7 mm area comprising 512 × 512 A-scans were obtained. In addition, in 19 (15.1%) eyes, 12-line radial scan images (12 mm long) were also obtained. By analyzing all the B-scan images from all of these scanning protocols, LMH, ERM-FS, and MPH were diagnosed. A patient was diagnosed as having the “mixed type” if at least two of the diagnostic criteria for LMH, ERM-FS, or MPH were satisfied in different scans. For example, if one scan satisfied the diagnostic criteria for LMH and another for ERM-FS, the patient was diagnosed as an ERM-FS/LMH “mixed type.” LMH, ERM-FS, or MPH that did not meet the criteria for mixed type were defined as "true" LMH, ERM-FS, or MPH, respectively. The diagnosis of LMH, ERM-FS, or MPH adhered to the OCT-based consensus definition proposed by Hubschman *et al*. in 2020.[5] Briefly, the mandatory diagnostic criteria are as follows: for LMH, the presence of (1) irregular foveal contour, (2) foveal cavity with undermined edges, and (3) apparent loss of foveal tissue;

for ERM-FS, the presence of (1) contractile ERM and (2) foveoschisis to the level of Henle's fiber layer; and for MPH, the presence of (1) foveal center-sparing ERM, (2) retinal thickening, and (3) verticalized or steepened foveal profile. We defined ERM as hyperreflective linear lines on the retinal surface and epiretinal proliferation (EP) as isoreflective lesions on the retinal surface. Additionally, the continuity of the ellipsoid zone (EZ) was evaluated using B-scan OCT images. To construct en-face images, three-dimensional OCT volume data of the retina were flattened along the internal limiting membrane (ILM) using IMAGEnet 6 software (version 1.22; Topcon Corporation, Tokyo, Japan). The retinal folds were identified as hyporeflective linear lesions below the ILM level on en-face images. To quantitatively assess the strength of the retinal traction force, the maximum depth of the retinal folds (MDRF) was measured using methods described previously.[2,11–19] Briefly, the distance from the ILM level to the level at which the deepest retinal folds existed was measured in the parafoveal area, defined as a 3 mm-diameter circle centered on the fovea. All OCT evaluation processes were performed by two retina specialists (R.M. and Y.M.).

Statistical analysis

BCVA was measured using a Landolt C chart in decimal units and subsequently converted to logarithms of the minimal angle of resolution (logMAR) units. Data are presented as mean ± standard deviation. Continuous variables were compared using a one-way analysis of variance (ANOVA), followed by the Bonferroni post-hoc test. The Fisher's exact test was used to analyze categorical variables. Spearman’s rank correlation coefficient (rs) was calculated to analyze the correlation between MDRF and M-CHARTS scores. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The distribution of true LMH, ERM-FS, and MPH cases was 43 (34.1%), 25 (19.8%), and 15 (11.9%), respectively. Mixed types were identified in 43 (34.1%) eyes, which included 19 (15.1%), 8 (6.3%), 13 (10.3%), and 3 (2.4%) eyes with ERM-FS/MPH, ERM-FS/LMH, MPH/LMH, and ERM-FS/MPH/LMH, respectively. Figure 1 shows representative mixed-type cases of ERM-FS/MPH (Figure 1A and B), ERM-FS/LMH (Figure 1C and D), and MPH/LMH (Figure 1E and F).

Retinal traction caused by ERM is reportedly the pathophysiology of ERM-FS and MPH.[2,5,6,20] Conversely, LMH is primarily attributed to retinal tissue loss, although it may be accompanied by weak retinal traction.[2,5,6,20] Accordingly, to elucidate the pathophysiology of the mixed types (Figure 2A), we categorized the patients into three groups based on retinal traction: the "ERM-FS/MPH group," including true ERM-FS, true MPH, and ERM-FS/MPH mixed types; the true LMH group; and the "LMH-related mixed group," including ERM-FS/LMH, MPH/LMH, and ERM-FS/MPH/LMH mixed types (Figure 2B). Retinal traction was considered the main pathophysiology for the ERM-FS/MPH group but not for the true LMH group. No significant differences in age ($P = 0.15$), sex ($P = 0.53$), mean M-CHARTS score ($P = 0.74$), or axial length ($P = 0.75$) were observed between these three groups. LogMAR BCVA was significantly different between the three groups ($P = 0.02$). ERM with retinal folds was significantly lower, and EP and EZ disruption rates were significantly higher in the true LMH group than in the ERM-FS/MPH and LMH-related mixed groups (all $P < 0.01$) (Table 1). Next, MDRF was measured to quantitatively evaluate the strength of the retinal traction force. MDRF was 79.0 ± 28.5 μm, 60.9 ± 23.1 μm, and 3.6 ± 9.6 μm in the ERM-FS/MPH, LMH-related mixed, and true LMH groups, respectively, with significant differences between the groups ($P < 0.01$; Figure 3A). Furthermore, a significant positive correlation was observed between MDRF and mean M-CHARTS scores in both the ERM-FS/MPH ($r_s = 0.562$, $P < 0.001$, Figure 3B) and LMH-related mixed groups ($r_s = 0.502$, $P = 0.034$, Figure 3C). Figure 4 shows a representative case of ERM-FS/LMH mixed type with both EP and contractile ERM that underwent ERM and ILM removal combined with EP embedding surgery.

