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Epiretinal proliferation embedding combined with internal limiting membrane flap inversion for secondary macular hole: Two case reports

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ABSTRACT

Purpose: We describe the cases of two patients for whom we performed an epiretinal proliferation (EP) embedding technique combined with internal limiting membrane (ILM) flap inversion for a full-thickness macular hole (FTMH) with EP.

Observations: Patient 1 was a 69-year-old Japanese man with decreased vision in his left eye (20/40). He underwent pars plana vitrectomy (PPV) twice for rhegmatogenous retinal detachment and intraocular lens (IOL) dislocation in his left eye. B-scan optical coherence tomography (OCT) imaging revealed FTMH and EP on the surface of a macular hole (MH). We performed a vitrectomy, EP embedding, and ILM inversion (fill). Patient 2 was a 73-year-old Japanese man with decreased vision in his right eye (20/32). He underwent PPV for vitreous hemorrhage and proliferative diabetic retinopathy in his right eye. B-scan OCT imaging revealed FTMH and EP on the surface of an MH. We performed a vitrectomy, EP embedding, and ILM inversion (cover). Six months post-surgery, the FTMH in both patients had closed completely, and each patient's foveal contour and visual acuity (20/20) had improved.

Conclusions and importance: EP embedding combined with ILM flap inversion may be effective for treating secondary MHs with EP.

1. Introduction

Many cases of the proliferation of epiretinal tissue that is distinct from the epiretinal membrane (ERM) have been observed accompanying lamellar macular holes (LMHs).[1–8] Epiretinal proliferation (EP) tissue was first described by Witkin et al. in 2006 as a thick membrane seen on ultra-high-resolution optical coherence tomography (OCT).[2] EP was also reported to be associated with LMHs, full-thickness macular holes (FTMHs), and the ERM. Pang, Spaide, and Freund termed this finding "lamellar hole-associated epiretinal proliferation" or "LHEP."[9] EP and LHEP are the same concept, but in recent years the term EP has been used for both because such tissue is found in diseases other than LMH."

The technique in which LHEP tissue was "embedded" into the retinal cleavage of a degenerative LMH was first reported in 2013.[8] Later authors sometimes describe the technique as "plugging." It has also been suggested that LHEP tissue can safely be used as a material for autologous transplantation to an FTMH.[10,11]

In addition, one paper has previously described the effectiveness of combining the LHEP embedding technique with internal limiting membrane (ILM) inversion for an LMH with LHEP.[12] Below, we describe two cases of patients with an FTMH for whom we performed the EP embedding technique combined with ILM flap inversion.

2. Case reports

2.1. Patient 1

A 69-year-old Japanese man presented with decreased vision in his left eye. The duration of symptoms was 2 weeks. The best-corrected visual acuity (BCVA) was 20/40, and slit-lamp examination revealed an intraocular lens (IOL). Fundus photography and optical coherence tomography (OCT) revealed an FTMH with EP (Fig. 1a and b). Twelve years earlier, the patient had undergone simultaneous phacoemulsification, IOL implantation, and pars plana vitrectomy (PPV) for rhegmatogenous retinal detachment in his left eye. Three years before he came to our institute, he had undergone IOL extraction and intrascleral IOL fixation for IOL dislocation in his left eye.

We performed a PPV with EP embedding and ILM inversion (fill) in

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his left eye. In the operation, a 25-gauge micro-incision vitrectomy was conducted using an EVA system (D.O.R.C., Zuidland, Netherlands). Brilliant blue G (BBG) ophthalmic solution was sprayed before macular processing. The EP was centripetally peeled off of the retina with the use of intraocular forceps and was left attached to the edge of the macular hole (MH) (Fig. 2a).

BBG solution was sprayed again, and the ILM was peeled from the periphery toward the MH. During this peeling, the ILM was not completely removed from the retina but was instead left attached to the edge of the MH (Fig. 2c and d). The ILM was trimmed with a vitreous cutter (Fig. 2e). The remaining EP and ILM were embedded in the MH with the use of intraocular forceps (Fig. 2f). At the end of the surgery, fluid-air exchange was performed, and the vitreous cavity was filled with 20% sulfur hexafluoride (SF_6) gas. The patient remained in the prone position for 1 hr after the surgery.

