• Letter to the Editor •

Two cases of lamellar macular hole secondary to the rupture of the cystoid inner wall in patients with diabetic macular edema

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Dear Editor,

Diabetic macular edema (DME) is a major cause of visual loss in diabetic patients, which is mainly caused by disruption of the blood-retinal barrier and loss of pericytes and endothelial cells, resulting in the leakage of plasma and lipids[1]. Nowadays, laser photocoagulation, intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) drugs and dexamethasone implant, as well as vitrectomy are used to treat DME[1]. DME complicated with lamellar macular hole (LMH) is relatively rare. Previous studies reported different outcomes of LMHs in patients with DME, *i.e.*, closure following anti-VEGF treatment[2]; occurred after DME treatment[2-3]; or spontaneous formation in persisted DME[4], suggesting a complicated relationship between LMH and DME with or without treatments. Here we report two cases of LMHs due to the rupture of the cystoid inner wall in two female patients with DME, who underwent intravitreal injections of anti-VEGF drugs.

Ethics Approval This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Clinical Research Ethical Committee of Shanghai General Hospital affiliated to Shanghai Jiao Tong University School of Medicine (Permit No.2023263). Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

CASE PRESENTATION

Patient 1 A 65-year-old female with diabetes mellitus complained of low vision in her left eye at her first presence in clinic. She had no history of ocular or major systemic surgeries. The Snellen best-corrected visual acuity (BCVA) was 20/200 in her left eye with the intraocular pressure of 12.5 mm Hg. There was a dense cataract in her left eye under the slit-lamp examination. The optical coherence tomography angiography (OCTA) revealed DME and a thin epiretinal membrane (ERM) with no obvious contraction in her left eye. The LMH, with a diameter of approximately 159 μm, was observed on OCTA with the consecutive b-scans, showing the rupture of the inner wall of the cyst (Figure 1A-1C, 1E). After 3 consecutive monthly intravitreal injections of conbercept, the closure of LMH was achieved with complete DME resolution and macular fovea restoration (Figure 1D, 1F). However, the BCVA at final follow-up was decreased to 20/400, which was believed to be the progression of cataract.

Patient 2 A 70-year-old female with diabetes mellitus presented low vision in left eye. There was no history of ocular or serious systemic surgeries. The BCVA was count finger/30 cm and intraocular pressure was 14.2 mm Hg in left eye. OCTA revealed DME, along with a large LMH with the diameter

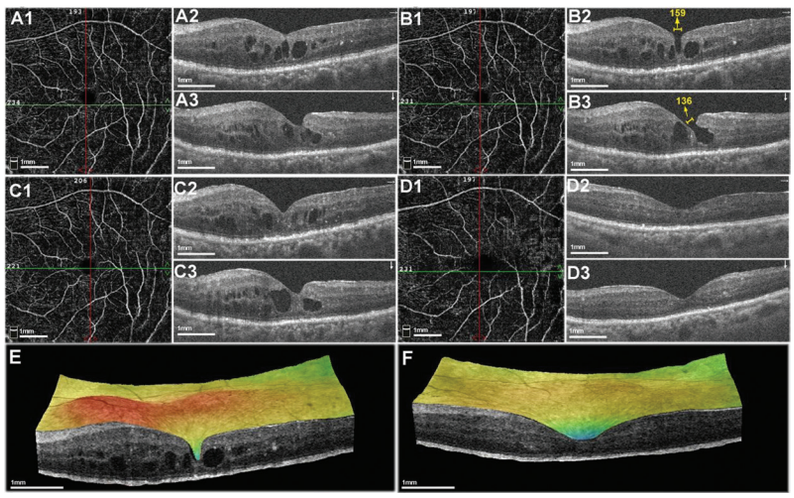

Figure 1 OCTA images (6×6 mm scan size) of patient 1 at baseline and after anti-VEGF treatments A1-C3: The consecutive changes of cystoid edema and LMH examined with OCTA images when segmented on superficial capillary plexus at baseline. A2, B2, C2 were B-scans of OCTA images acquired from green horizontal linear scans from A1, B1, C1, ranging from 234 to 231 and then to 221. The same situation also occurred in the red vertical linear OCTA scans of A3, B3, and C3, ranging from 193 to 197 and then to 206. The B-scans illustrated the dynamic changes of the cyst (A2, A3) until LMH formation with a diameter of approximately 159/136 μm (B2, B3), which was re-connected (C2, C3). Yellow line indicates the measured size for LMH. D1-D3 were OCTA images 3mo after treatment, showing disappearance of LMH and complete absorption of edema with no change on ERM. Three-dimensional images on OCTA showed the baseline (E) and after 3mo of treatment (F), demonstrating the improvements in DME and LMH. DME: Diabetic macular edema; ERM: Epiretinal membrane; LMH: Lamellar macular hole; OCTA: Optical coherence tomography angiography; VEGF: Vascular endothelial growth factor. Scale bar: 1 mm.

