Features of idiopathic and intermediate uveitis—associated epiretinal membranes on OCT and multi-color imaging

Xiao Wang

Sun Yat-Sen University Zhongshan Ophthalmic Center

Shaofen Lin

Sun Yat-Sen University Zhongshan Ophthalmic Center

Jing Lu

Sun Yat-Sen University Zhongshan Ophthalmic Center

Qiuhui Liu

Sun Yat-Sen University Zhongshan Ophthalmic Center

Guiying Mai

Sun Yat-Sen University Zhongshan Ophthalmic Center

Ruyuan Liu

Sun Yat-Sen University Zhongshan Ophthalmic Center

Xiaoyu Cai

Sun Yat-Sen University Zhongshan Ophthalmic Center

SriniVas Sadda

Sun Yat-Sen University Zhongshan Ophthalmic Center

Yan Luo (✉ luoyan2@mail.sysu.edu.cn)

Sun Yat-Sen University Zhongshan Ophthalmic Center

Lin Lu

Sun Yat-Sen University Zhongshan Ophthalmic Center

Research article

Keywords: Epiretinal membrane, idiopathic, intermediate uveitis, multi-color imaging, ultrasound biomicroscopy

Posted Date: October 1st, 2019

DOI: <https://doi.org/10.21203/rs.2.15381/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

BACKGROUND To characterize the morphologic features of idiopathic epiretinal membrane (iERM) and subtle intermediate uveitis-associated epiretinal membrane (IU-ERM) using optical coherence tomography (OCT) with multi-color imaging.

METHODS Forty-three eyes of 36 patients diagnosed as iERM and IU-ERM by fundus examination and ultrasound biomicroscopy were underwent multi-color scanning laser ophthalmoscopy imaging using a Heidelberg Spectralis HRA+OCT. Area and thickness of the ERM, central foveal thickness (CFT), and best-corrected visual acuity (BCVA) were compared between these two groups.

RESULTS The ERM area of the IU-ERM group was larger than that of the iERM group ($33.03 \pm 14.62 \text{ mm}^2$ vs. $13.03 \pm 7.00 \text{ mm}^2$, $P < 0.001$). The ERM thickness of the IU-ERM group was also thicker than that of iERM group ($20.14 \pm 1.52 \text{ } \mu\text{m}$ vs. $17.92 \pm 1.28 \text{ } \mu\text{m}$, $P < 0.001$). The BCVA of the eyes with iERM was better (0.10 ± 0.18 vs. 0.35 ± 0.28 , $P < 0.001$) and the CFT was thinner ($217.66 \pm 64.21 \text{ } \mu\text{m}$ vs. $359.19 \pm 128.72 \text{ } \mu\text{m}$, $P = 0.002$) compared to the IU-ERM group.

CONCLUSION IU-ERM was larger and thicker than iERM. OCT with multi-color imaging could facilitate the assessment of ERM morphology, which might aid in differentiating IU-ERM from iERM.

Background

Epiretinal membranes (ERMs) are a common fundus finding which can lead to metamorphopsia, blurred vision, and eventually vision loss.[1, 2] The causes of most idiopathic ERMs (iERMs) are not readily apparent. These iERMs have been theorized to the proliferation on the retinal surface and the cortical vitreous which is thought to serve as a scaffold. In other cases, ERMs develop secondary to other associated ocular pathologies such as retinal vascular disease, inflammation/uveitis, or surgery. [3–6] The wide availability of OCT has increased the detection of ERMs, as OCT can often reveal a subtle ERM which is asymptomatic and difficult to discern by biomicroscopy.[7] iERMs are easy to distinguish from some secondary ERMs based on patients' history. While, intermediate uveitis-associated epiretinal membranes (IU-ERMs) in particular may be misdiagnosed as iERMs because the inflammatory disease may be mild or asymptomatic.[8, 9] ERMs is a common complication of IU and can be detected in 39.6–57.0% of IU cases.[10, 11] The incidence of ERMs in IU cases increases with age in a 20-year study,[9] which coincides with the peak prevalence of iERMs observed in elderly individuals.[12] Patients initially thought to have iERMs in our study were noted on closer inspection to accompanied with ciliary body edema and / or exudation on ultrasound biomicroscopy (UBM), suggesting an underlying intermediate uveitis. As intermediate uveitis can have a chronic or relapsing/remitting course with associated ocular complications, distinguishing iERMs from IU-ERMs may be of clinical importance in these cases with subtle and un-diagnosed IU.