Two weeks after the surgery, the MH had completely closed (Fig. 1c and d). At 3 months after the surgery, the external limiting membrane (ELM) and ellipsoid zone (EZ) had recovered (Fig. 1g and h). Six months after the surgery, a continuous ELM was identified (Fig. 1i and j).

The patient was followed up for 6 months postoperatively. At that time, his visual acuity had improved to 20/20, and no complications were observed.

2.2. Patient 2

A 73-year-old Japanese man presented with decreased vision in his right eye. The duration of symptoms was 2 months. The BCVA was 20/32, and slit-lamp examination revealed an IOL. Fundus photography and OCT revealed an FTMH with EP (Fig. 3a and b). Four years earlier, the patient had undergone simultaneous phacoemulsification, IOL implantation, a PPV, and pan-retinal photocoagulation for vitreous hemorrhage and proliferative diabetic retinopathy in his right eye. We performed a PPV with EP embedding and ILM inversion (cover) in his right eye.

The same procedure as that described for Patient 1 was performed, except for the ILM peeling process. After EP peeling and trimming by a vitreous cutter (Fig. 4a and b) and the second spraying of BBG solution, a two-disc-diameter inferior area of the ILM was peeled off completely (Fig. 4c). The EP was embedded in the MH using intraocular forceps

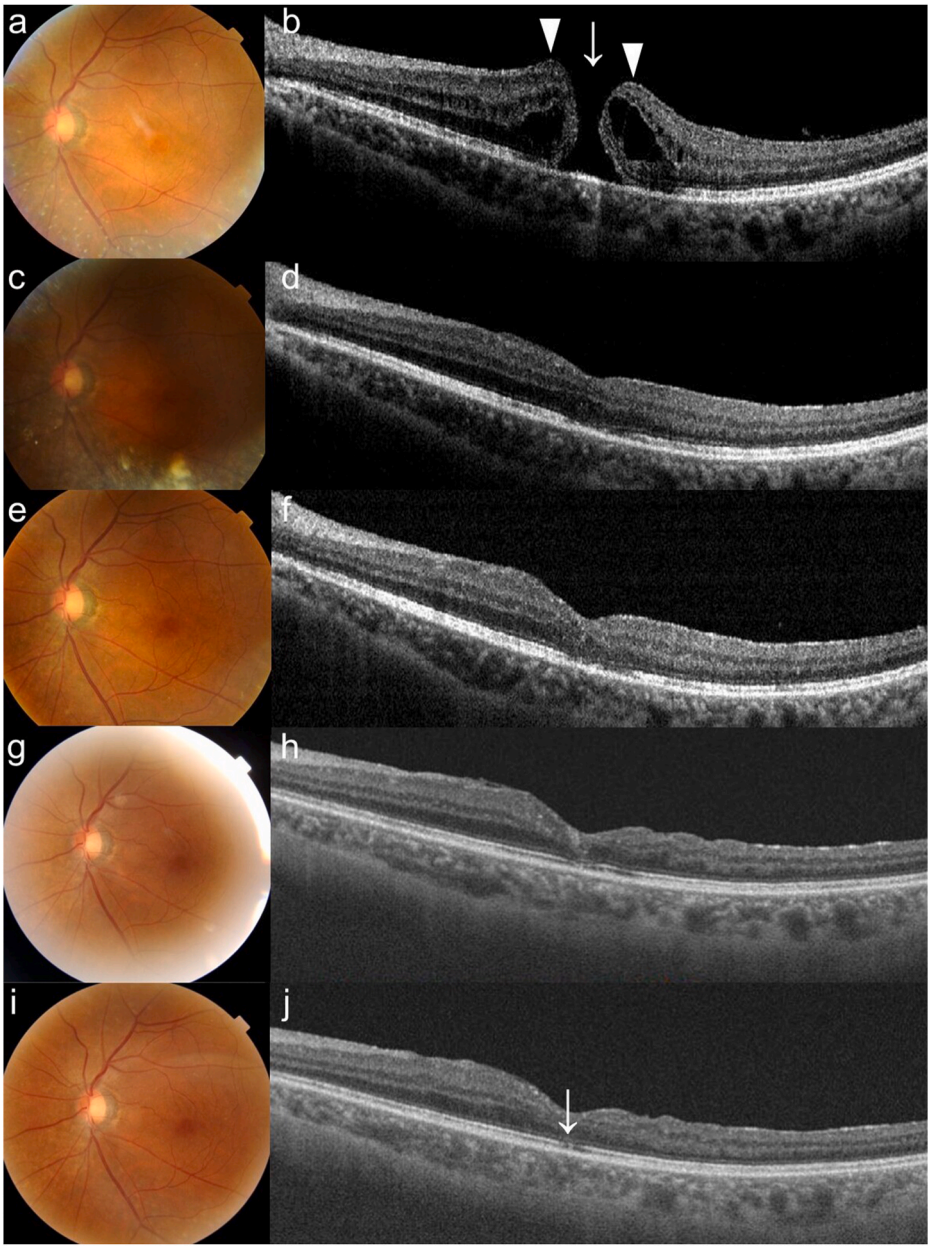

Fig. 1. Preoperative and postoperative fundus photographs and OCT images of Patient 1's left eye. **a,b:** Preoperative images. The best-corrected visual acuity (BCVA) was 20/40. Optical coherence tomography (OCT) imaging showing the full-thickness macular hole (FTMH) (*white arrow*, **b**) and epiretinal proliferation (EP) (*arrowheads*, **b**). **c, d:** At 2 weeks post-surgery, the BCVA was 20/25. The macular hole (MH) had completely closed. **e,f:** At 1 month post-surgery, the BCVA was 20/20. **g,h:** At 3 months post-surgery, the BCVA was still 20/20. The external limiting membrane (ELM) and ellipsoid zone (EZ) had recovered gradually. **i,j:** At 6 months post-surgery, the BCVA remained 20/20. A continuous ELM (*white arrow*, **j**) was identified.

