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Proliferative gliosis, a rare finding following multilayered inverted internal limiting membrane flap technique for concurrent macular hole and retinal detachment: Case series

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Claims of priority

After conducting a literature review on the September 20, 2024 utilizing PubMed, Google Scholar and Scopus, using the keywords (macular pucker; internal limiting membrane flap contraction; macular hole with concurrent retinal detachment; glial proliferation) we did not find any prior reports.

1. Introduction

Rhegmatogenous retinal detachment (RRD) with a concomitant macular hole (MH) is a rare association, with an estimated incidence of 2%.[1–3] It is a different entity from a macular detachment in high myopic patients, where a peripheral break is not present.[4] Proliferative vitreoretinopathy (PVR) remains the main risk factor for RRD with concurrent MH.[1–3] The advent of internal limiting membrane (ILM) peeling during vitrectomy has significantly improved MH closure rates, witnessing an increase from around 33% without it to between 77 and 90 % after its implementation.[3,5] The emergence of ILM inverted flaps for this indication has been associated with significant improvement of anatomical and visual outcomes.[6] However, complications related to the flap glial proliferation have poorly been described before.

We report two novel cases of proliferative gliosis (PG)-type of MH closure, following the multilayered inverted (MLI) ILM flap technique, for the management of MH concomitant with RRD. Additionally, we include 3 control cases that benefited from the same technique with favorable macular hole closure.

We reviewed the medical records of 10 cases of RRD with a concomitant macular hole operated at Oued Eddahab Military Hospital, which underwent the MLI ILM flap technique between September 2021 and August 2023. All of the cases demonstrated closure of the macular hole. 8 of the cases underwent nonexpansile gas tamponade and presented a U-shape or V-shape macular hole closure type, whereas the 2 remaining cases that underwent silicon oil tamponade showed a PG MH closure type. After conducting a literature review on the September 20, 2024 utilizing PubMed, Google Scholar, and Scopus, using the keywords (macular pucker; internal limiting membrane flap contraction; macular hole with concurrent retinal detachment; glial proliferation) we did not find any prior reports. In this report, we describe the clinical course of 2 patients operated by Y.M. who presented PG-type closure and 3 others who did not.

The MLI ILM flap technique (Fig. 1) was performed following a core vitrectomy, induction of a posterior vitreous detachment and vitreous base shaving, all while stabilizing the macula with perfluorocarbon liquid (PFCL). The ILM was positively stained by injecting Brillant Blue G (BBG) dye under the PFCL. Subsequently, multiple continuous triangular-shaped ILM flaps were meticulously fashioned, starting inferiorly and proceeding sequentially to nasal, superior, and temporal locations. These flaps remained anchored to the MH borders at their base, and were bridged one over the other in front of the MH to create a multistratified envelope that did not dislodge after the PFCL removal. The remaining ILM was peeled extensively up to the temporal arcades.

Case 1. A 63-year-old female presented to our ophthalmology department, reporting a sudden painless vision loss in her right eye (RE) persisting for 35 days. The patient's general history was unremarkable. She was myopic and underwent an uneventful phacoemulsification in her RE one year ago. On examination, her best corrected visual acuity (BCVA) was hand motion in the RE, and 20/20 in the left eye. Anterior segment examination of the RE revealed a mild conjunctival congestion, a positive Tyndall sign, and an intraocular lens implanted into the capsular bag with posterior capsule opacification.