Since OCT B-scans do not appear to be effective for distinguishing iERMs from IU-ERMs, we wondered whether other imaging modalities could demonstrate differentiating features. Recently, multi-color fundus

imaging using a scanning laser ophthalmoscope (SLO) with three separate lasers (blue, green, infrared) has been suggested to better display the morphology and extent of ERM compared to traditional fundus photos and OCT B-scan.[13] In the present study, we sought to better characterize and compare the morphologic features of IU-ERMs and iERMs on multi-color imaging.

Methods

All study procedures adhered to the tenets of the Declaration of Helsinki and were approved by the investigational review board of Ethics Committee of Zhongshan Ophthalmic Center, Sun Yat-sen University (Guangzhou, China, 2018KYPJ054). All subjects signed informed consent for participation in this research.

Subjects

Forty-two eyes of 36 patients diagnosed as iERM and subtle IU-ERM by fundus examination and ultrasound biomicroscopy were recruited in this cross-sectional observational study at the Zhongshan Ophthalmic Center from Oct. 2014 to Oct. 2017. Twenty-seven eyes of 22 patients diagnosed with IU were IU-ERM group, and 15 eyes of 14 patients diagnosed as iERM were iERM group. The diagnosis of IU was made in accordance with The Standardization for Uveitis Nomenclature (SUN) Working Group guidelines. The vitreous is the key inflammation site which is affected by vitreous cell and haze.[13] But for subtle intermediate uveitis enrolled in this study, the vitreous cell and haze was difficult to observe by fundus examination which might lead to misdiagnosis.[7, 8] As the ERM eyes eligible for this study were not thought to have much in the way of inflammatory signs at the time of study enrollment, undilated ciliary body morphology and vitreous cells in OCT image were the key parameters used to facilitate a diagnosis of IU in these cases.[14] All patients were taken UBM examination to measure the thickness of ciliary body at a position 1 mm posterior to the scleral spur (CBT1). As the CBT1 may be altered in eyes with high myopia, high hypermetropia or narrow angle, such eyes were not enrolled in the study. Individuals with other ocular diseases including diabetic retinopathy, vascular occlusion, active or a history of definite uveitis, retinal detachment, or history of intraocular trauma, previous surgery, intraocular injection or laser treatment were also excluded from the study. Patients with severe cataract preventing high-quality of the retinal imaging were also excluded.

For this study, ERM was observed by fundus examination and identified by OCT as a hyperreflective signal at the inner retinal surface with some evidence on traction, distortion, surface contour alteration, or gathering of the underlying retina. Demographic features and best-corrected Snellen visual acuity (BCVA) were recorded.

Measurement of CBT1

UBM (Suoer electronic Ltd, model SW-3200L) imaging was performed with patients in the supine position and with the pupils undilated. The probe was used to scan the ciliary body in 4 meridians (12, 3, 6 and 9 o'clock positions). The CBT1 (Fig. 1A) in all four meridians was measured with Image J (A free open source image processing software provided by the National Institutes of Health, <http://imagej.nih.gov/ij/>). The average of the measurements above 0.74 mm was defined to have IU for this study, according a research that the CBT1 in normal chinese individuals was shown to be 0.651 ± 0.089 mm.[15] The increase of the CBT1 was indicated the ciliary body edema and exudate. Edema was defined as an increase in ciliary body thickness and disruption of the normally strong reflection from the pigment epithelium (Fig. 1B). The exudate was defined as irregular mass attached to ciliary body (Fig. 1C). While the normal ciliary body showed intact strong reflection of pigment epithelium and without attachments in the ciliary body-vitreous interface (Fig. 1D).