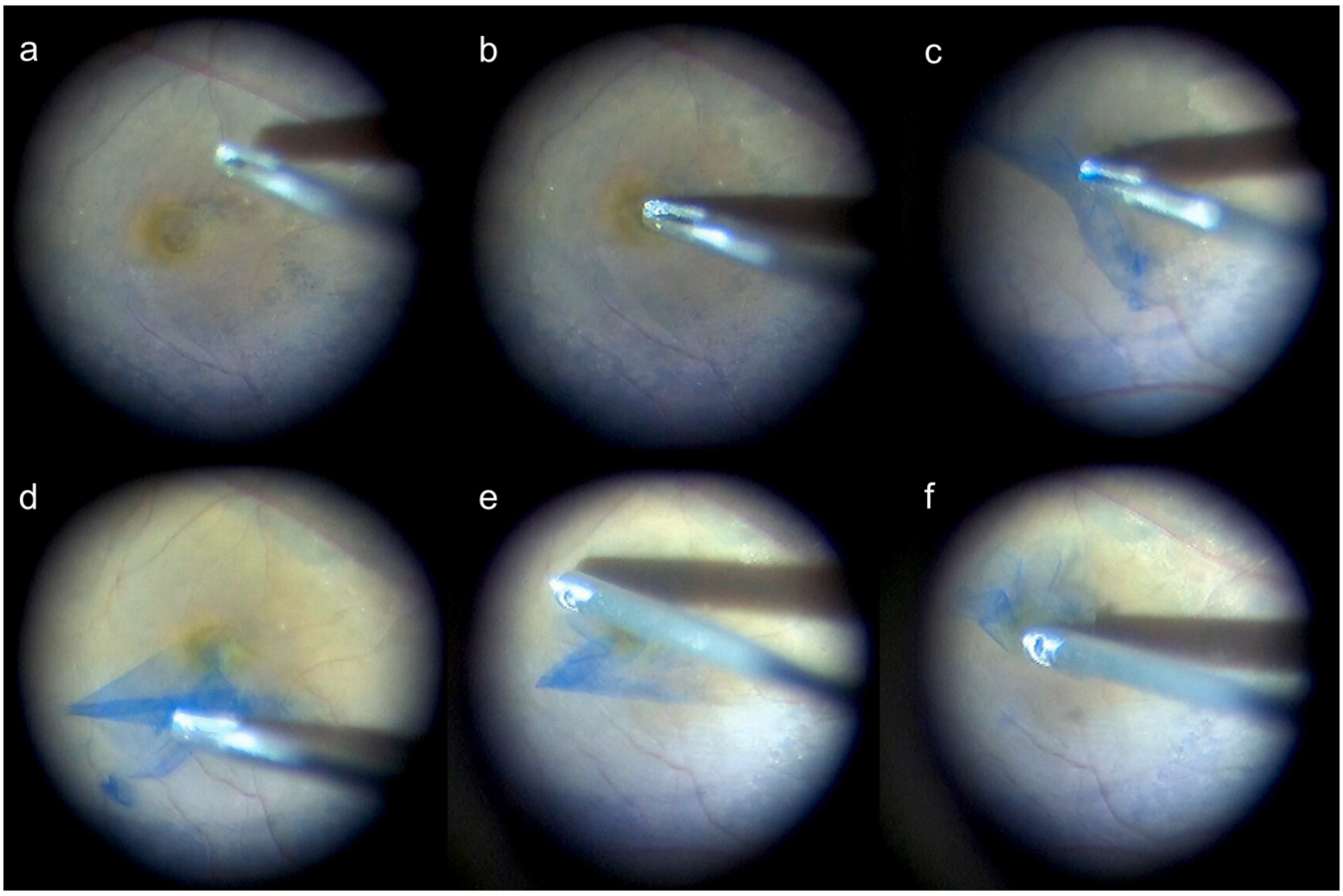

Fig. 2. Intraoperative photographs of EP embedding combined with ILM fill inversion for the treatment of an FTMH. **a:** The EP was centripetally peeled off of the retina with intraocular forceps and was left attached to the edge of the MH. **b:** The EP was embedded in the MH with intraocular forceps. **c,d:** The ILM was peeled from the periphery toward the MH and was not completely removed from the retina but was instead left attached to the edge of the MH. **e:** The ILM was trimmed by a vitreous cutter. **f:** The remaining EP and ILM were embedded in the MH again with intraocular forceps.

(Fig. 4d). The superior area of the ILM was peeled off circumferentially and was left attached to the edge of the MH. The superior ILM flap was then inverted from the upper to lower direction so that it completely covered the MH with the embedded EP (Fig. 4e). Sodium hyaluronate-chondroitin sulphate (Viscoat; Alcon Laboratories, Fort Worth, TX, USA) was placed on the inverted ILM in order to stabilize the flap (Fig. 4f). At the end of the surgery, fluid-air exchange was performed, and the vitreous cavity was filled with 20% SF_6 gas. The patient remained in the prone position for 1 hr after the surgery.

Two weeks post-surgery, the MH was completely closed (Fig. 3c and d). At 3 months after the surgery, the ELM and EZ had recovered (Fig. 3g and h). A continuous ELM and EZ were identified 6 months post-operatively (Fig. 3i and j). The patient was followed up for 6 months. His visual acuity improved to 20/20, and no complications were observed.

3. Discussion

Pang reported that spectral domain optical coherence tomography (SD-OCT) imaging detected EP in 8 of 99 eyes (8.0%) with FTMH.[9] Lee reported the SD-OCT detection of EP in 30 of 113 eyes (26.5%) with FTMH.[13] Macular holes with EP are associated with more advanced FTMH stages and with the presence of an ERM, and patients with these features achieved significantly less improvement in BCVA, with higher rates of EZ and ELM defects and a higher rate of failure to close compared to patients with macular holes without EP.[13] However, it has also been reported that the closure rates and postoperative BCVA were not significantly different between MH patients with and without EP.[14] When taking the outer retina into account, cases of macular holes with EP showed worse postoperative BCVA and a higher frequency of disrupted continuity of ELM and EZ compared to MH cases without EP.[15] In light of these results, the preoperative presence of EP may be inversely associated with the postoperative functional and morphological outcomes.