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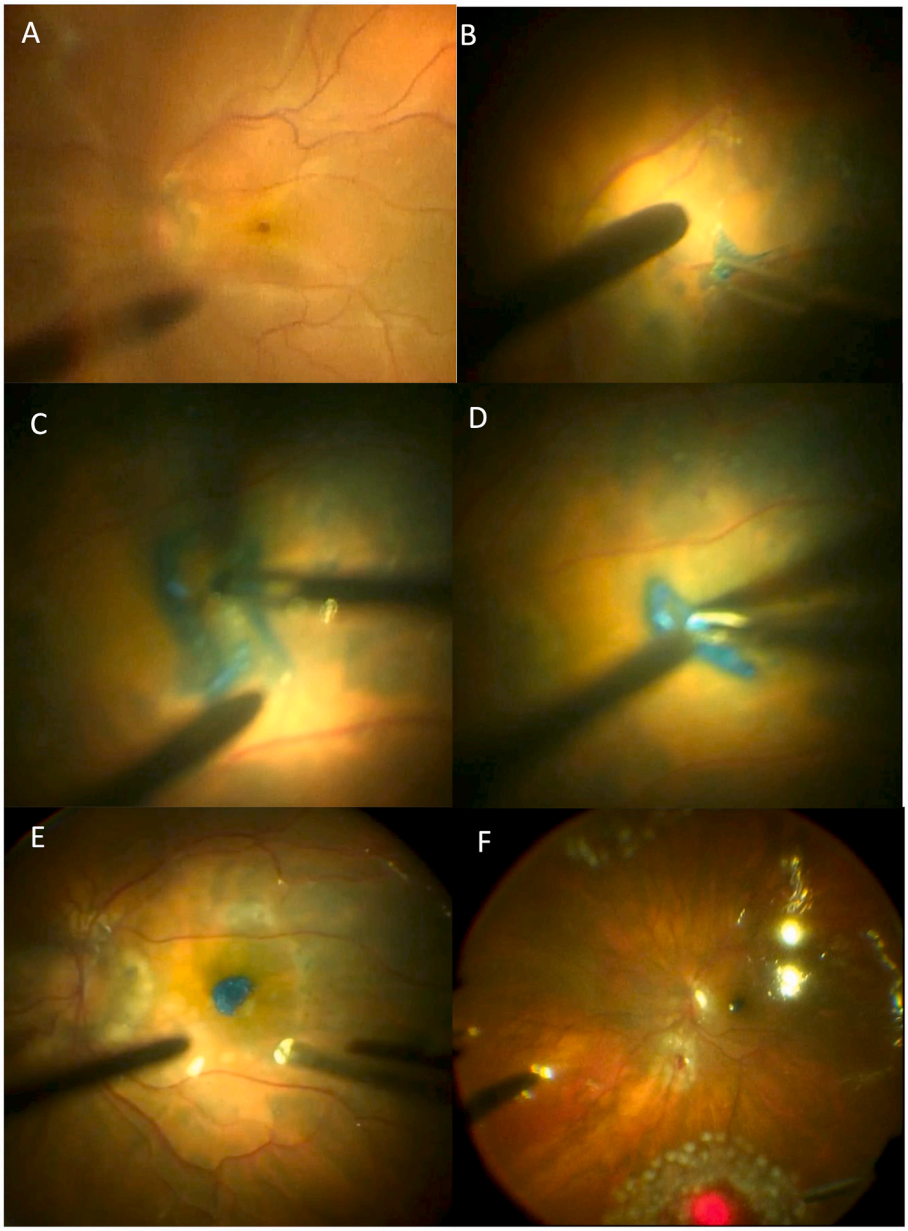

Fig. 1. Case 1 Intraoperative image of pars plana vitrectomy and Multilayered inverted (MLI) internal limiting membrane (ILM) flap technique. A: Intraoperative view of the rhegmatogenous retinal detachment with macular hole after completing the core and peripheral vitrectomy. B: ILM peeling with 23-gauge end gripping forceps starting with a pinch and peel technique next to the inferior temporal arcade, and grabbing the ILM tangentially by its free edge under Perfluorodecalin. C: Rolled-free edges of the ILM are visible while the forceps is grabbing its temporal side. D: Completion of a circumferential envelope MLI ILM flap technique. E: The MLI ILM flap is covering the macular hole without being tucked in it. F: Attached retina under air without displacement of the MLI ILM flap.