Measurement of vitreous cells

In accordance with Saito et al' s study, the presence of vitreous cells was also assessed on the OCT images. These vitreous cells were defined as hyperreflective dots in the vitreous which were larger and more reflective compared to the background speckle noise (Fig. 2).[14]

Measurement of epiretinal membranes

The macular of all eligible study eyes was captured the multi-color SLO images with 30 degree using a Spectralis HRA+OCT (Heidelberg Engineering, Germany). Structural OCT was also obtained using a 30 x 25 degree volume scan centered on the fovea with 31 horizontal B-scans 240 microns apart.

The multi-color imaging provided a good delineation of the boundaries of the ERM when compared with the flash white-light color photograph (Fig. 3A). The boundaries of the ERM were manually segmented using Image J (Fig. 3B). To further optimize the delineation of the ERM boundaries, the multi-color image was simultaneously correlated with OCT B scans at the corresponding locations, and then the ERM boundary was adjusted (Fig. 3C) based on the termination of the hyper-reflective line on the OCT. Following the manual delineation and adjustment, the ERM area (ERMA) was calculated. The representative multi-color images of ERMs from the two groups were shown in Figure 4.

In addition, the central thickness of ERM (ERMT) was also measured using image J by applying a grid composed of four concentric circles with the radii of 200 μ m, 400 μ m, 600 μ m and 800 μ m in the multi-color image. The grid was placed at the "center" of the ERM which was defined as the darkest point on the multi-color image (Fig. 5A and 5B). The thickness of ERM was measured at the intersections between the circular grid lines and the OCT B-scans, amounting to a total of 29 points. The mean of these 29 measurements was taken to be the ERMT for subsequent analysis, and the central foveal thickness (CFT) was also measured.

Statistical analysis

The data were statistically analyzed using a commercial analytical software program (SPSS 13.0; SPSS, Inc., Chicago, IL). All tests were two sided, and a *P* value less than 0.05 was considered statistically significant. Snellen BCVA was converted to logMAR value for statistical analysis. Two-sample independent *t*-test was used for the continuous variables. Fisher exact test was used for the categorical variables. Mean ± SD was calculated for quantiative parameters. The correlation analysis was examined by Pearson correlation.

Results

Mean age of subjects was 64 years. The BCVA in the iERM group was better than the IU-ERM group (*P* = 0.001), whereas there was no significant difference in age or gender of these two groups (Table 1).

Table 1 Demographic characteristics of the two epiretinal membrane groups.

	iERM	IU-ERM	<i>P</i>
Number	15	27	--
Female: Male, n(%)	8:2 (80.00%)	19:8 (70.37%)	0.571*
Age (mean ± SD), years	67.50 ± 6.33	62.63 ± 6.90	0.059†
BCVA, logMAR (mean ± SD)	0.10 ± 0.18	0.35 ± 0.28	0.001†

*Fisher exact test.

†Independent Samples Test.

Six eyes were found hyperreflective dots in OCT images in IU-ERM group (Fig. 2).

Contrast with the flash white-light color photograph, the ERM in multi-color picture manifested as yellow-green area accompany with a clean, crisp outline. The darkest area of both the iERM and IU-ERM usually avoided the foveola.

Representative multi-color images of iERM and IU-ERM were shown in Figure 3. On the planar area measurement from multi-color imaging, the ERMA of the IU-ERM group was significantly larger than that of the iERM group (*P* = 0.001, fig. 4C). In contrast, the average ERMT of the IU-ERM group was greater than that of the iERM group (*P* = 0.001, fig. 5E). The CFT of iERM group was thinner than that of IU-ERM group (217.66 ± 64.21 μm vs. 359.19 ± 128.72 μm, *P* = 0.002).

On Pearson correlation analysis, BCVA was negatively correlated to CFT (*t* = 0.564; *P* = 0.001), but was not related to the ERMA or the ERMT.

Discussion

In this study, we firstly evaluated the morphology of idiopathic and IU-associated ERMs on multi-color imaging and OCT. Multi-color images appeared to show superior visualization of the ERMs compared to the standard flash white-light color images of the retina, allowing more precise delineation of the transverse borders of the lesion.