Lamellar macular holes (LMHs) usually remain stable over time. Very few evolve into an FTMH,[2,4,16–18] and the pathogenesis of LMH progression to FTMH is poorly understood. Macular holes that progress from LMH have frequently been reported to have EP,[16,19] and macular holes with EP, as mentioned, are associated with more advanced FTMH stage (typically stage 4 or 5).[13,14] These reports indicate that the formation of MH with EP may not be associated with PVD as opposed to idiopathic MH, which is caused by PVD. The pathogeneses of LMH and MH with EP may therefore be identical. It was suggested that epiretinal proliferative tissue can be safely used as a material for autologous transplantation to an FTMH.[10,11]There are many reports showing the efficacy of EP embedding for LMHs, but the efficacy of EP embedding for macular holes with EP is not yet clear.

On rare occasion, FTMH have been reported to occur to patients after PPV.[20–23] FTMH that develops after PPV occurs despite the absence of vitreomacular traction as in PVD. Furthermore, the two cases presented here were FTMH with EP. These cases suggest that the mechanism may be similar to that of FTMH progressing from LMH.

The inverted ILM flap technique has been shown to increase the success rate in large FTMHs, in FTMHs associated with high myopia, and in refractory FTMH.[24] However, this technique may delay the recovery of the outer retinal layer compared to the conventional ILM peeling technique.[25] Poorer anatomical and visual results have been associated