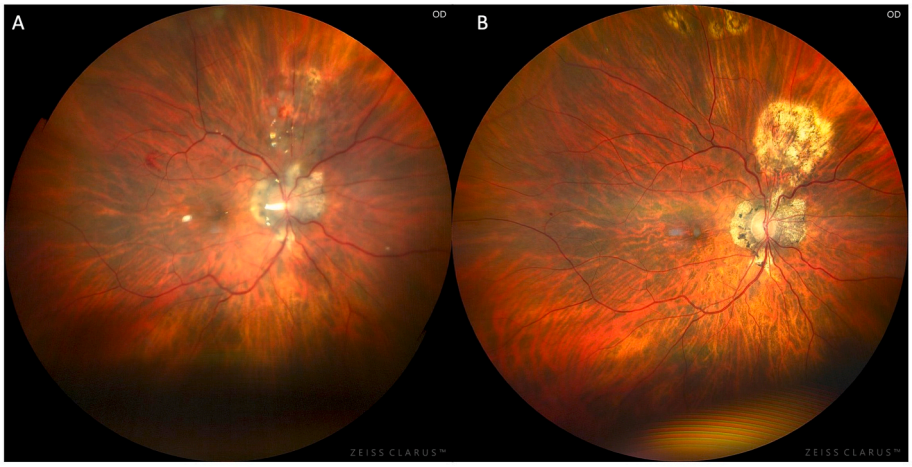

Fig. 2. Case 1 Widefield Retinography (WR). A: Immediate postoperative fundus retinography revealing a complete attached retina under silicon oil. B: WR following silicon oil removal showing a complete attached retina, superonasal laser retinopexy scars, and a grey macular proliferative gliosis (Clarus, Zeiss, Jena, Germany).

Dilated fundus examination unveiled a total rhegmatogenous retinal detachment, macula-off, with grade B proliferative vitreoretinopathy (PVR), a macular hole, and three retinal breaks: one posterior parapapillary, one at 5 o'clock, and one at 12 o'clock. The axial length measured by B-ultrasound was 26 mm. Management consisted of a 23-gauge pars plana vitrectomy. Following posterior vitreous detachment, a complete central and peripheral vitrectomy (Fig. 1A) was performed, along with staining of the ILM with 0.025% Brilliant Blue G (Brilliant Peel, Fluoron, Germany) under perfluorodecalin liquid (DK-Line, Bausch Lomb, USA) (PFCL) to stabilize the macula, resulting in positive staining that confirmed the absence of any epiretinal membrane (ERM).

The multilayered envelope technique was then performed, starting by pinching and peeling off the ILM next to the inferior arcade under the PFCL (Fig. 1B). The triangular-shaped free edge was grasped multiple times (Fig. 1C) in a circumferential pattern (Fig. 1D). The MLI ILM flap was left attached to the rim of the MH, covering it without being tucked in (Fig. 1E). PFCL was carefully removed to avoid displacing the flaps, followed by a complete fluid-air exchange, resulting in retinal reattachment (Fig. 1F). Three confluent rows of laser retinopexy were performed around the breaks. Silicon oil 1300 centistoke (Oxane, Bausch + Lomb, USA) was used as an endotamponade.

One week postoperatively, the retina was completely attached (Fig. 2A), and B-Scan Swept-Source Optical Coherence Tomography (OCT) (Fig. 3A) showed a closed macular hole covered by hyperreflective strands corresponding to the MLI ILM. BCVA was 20/63. One month after surgery, the patient reported distortion in vision, with an unchanged BCVA of 20/63. OCT B-scan (Fig. 3B) revealed a thickened hyperreflective multilayered proliferation over the macula, corresponding to the area of the previous MLI ILM flaps, leading to a presumed diagnosis of proliferative gliosis.

At 3 months, the SS-OCT B-scan (Fig. 3C) indicated a thickening and migration of the proliferative gliosis from the epiretinal space into the intraretinal space, with a dome-shaped appearance. This was accompanied by a decrease in BCVA to 20/100. Silicon oil was removed, but the peeling of the PG failed due to strong adhesions. Postoperative widefield retinography at 7 months (Fig. 2B) demonstrated a completely attached retina, with a grey macular proliferation. OCT B-scan (Fig. 3D) revealed an ogival intraretinal gliosis, fully incorporated into the retinal layers, with hyperreflective dots, and a nasal hyperreflective band going from the inner retinal layers toward the RPE. BCVA was 20/100 at a 7-month follow-up and remained unchanged at 12 months.

Case 2. A 58-year-old phakic myopic male presented to our ophthalmology department with acute vision loss in his RE over the past 2 weeks. The patient denied any ocular trauma. Ophthalmic examination revealed a BCVA of hand motion in the RE and 20/20 in the LE, with a Tyndal sign. Widefield retinography revealed a total RRD, with a MH and numerous retinal breaks all along the superior arcade (Fig. 4A), with a grade B PVR. The axial length measured by B-Ultrasound was 25 mm.