Compared with iERMs, IU-ERMs were noted to be thicker and larger. This might be caused by the infiltration of inflammatory cells in IU eyes,[15] which can promote tissue proliferation. In the histological analysis of eyes with iERM, only abnormal migration of a few RPE and glial cells are observed.[15] This findings of substantially larger ERMs in eyes with IU suggested that the underlying inflammatory (albeit possibly quiescent at any given time) might need to be considered in eyes which present with very extensive membranes.

Mean BCVA was also better and mean CFT was thinner in eyes with thinner ERMs. Correlation analysis demonstrated that BCVA was negatively correlated with CFT, but did not vary according to the ERMA or the ERMT. The correlations between retinal thickness and BCVA have been well investigated in the setting of ERM.[16] In our study, we found that the thickest portion of the ERM did not coincide with the foveal center in most of the study eyes, which might be one reason why the BCVA did not correlate with the ERMT. We hypothesized that due to the normal point of tighter attachment between the posterior hyaloid and the retina in the foveola, the vitreous might separate from retina later in this area, preventing the growth of the ERM into this area during in the disease course. As a result, the ERM might have been thinner in the central macular area than other area.

In our study, IU-ERM patients were only diagnosed to have IU-ERM following CBT1 assessment by UBM and showed the minimal evidence of inflammation at the time of scanning. These eyes were further confirmed to have evidence of vitreous cells by OCT. It was important to recognize the mild nature of the uveitis in these subjects, as our findings might not extrapolate to patients with more severe or active IU.

UBM was an important component of our study. We observed that 64.28% (27/42) of our study eyes grouped to IU-ERM. In previous studies, idiopathic ERM has been reported to account for 42% to 80% of all ERMs.[17–19] However, based on our findings, we worried that previous studies might have over-estimated iERMs as the subtle associated inflammatory disease might not have been recognized. As obtaining UBMs on all patients with ERMs may not be practical, consideration of morphologic parameters of the ERM itself, as assessed in this study, may be of value.

Distinguishing IU-ERM from iERM may not be trivial, and may be of clinical and therapeutic importance. Generally, most surgeons will observe or monitor idiopathic ERMs until symptoms, vision, and/or structural alterations to the underlying retina warrant surgical intervention. With mild IU as present in our study, topical anti-inflammatory maintenance therapy may be sufficient.[20] Previous studies have shown that recurrent ERM may develop after iERM surgery in 10% to 21%,[21, 22] whereas only 2.78% of patients develop a new ERM after PPV for other retinal disorders.[23] This higher (10% to 21%) rate of recurrent ERM might suggest that other factors aside from the operation itself might be contributing to recurrence in these cases. We wondered whether the on-going subtle inflammation might be a contributor.

There was a limitation of the sample size is somewhat limited, particularly for eyes with idiopathic ERM in this study. Our study, however, was also the first to specifically describe differences between iERM and IU-ERM revealed by multi-color imaging.

Conclusion

In summary, multi-color imaging and OCT can be useful for more precisely mapping the morphology of ERMs, and the differences in ERM morphology might be helpful in aiding discrimination of the IU-ERM from the iERM.

Abbreviations

idiopathic epiretinal membrane, iERM; uveitis-associated epiretinal membrane, IU-ERM; optical coherence tomography, OCT; central foveal thickness, CFT; best-corrected visual acuity, BCVA; scanning laser ophthalmoscope, SLO; ultrasound biomicroscopy, UBM; the thickness of ciliary body at a position 1 mm posterior to the scleral spur, CBT1; ERM area, ERMA; central thickness of ERM, ERMT

Declarations

Ethics approval and consent to participate: All study procedures adhered to the tenets of the Declaration of Helsinki and were approved by the investigational review board of Ehtics Committee of Zhongshan Ophthalmic Center, Sun Yat-sen University (Guangzhou, China, 2018KYPJ054). All subjects signed informed consent for participation in this research.

Consent for publication: All athours are consent for publication.

Availability of data and materials: Not applicable.

Competing interests: There are no competing interests in this study.