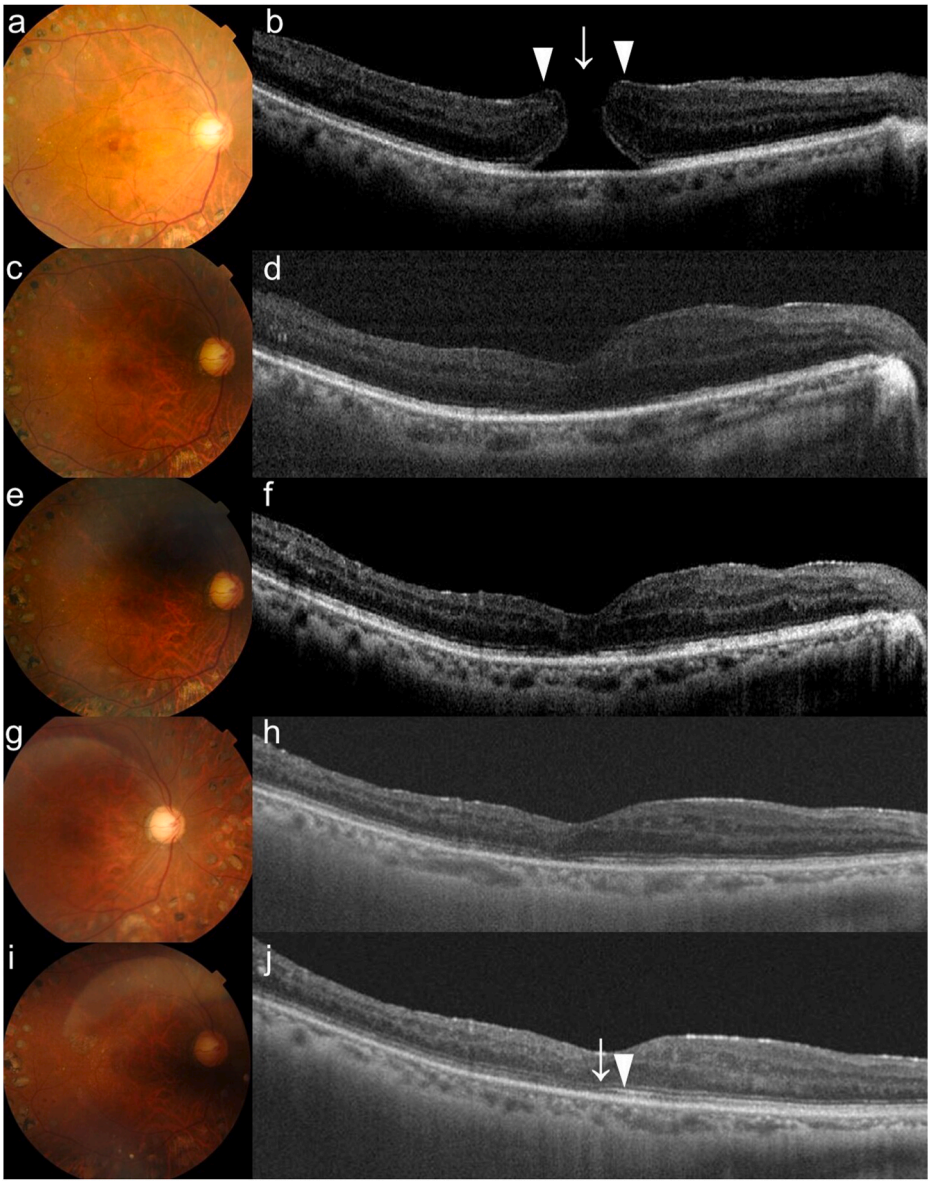

Fig. 3. Preoperative and postoperative fundus photographs and OCT images of Patient 2's right eye. **a,b:** Preoperative images. The BCVA was 20/32. OCT imaging showing the FTMH (*white arrow*, **b**) and EP (*arrowheads*, **b**). **c,d:** At 2 weeks post-surgery, the BCVA was 20/32. The MH had completely closed. **e,f:** At 1 month post-surgery, the BCVA was 20/25. **g,h:** At 3 months post-surgery, the BCVA was 20/25. The ELM and EZ had recovered. **i,j:** At 6 months post-surgery, the BCVA was 20/20. A continuous ELM (*white arrow*, **j**) and EZ (*arrowheads*, **j**) were observed.

with inverted ILM flap compared with ILM peeling.[26] The filling of the MH by an ILM flap may promote glial hypertrophy in the space that should be filled with retinal neurons and may inhibit extension of the ELM and EZ.[25]

EP embedding has shown good visual improvement and EZ recovery in patients with LMH[27] whereas EP removal can mechanically damage the retinal tissue. Pang et al. reported that one of the major constituents of the EP is glial cells migrating from the middle layers of the retina.[9] EP tissue becomes integrated with the retinal tissue at the edge of the foveal aperture in LMH and cannot be removed easily from the retina as can a normal ERM. At present, the mechanism of EZ recovery is unknown. It also has been reported that removal of EP tissue does not improve visual function in LMH[28] and increases the risk of developing a FTMH post-operatively.