Management consisted of a 23-gauge lens sparing pars plana vitrectomy, with the creation of a MLI ILM flap as described in the first case, followed by a fluid-air exchange, laser retinopexy, and 1300 cSt silicon oil (Oxane, Bausch + Lomb, USA) tamponade. The first week fundoscopy revealed a complete attached retina (Fig. 4B), with MH closure confirmed on the OCT B-scan (Fig. 4C). One month postoperatively, BCVA was 20/100 and the retina remained attached under silicon oil. The OCT B-scan (Fig. 4D) revealed a hyperreflective proliferative gliosis MH closure type, characterized by intralesional hyperreflective dots, and discontinuation of inner and outer retinal layers. The patient was lost to follow-up.

Case 3. A 66-year-old pseudophakic female was referred to our facility for a chronic RRD of her RE. Examination revealed a BCVA of hand motion in the RE and 20/20 in the LE. There was no evidence of anterior segment inflammation on the RE during the slit lamp examination. Widefield retinography showed a total RRD (Fig. 5A) with a MH (Fig. 5B), grade C PVR with a temporal starfold, and an inferotemporal retinal break. The axial length measured by B-Ultrasound was 21 mm. Management consisted of a 23-gauge pars plana vitrectomy, peeling of the PVR membranes, followed by a MLI ILM flap for the MH, fluid-air exchange, laser retinopexy, and 14% C3F8 gas tamponade. The OCT B-scan at the 1-month follow-up showed a U-shape macular hole closure (Fig. 5C), and a 3-month widefield retinography revealed a completely attached retina (Fig. 5D). The final BCVA was 20/200.

Case 4. A 59-year-old phakic male presented to the ophthalmology department with acute vision loss in his left eye for the past 10 days. Ophthalmic examination revealed a BCVA of 20/20 in his RE and counting fingers in his LE. Widefield retinography revealed a RRD extending from 1 to 11 o'clock (Fig. 6A), with a macular hole (Fig. 6B) and a superonasal break. The axial length measured by B-Ultrasound was 22 mm. Management consisted of a 23-gauge pars plana vitrectomy with a MLI ILM flap for the MH (Fig. 6C), fluid-air exchange, laser retinopexy, and 14% C3F8 gas tamponade. OCT B-scan at the 1-month follow-up showed a U-shape macular hole closure with a residual flap still visible over the fovea, without any significant PG (Fig. 6D). Two-month widefield retinography revealed a completely attached retina (Fig. 6E). The final BCVA was 20/80.

Case 5. A 62-year-old pseudophakic high myope female presented to the emergency department with acute vision loss in her right eye for the