Funding: This work was supported by grant from the National Natural Science Foundation of China to YAN LUO (81770971). They do not have any proprietary interests in the materials described in the article.

Authors' contributions: WX, LSF, LQH, MGY, LRY and CXY participated in data and picture collection, WX and LJ wrote the primary paper of this paper, LY and S. Sadda further revised this paper, LL and LY designed this study.

Acknowledgements: Not applicable.

References

1. Bu SC, Kuijer R, Li XR, Hooymans JM, Los LI: Idiopathic epiretinal membrane. *Retina* 2014, 34:2317–2335.

- 2.Liu L, Wang Y, Liu J, Liu W: Retinal-image quality and contrast sensitivity function in eyes with epiretinal membrane: a cross-sectional observational clinical study. *BMC Ophthalmol* 2018, 18:290.
- 3.Pierro L, Gagliardi M, Giatsidis S, Iuliano L, Berchicci L, Battaglia PM: Spectral-domain optical coherence tomography evaluation of vitreoretinal adhesions in idiopathic epiretinal membranes. *Graefes Arch Clin Exp Ophthalmol* 2014, 252:1041–1047.
- 4.Elbandary AM: Three-dimensional characterization of epiretinal membrane using spectral domain optical coherence tomography. *Saudi J Ophthalmol* 2010, 24:37–43.
- 5.Reibaldi M, Longo A, Avitabile T, Bonfiglio V, Toro MD, Russo A, Viti F, Nicolai M, Saitta A, Giovannini A et al: Transconjunctival nonvitrectomizing vitreous surgery versus 25-gauge vitrectomy in patients with epiretinal membrane: A prospective randomized study. *Retina* 2015, 35:873–879.
- 6.Yang HS, Hong JW, Kim YJ, Kim JG, Joe SG: Characteristics of spontaneous idiopathic epiretinal membrane separation in spectral domain optical coherence tomography. *Retina* 2014, 34(10):2079–2087.
- 7.Greven MA, Elkin Z, Nelson RW, Leng T: En Face Imaging of Epiretinal Membranes and the Retinal Nerve Fiber Layer Using Swept-Source Optical Coherence Tomography. *Ophthalmic Surg Lasers Imaging Retina* 2016, 47:730–734.
- 8.Aaberg TM: The enigma of pars planitis. *Am J Ophthalmol* 1987, 103:828–830.
- 9.Donaldson MJ, Pulido JS, Herman DC, Diehl N, Hodge D: Pars planitis: a 20-year study of incidence, clinical features, and outcomes. *Am J Ophthalmol* 2007, 144:812–817.
- 10.Raja SC, Jabs DA, Dunn JP, Fekrat S, Machan CH, Marsh MJ, Bressler NM: Pars planitis: clinical features and class II HLA associations. *Ophthalmology* 1999, 106:594–599.
- 11.Nicholson BP, Zhou M, Rostamizadeh M, Mehta P, Agron E, Wong W, Wiley H, Nussenblatt R, Sen HN: Epidemiology of epiretinal membrane in a large cohort of patients with uveitis. *Ophthalmology* 2014, 121:2393–2398.
- 12.Mitchell P, Smith W, Chey T, Wang JJ, Chang A: Prevalence and associations of epiretinal membranes. The Blue Mountains Eye Study, Australia. *Ophthalmology* 1997, 104:1033–1040.
- 13.Reznicek L, Dabov S, Kayat B, Liegl R, Kampik A, Ulbig M, Kernt M: Scanning laser ‘en face’ retinal imaging of epiretinal membranes. *Saudi J Ophthalmol* 2014, 28:134–138.
- 14.Saito M, Barbazetto IA, Spaide RF: Intravitreal cellular infiltrate imaged as punctate spots by spectral-domain optical coherence tomography in eyes with posterior segment inflammatory disease. *Retina* 2013, 33:559–565.