DISCUSSION

To the best of our knowledge, this is the first study to analyze the frequency and characteristics of mixed types of LMH and related diseases. A detailed examination of multiple OCT scans of 126 eyes revealed that 34.1% were of mixed types, exhibiting at least two overlapping pathophysiologies of LMH, ERM-FS, and MPH. Therefore, analyzing multiple OCT scans to accurately assess the pathophysiology of LMH and related diseases is essential.

Based on previous reports on retinal traction in each disease,[2,5,6,20] we classified the patients into three groups: ERM-FS/MPH, LMH-related mixed, and true LMH. Similar to the ERM-FS/MPH group, all patients in the LMH-related mixed group showed ERM with retinal folds, suggesting the presence of ERM-induced retinal traction (Table 1). Based on MDRF, the strength of the retinal traction force was highest in the ERM-FS/MPH group, followed by the LMH-related mixed and true LMH groups (Figure 3A). The MDRF scores were significantly correlated with the metamorphopsia scores both in the ERM-FS/MPH (Figure 3B) and LMH-related mixed groups (Figure 3C). Thus, along with prior studies that have reported the potential usefulness of MDRF in determining the indications for surgery in idiopathic ERM, ERM-FS, and MPH,[2,16] quantitative evaluation of retinal traction force in the LMH-related mixed group may be beneficial in determining whether ERM (and ILM) removal should be performed to relieve retinal traction.

In this study, we evaluated the foveal morphology of LMH, ERM-FS, and MPH using multidirectional OCT imaging. We revealed that 34.1% of the cases were of a mixed type, which is difficult to classify based on a horizontal scan alone. This result indicates the importance of detailed observation of LMH and related diseases using multidirectional imaging. However, it is difficult to always take many scans, including volume scan imaging, and analyze all the images in daily practice. Among horizontal and vertical 5-line B-scan, radial scan, and macular three-dimensional volume scan, we believe that radial scans are considered the most useful in terms of the ability to analyze sections in various directions as long as the center of the scan matches the center of the fovea. Since radial scans were performed in only 15% of the cases in this study, further studies are needed to clarify the most efficient examination method for diagnosing LMH, ERM-FS, and MPH.

EP and EZ disruption rates are characteristics of LMH and optional criteria for LMH diagnosis in the consensus definition.[5] The LMH-related mixed group had intermediate EP and EZ rates compared to the ERM-FS/MPH and true LMH groups (Table 1). EP embedding surgery was reportedly effective in LMH with EP.[21–27] Recently, EP-sparing surgery has been reportedly effective for LMH.[28] Since the LMH-related mixed group has some LMH characteristics, both EP embedding and sparing surgeries may be useful treatment strategies.

Based on these results and previous reports,[2,13,21–28] we recommend the following treatment strategies according to the pathophysiologies of LMH and related diseases: Retinal traction and tissue loss are the two main pathophysiologies involved in LMH, ERM-FS, and MPH. Retinal traction, which is the main pathophysiology of ERM-FS and MPH, is treated by releasing retinal traction through ERM (and ILM) removal. However, retinal tissue loss, which is the primary pathophysiology of LMH, is treated by restoring the foveal structure by EP embedding (or sparing) surgery. Importantly, these pathophysiologies often overlap. Therefore, in patients in the LMH-related mixed group who have both retinal traction and retinal tissue loss, the presence or absence of EP should be evaluated to plan surgical procedures. In the absence of EP, ERM (and ILM) removal is suggested. However, if EP is present, a combined approach of ERM (and ILM) removal and EP embedding (or sparing) can be considered, as illustrated in Figure 5.