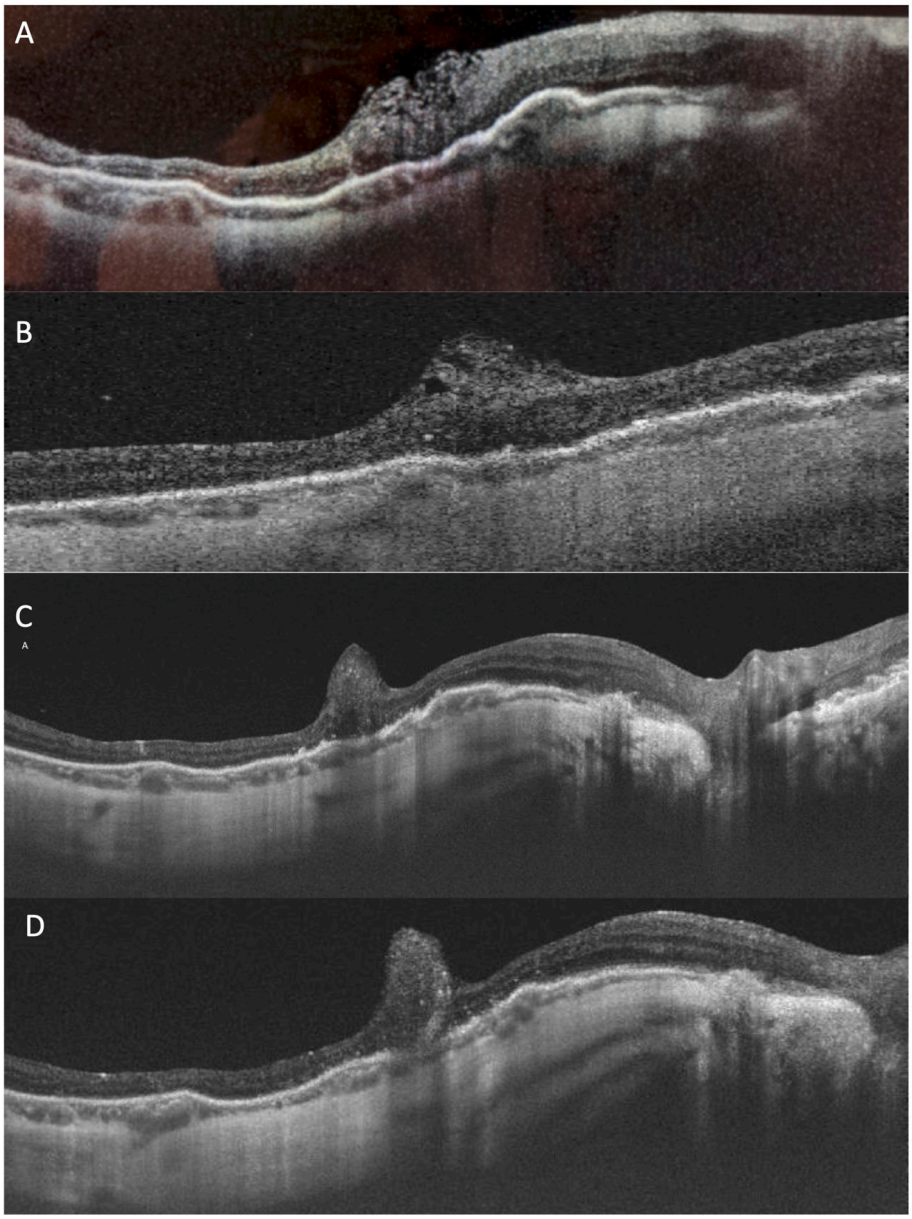

Fig. 3. Case 1 Horizontal B-Scan Swept-source Optical Coherence Tomography timeline. A: Image acquired one week after the surgery showing an attached retina, with the macular hole closed and overlayed with the multiple ILM flaps. B: Image acquired one month after surgery demonstrating a thickened hyperreflective multilayered proliferation over the macula, corresponding to the area of the previous MLI ILM flaps with some intraproliferative and intraretinal hyperreflective foci. C: Image acquired at 3 months after surgery, showing a thickening and migration of the proliferative gliosis from the epiretinal space into the intraretinal space, with a dome-shaped appearance. D: Image acquired after silicon oil removal revealing an ogival intraretinal gliosis, fully incorporated into the retinal layers, with hyperreflective dots, and a nasal hyperreflective band in continuation with the RPE. (Triton, Topcon, Japan).