[2,6] EP tissue is thought to promote closure of the hole and initiate photoreceptor cell rearrangement, resulting in EZ recovery. These previous findings suggest that in MH with EP, embedding without removal of EP may have better anatomic and visual outcomes than performing the inverted ILM flap technique alone. EP may promote photoreceptor recovery and even protect photoreceptor cells from the abnormal glial cell proliferation that is associated with ILM flap inversion.

There is one prior case report that describes embedding of the LHEP in combination with ILM inversion for LMH.[12] In the present two cases we applied this combination of surgical techniques to MHs with EP, and the patients achieved good outcomes. These positive outcomes may be due to the following: (1) combining the techniques makes it more likely that the EP that is embedded in the macular hole is kept in place by the inverted flap during the fluid-gas exchange, and (2) the inverted ILM flap might facilitate the healing effects of the embedded EP on the macula.[12] In a monkey model, the ILM, which is the basement membrane of Müller cells, functioned as a scaffold to promote the proliferation and migration of glial cells, and the activated glial cells produced various neurotrophic factors as well as basic fibroblast growth factor (bFGF).[29] It is thus reasonable to speculate that in our patients, the inverted ILM might have acted as a scaffold of embedded glial cells and facilitated the repair process of the macula by glial cells.

There are several limitations to this report. We describe only two cases. The follow-up periods were short (6 months), and it is possible that longer-term follow-ups would reveal the recurrence of EP or ERM. There is also a risk that an excessive proliferation of glial cells and an inverted ILM may occur, with the possibility of worse visual function.