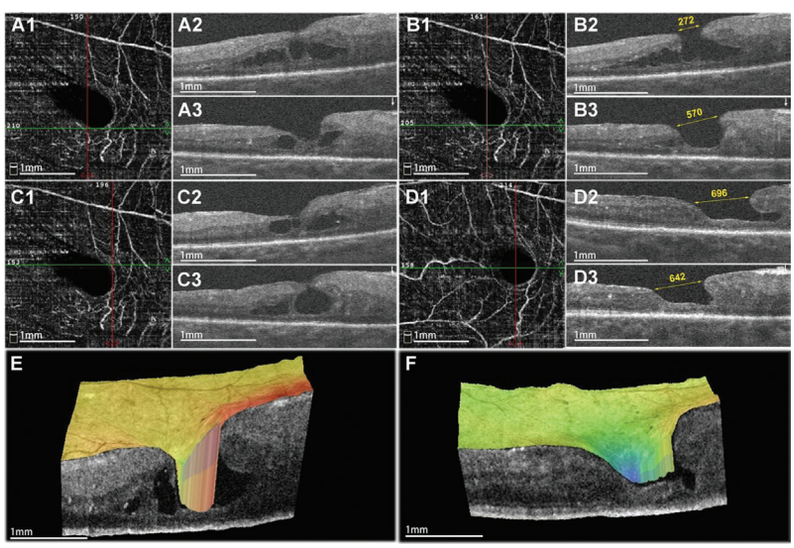

Figure 2 OCTA images (3 × 3 mm scan size) of patient 2 at baseline and after anti-VEGF treatment A1-C3 revealed the dynamic changes of cystoid edema and LMH examined with OCTA images when segmented on superficial capillary plexus at baseline. A2, B2, C2 were OCTA images obtained from green horizontal linear scans from A1, B1, C1, respectively. The scans ranged from 210 to 205 and then to 153. The same situation also occurred in the red vertical linear OCTA scans of A3, B3, and C3, with the scanning range from 150 to 161 and then to 196. These scans showed an impending inner wall rupture (A2, A3), leading to the formation of an LMH with a largest diameter of approximately 272/570 μm (B2, B3), which was re-connected (C2, C3). D1-D3 were OCTA images after 4mo of treatment, demonstrating an improvement of DME, although LMH persisted and increased in size. Yellow double arrow indicates the measured size of LMH. Three-dimensional images on OCTA showed the baseline (E) and after 4mo of treatment (F) by manual adjustment, showing the changes in DME and LMH. DME: Diabetic macular edema; LMH: Lamellar macular hole; OCTA: Optical coherence tomography angiography; VEGF: Vascular endothelial growth factor. Scale bar: 1 mm.

approximately 570 μm, in her left eye (Figure 2A-2E). No ERM was found. The macular edema was decreased and the BCVA improve to 20/400 after 4 consecutive intravitreal injections of conbercept, but the LMH remained unchanged (Figure 2F).

DISCUSSION

Macular hole (MH) and LMH are typically caused by vitreomacular traction or tangential vitreous cortex traction[5]. DME complicated with LMH is relatively rare, and researchers

have identified only a small number of cases of LMH combined with DME[2-4]. Shah and Bakri[2] and Querques *et al*[3] reported one case of LMH independently following intravitreal injection treatment for DME. Some scholars had found full-thickness MH after intravitreal injection therapy[6-7]. They indicated that the persistent chronic inflammation caused by diabetic retinopathy and the occurrence of ERM or posterior vitreous detachment after anti-VEGF treatment may result in the formation of MH. Although no full-thickness MH was present in any of our two cases, similar mechanisms might be extrapolated to the formation of LMH in our cases.

The LMHs are categorized into tractional and degenerative types according to morphological and pathophysiological features according to the recent publication[8]. Long-term DME and diabetic retinopathy will result in the cell damage, including Müller cell and adjacent neural cells necrosis due to continuous ischemia[9-10]. Defects in Müller cells and decreasing of ganglion cell layer lead to fragility of retinal lamellar structures, and horizontal traction caused by cystoid enlargement or shrinkage results in rupture of the cystoid inner wall, suggesting a major causal factor in LMH or MH[2,4]. In our study, in patient 1, there were no noticeable contraction signs and the ERM was thin (Figure 1), the contribution of ERM to the development of the LMH may be limited; while in patient 2, no ERM or posterior vitreous detachment was observed (Figure 2), which promoted us to hypothesize the degeneration or rupture, rather than the contraction, of the inner wall of the cyst might account for the formation of LMH in our cases. As for the dynamic change of LMH after intravitreal injection of anti-VEGF treatment, one patient demonstrated successful closure, which was consistent with the previous reports[2,11], while the other not even after consecutive intravitreal injection of anti-VEGF drugs. In patient 1, the closure of LMH might be due to the shrinkage of the cyst after anti-VEGF treatment, which connected the retinal tissues on both sides of the tiny hole and promoted the LMH repairment. The changes of LMH might depend on multiple factors, such as the baseline size of LMH, the duration of DME, the persistent edema, etc., which merits further exploration. The close of LMH may be more challenging and some need vitrectomy in those that do not respond well to anti-VEGF treatment or have large lamellar holes.

In conclusion, our study reported two cases of LMHs in DME patients with different outcomes after intravitreal injection of anti-VEGF drugs. Our findings suggested that smaller LMHs may result in the closure, while larger LMHs remained unchanged after anti-VEGF treatments.

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Data Availability Declaration: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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