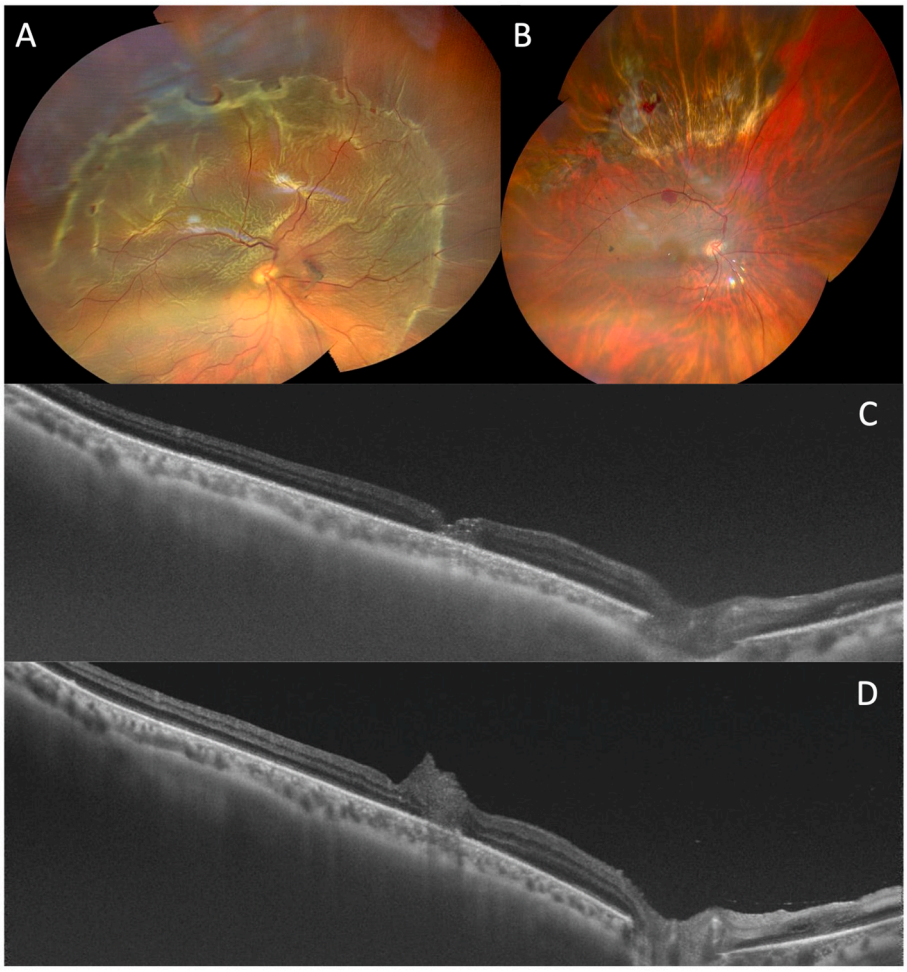

Fig. 4. Case 2. A: Preoperative Widefield retinography (WR) showing the total rhegmatogenous retinal detachment, with a macular hole, multiple equatorial retinal breaks, and grade B PVR. B: Postoperative WR demonstrating an attached retina under silicon oil, with laser retinopexy scars. C: B-scan Swept-source OCT at one week after surgery revealing macular hole closure with hyperreflective foci under silicon oil. D: B-scan SS OCT at 1 month after surgery revealing a hyperreflective proliferation over and within the retina nasally to the fovea, disrupting the inner and outer retinal layers. Note the silicon oil interface with hyperreflective dots in front of the optic nerve.

past 3 days. She had a history of previous laser photocoagulation in the same eye 5 years ago. Ophthalmic examination revealed a BCVA of hand motion in her RE and 20/20 in her LE. Widefield retinography revealed a total RRD (Fig. 7A) with a macular hole (Fig. 7B), inferonasal chorioretinal scars from previous laser photocoagulation, and a retinal tear at 8′clock. The axial length measured by B-ultrasound was 31 mm. Management consisted of a 23-gauge pars plana vitrectomy with a MLI ILM flap fashioned with high myope forceps (Fig. 7C), fluid-air exchange, laser retinopexy around the tear with a 360-degree barrage, and 16% C3F8 gas tamponade. One-month postoperative widefield retinography (Fig. 7D) revealed an attached retina with 360 laser barrage scars. The OCT B-scan at the 3-month follow-up (Fig. 7E) showed a complete macular hole closure without any PG. The final BCVA at 6 months was 20/200.

2. Discussion

In this report, we describe 2 cases that developed proliferative gliosis following the MLI ILM flap technique for the treatment of MH with a concomitant RRD, along with 3 control cases that did not encounter this outcome. The first case illustrated the development of the proliferation over a few months, with its migration toward the outer retinal layers. This had a deleterious effect on the quality of vision and the BCVA. Yet, this process appears to have stabilized at 12 months. The second case showed an earlier and faster proliferation. Both cases shared similar findings, namely preoperative inflammation (Tyndall Sign), preoperative PVR, silicon oil tamponade, and not sufficiently trimmed edges of the MLI ILM flap. All of these findings may have contributed synergically to the development of proliferative gliosis over and within the MLI ILM flap, a novel finding never described before during MH with concurrent RRD. In contrast, none of the three control cases that underwent gas tamponade developed proliferative gliosis. However, the type of tamponade was not the only common finding among them, as they all exhibited a well-trimmed MLI ILM flap and showed no preoperative signs of anterior segment inflammation.

MHs with concurrent RRDs have always represented a surgical challenge.[3] Recent advancements in ILM peeling[5] and ILM flaps[6,7] have significantly enhanced their closure rates. However, none of the studies describing the use of ILM flaps reported any related proliferation or contraction. Alternatively, ILM flap has revolutionized the approach to operating on MH since its initial description by Michalewska et al., in 2010,[8] significantly improving closure rates for large MH.[9,10] However, unlike MH concurrent with RRD, complications related to flap contractions,[11] macular pucker formation,[12,13] and even glial plug[14] have been described.