This study had some limitations. First, it is a retrospective study with a small sample size. Second, OCT imaging protocols were not fully standardized, as mentioned above. Third, the number of patients who underwent surgery was small, and the results of surgery in each disease category were not examined. Fourth, the patients were divided into three groups based on retinal traction; however, there were seven categories when LMH, ERM-FS, MPH, and their mixed types were subdivided. Owing to the limited number of cases, a comparative analysis of the seven categories was not performed. Fifth, the OCT evaluation was not performed independently by each grader; therefore, inter-grader agreement was not assessed. Sixth, patients with high myopia, a condition associated with LMH, were excluded from this study. Consequently, the association between LMH, related diseases, and high myopia is unknown. Sixth, this was a morphological analysis study using OCT. A pathological study using actual human tissues was not conducted. Future large-scale prospective studies with standardized imaging protocol, including surgical outcomes and pathological findings, are needed to further investigate the pathophysiologies of each disease category.

In conclusion, a thorough examination of multiple OCT scans is essential for an accurate diagnosis of LMH and related diseases. The LMH-related mixed group, whose pathophysiology was previously unknown, had some LMH characteristics and moderate retinal traction compared to the ERM-FS/MPH and true LMH groups. Additionally, a significant positive correlation was found between the retinal traction force and the degree of metamorphopsia in the LMH-related mixed group.

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Figure Legends

Figure 1 Representative cases with mixed types of epiretinal membrane foveoschisis (ERM-FS), macular pseudohole (MPH), and lamellar macular hole (LMH).

The B-scan optical coherence tomography (OCT) images are shown. The arrows on the infrared reflectance images to the right of each OCT image indicate the scan direction of the OCT image. A and B, C and D, and E and F show images of different scans of the same eye.

Mixed ERM-FS/MPH type (A and B). ERM is observed (arrowheads in A and B). Foveoschisis is present in one scan (asterisk in A); however, the foveal structure is verticalized in another scan (asterisk in B).

ERM-FS/LMH mixed types (C and D). ERM (arrowheads in C and D) and EP (arrows in C and D) were observed. Foveoschisis is visible in one scan (asterisk in C); however, a foveal cavity with an undermined edge is observed in another scan (asterisk in D).

MPH/LMH mixed types (E and F). ERM (arrowheads in E and F). The foveal structure is steepened in one scan (asterisk in E); however, a foveal cavity with an undermined edge is observed in another scan (asterisk in F).

Figure 2 Epiretinal membrane foveoschisis (ERM-FS), macular pseudohole (MPH), lamellar macular hole (LMH), and their mixed types.

(A) Seven categories of ERM-FS, MPH, and LMH, as well as their mixed types, are shown as Venn diagrams. Forty-three (34.1%) eyes were mixed types.

(B) Three groups classified from the perspective of retinal traction are shown.

Figure 3 Comparison of the maximum depth of retinal folds (MDRF) between the epiretinal membrane foveoschisis (ERM-FS)/macular pseudohole (MPH) group, the lamellar macular hole (LMH)-related mixed group, and true LMH; and the association between the MDRF and metamorphopsia score.

Box plot showing the distribution of MDRF in each group (A). The scatter plot demonstrates the association between the MDRF and mean M-CHARTS scores in the ERM-FS/MPH group (B) and LMH-related mixed group (C). One-way analysis of variance followed by a Bonferroni post-hoc test was used in (A), and Spearman's rank correlation test was used in (B) and (C); rs, Spearman's rank correlation coefficient; * $P < 0.05$; ** $P < 0.01$.

Figure 4 A representative case of epiretinal membrane foveoschisis (ERM-FS)/lamellar macular hole (LMH) mixed type who had undergone vitrectomy.

A woman in her 60s. The preoperative BCVA (logarithm of the minimal angle of resolution; logMAR BCVA) was 0.00, and the mean M-CHARTS score was 1.9. (A) Color fundus photograph taken during the initial visit. (B) ERM (arrowheads) and epiretinal proliferation (EP) were observed on B-scan optical coherence tomography (OCT) images. The foveal structure was undermined on the horizontal scan (asterisk in the upper image); however, foveoschisis was observed on the vertical scan (asterisk in the lower image). (C) ERM is seen as a hyperreflective membranous lesion (arrowheads) on an internal limiting membrane (ILM)-flattened en-face image at the ILM level. (D) Retinal folds are seen as hyporeflective linear lesions (arrowheads) on an ILM-flattened en-face image 30 μm below the ILM level. (E) Color fundus photograph 3 months after surgery. (F) Horizontal and vertical B-scan OCT images 3 months after surgery (upper and lower images, respectively). The foveal structure is restored (asterisk). Postoperative logMAR BCVA was -0.08, and the mean M-CHARTS score was 0.1.

Figure 5 Summary of the pathophysiologies and treatment strategies of the epiretinal membrane foveoschisis (ERM-FS)/macular pseudohole (MPH) group, the lamellar macular hole (LMH)-related mixed group, and true LMH.

ILM, internal limiting membrane; EP, epiretinal proliferation