15. Sheybani A, Harocopos GJ, Rao PK: Immunohistochemical study of epiretinal membranes in patients with uveitis. *J Ophthalmic Inflamm Infect* 2012, 2:243–248.
16. Watanabe K, Tsunoda K, Mizuno Y, Akiyama K, Noda T: Outer retinal morphology and visual function in patients with idiopathic epiretinal membrane. *JAMA Ophthalmol* 2013, 131:172–177.
17. Yazici AT, Alagoz N, Celik HU, Bozkurt E, Alagoz C, Cakir M, Cekic O, Yilmaz OF: Idiopathic and secondary epiretinal membranes: do they differ in terms of morphology? An optical coherence tomography-based study. *Retina* 2011, 31:779–784.
18. Song SJ, Kuriyan AE, Smiddy WE: Results and prognostic factors for visual improvement after pars plana vitrectomy for idiopathic epiretinal membrane. *Retina* 2015, 35:866–872.
19. Kang KT, Kim KS, Kim YC: Surgical results of idiopathic and secondary epiretinal membrane. *Int Ophthalmol* 2014, 34:1227–1232.
20. Bonfioli AA, Damico FM, Curi AL, Orefice F: Intermediate uveitis. *Semin Ophthalmol* 2005, 20:147–154.
21. Park DW, Dugel PU, Garda J, Sipperley JO, Thach A, Sneed SR, Blaisdell J: Macular pucker removal with and without internal limiting membrane peeling: pilot study. *Ophthalmology* 2003, 110:62–64.
22. Sandali O, El SM, Basli E, Bonnel S, Lecuen N, Barale PO, Borderie V, Laroche L, Monin C: Epiretinal membrane recurrence: incidence, characteristics, evolution, and preventive and risk factors. *Retina* 2013, 33:2032–2038.
23. Tavolato M, Lo GG, Cian R, Galan A: Outcomes of 195 consecutive patients undergoing 2-port pars plana vitrectomy with slit-lamp illumination system for posterior segment disease: a retrospective study. *Retina* 2013, 33:785–790.

Figures

Figure 1

Measurement of ciliary body thickness by ultrasound biomicroscopy B-scan images. (A) Measurement of ciliary body thickness at 1 mm (CBT1) posterior to the scleral spur (black arrow). (B) Ciliary body of an eye with intermediate uveitis. Note the increase in thickness of the ciliary body and disruption of reflection from the retinal pigment epithelium (RPE, arrow). (C) Exudates were observed as irregular hyperdense material adherent to the surface of the ciliary body (arrow). (D) Ciliary body in a normal eye showed an intact and strong reflection from the overlying RPE (arrow). (E) Comparisons of CBT1 between iERM and IU-ERM. Paired-sample t-test, * $P < 0.05$.

Figure 2

Vitreous cells in OCT B-scans showing the low-grade intermediate uveitis in eyes. Note that vitreous cells in patients with IU-ERM (highlighted within gray rectangles) could be identified as hyperreflective dots in the vitreous that were larger and brighter compared to the background speckle noise.

Figure 3

The delineation of ERM boundary in a patient’s eye. In the flash white-light color photograph (A), the ERM is detectable, but its border was difficult to differentiate. Multi-color scanning laser ophthalmoscopic (SLO) image of the same eye more clearly depicted the ERM. Dotted line illustrated the manually segmented borders (B). Side-by-side comparison with the multi-color image of the ERM, the underlying structural OCT B-scans allowed the segmentation to be slightly refined to achieve more precise delineation of the ERM boundary (C).

Figure 4

Representative multi-color images of ERM from the two groups. The iERM were smaller (A) than the IU-ERM (B), with the comparisons of ERMA between iERM and IU-ERM (C), *P < 0.05.

Figure 5

The measurement for thickness of ERMT. (A) The grid was placed at the “center” of the ERM which was defined as the darkest point on the multi-color image. Applying a grid composed of four concentric circles with the radii of 200 μ m, 400 μ m, 600 μ m and 800 μ m in the multi-color image. (B, C) The ERMT was measured at the intersections between the circular grid lines and the OCT B-scans, amounting to a total of 29 points. (D) the comparisons of ERMT between iERM and IU-ERM, * $P \leq 0.05$.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [STROBEchecklistcrosssectional.doc](#)