It is crucial to recall that the ILM is a basement membrane formed by Muller cell's feet.[15] When used as a flap, it plays the role of a scaffold for the proliferation, migration, and gliosis phenomenon involved in MH

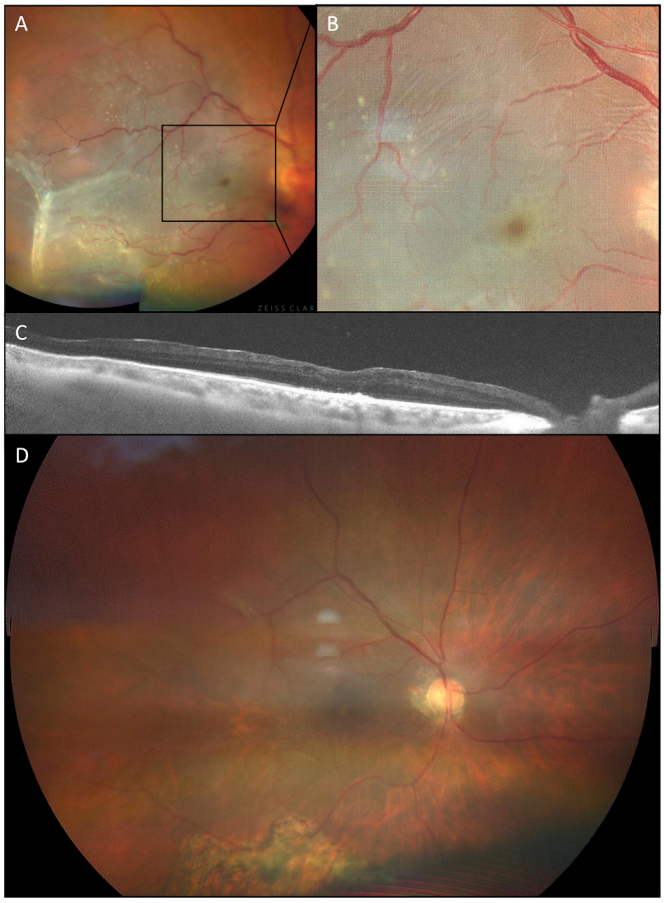

Fig. 5. Case 3: A: Preoperative Widefield Retinography (WR) showing the total rhegmatogenous retinal detachment with grade C PVR. B: Magnified view of the macular hole concurrent with the rhegmatogenous retinal detachment. C: B-scan OCT at one month after surgery showing a U-shape. Macular hole closure. D: WR 3 months after surgery demonstrating a completely attached retina.