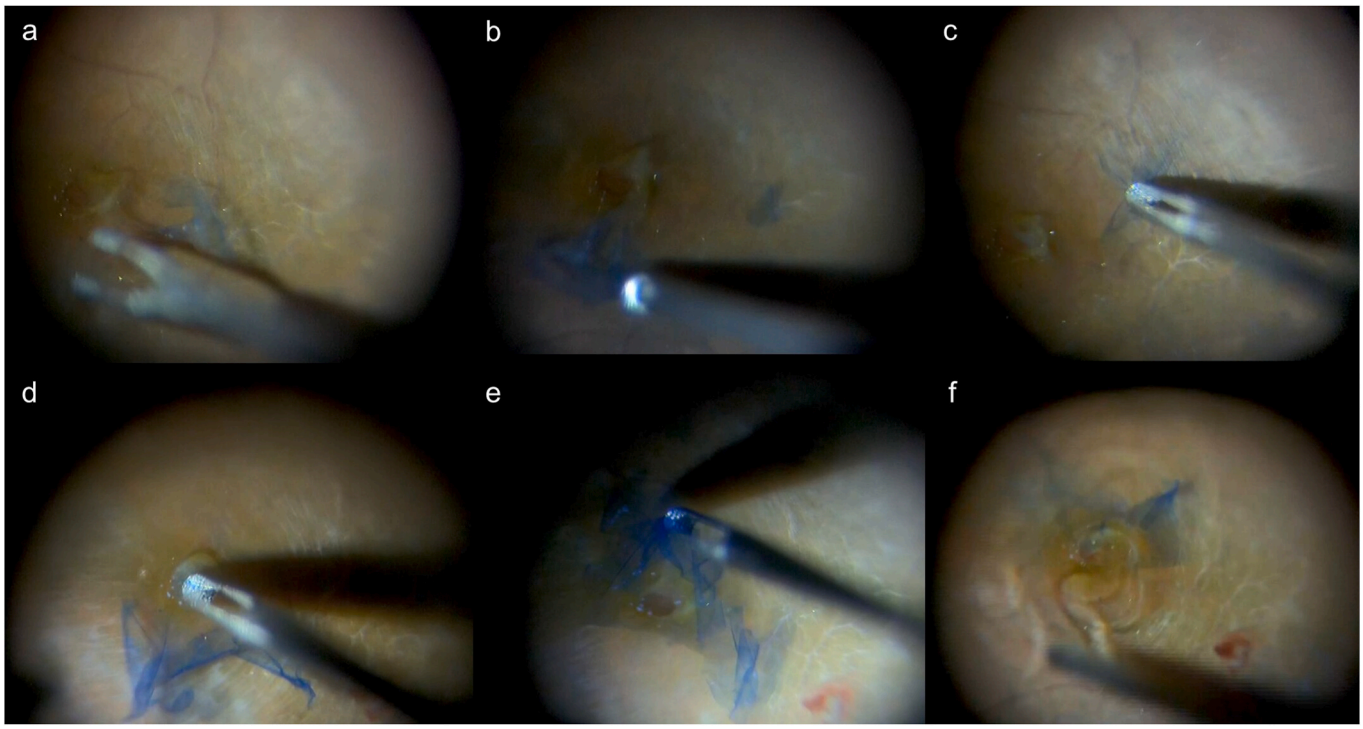

Fig. 4. Intraoperative photographs of epiretinal proliferation (EP) embedding combined with internal limiting membrane (ILM) cover inversion for the treatment of a full-thickness macular hole. **a:** The EP was centripetally peeled off of the retina with intraocular forceps and was left attached to the edge of the macular hole (MH). **b:** The EP was trimmed by a vitreous cutter. **c:** The two-disc-diameter inferior area of the ILM was peeled off completely. **d:** The EP was embedded in the MH with the use of intraocular forceps. **e:** The superior ILM flap was inverted from the upper to the lower direction so that it completely covered the MH with the embedded EP. **f:** Sodium hyaluronate-chondroitin sulphate (Viscoat) was placed on the inverted ILM in order to stabilize the flap.

4. Conclusions

The present two cases suggest that combining the EP embedding technique with ILM flap inversion might be an effective treatment for macular holes with EP. Further prospective studies involving a larger number of patients are required to establish the efficacy of this technique.

Ethics approval

This report was approved by the ethics committee at Takaoka City Hospital.

Patient consent

The patients provided their written informed consent prior to undergoing surgery and for inclusion in this case report.

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Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

Declaration of competing interest

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