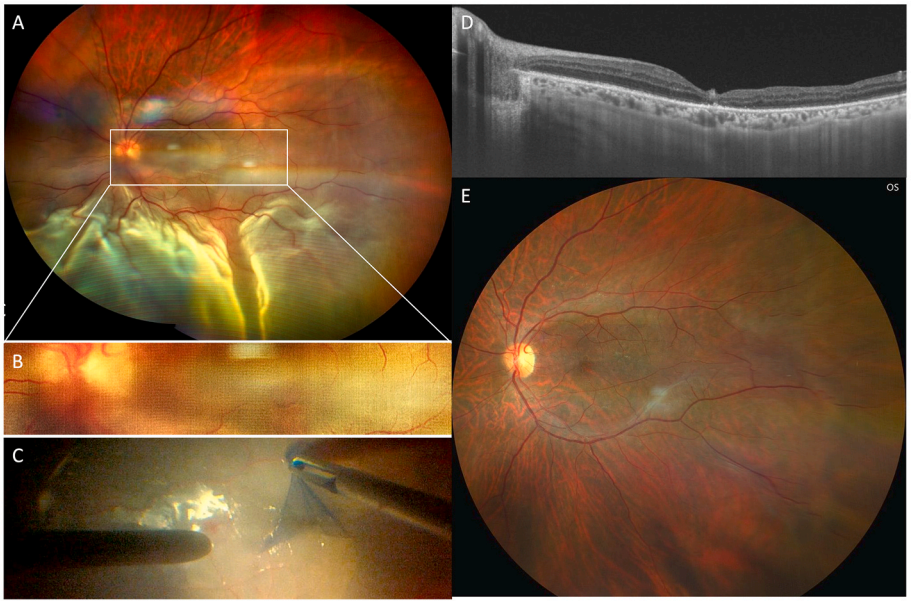

Fig. 6. Case 4: A: Preoperative Widefield Retinography (WR) showing the bullous rhegmatogenous retinal detachment extending from 1 o'clock to 11 o'clock. B: Magnified view of the macular hole concurrent with the rhegmatogenous retinal detachment. C: Intraoperative image of the fashioning of the MLI ILM flap. D: B-scan OCT one month after surgery showing a U-shape closure of the macular hole with hyperreflectivity over the fovea corresponding to the residual flap. E: WR 2 months after surgery revealing a completely attached retina.

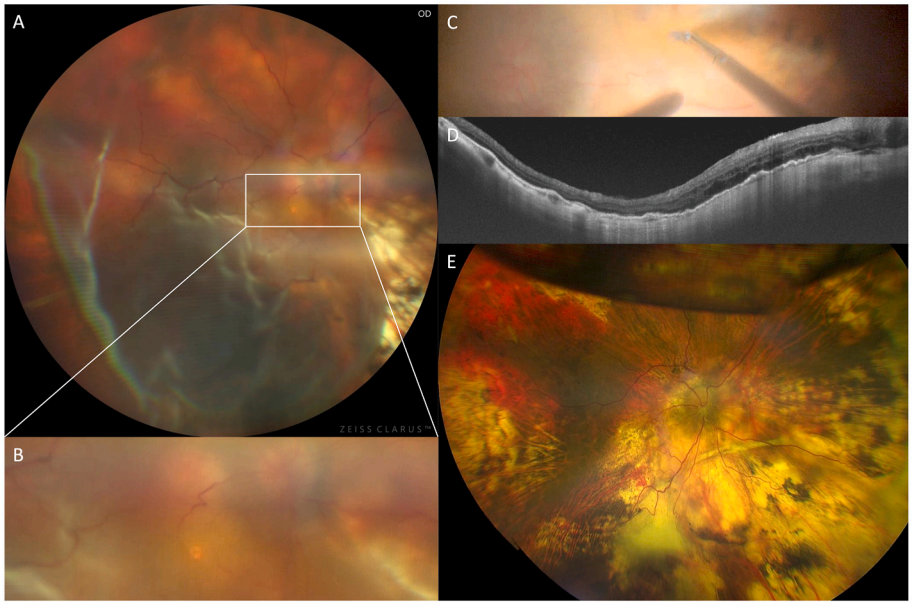

Fig. 7. Case 5. A: Preoperative Widefield Retinography (WR) showing the total rhegmatogenous retinal detachment, with the inferonasal laser scars. B: Magnified View of the small macular hole concurrent with the rhegmatogenous retinal detachment. C: Intraoperative image of the fashioning of the MLI ILM flap over the macular hole with high myope forceps. D: WR one month after surgery revealing an attached retina with 360 laser barrage scars. E: Swept-Source B-scan OCT 3 months after surgery showing a complete macular hole closure without any PG.

closure.[16] Histological studies of single-layered contracted ILM flaps have indicated that the original retinal side of the ILM, newly inverted and facing the vitreous, serves as the scaffold of cellular proliferation.[11,13] Its peeling in these cases allowed the restoration of the foveal anatomy and improvement of the BCVA.

We presume that in our case, the multilayered flap would act differently, by playing the role of a scaffold for cellular proliferation and gliosis on both sides and inside the flap, inducing preretinal and intraretinal gliosis, and corroborating the findings of our OCT scans.

Other factors may have contributed to the glial proliferation of the flap. Firstly, the coexistence of a RRD with preoperative PVR may be implicated in the presence of various cells over the ILM,[17] including RPE cells.[18] These cells may subsequently contract and differentiate into myofibroblasts within the flap, inducing proliferative gliosis. Even though epiretinal membranes were peeled during the surgeries, and all the cases showed positive staining with the BBG, implying that only the ILM was used to fashion the MLI ILM flap, it is not impossible that some thin residual membranes may have been placed over the MH, and may have contributed partially to the PG.

Secondly, the use of silicon oil might have played a major role by increasing the intraocular inflammatory response[19] and sequestering macrophages at the silicon oil flap interface. This, in turn, could increase the proliferative process. Similar findings have been described by Akira[13] with a histopathological study of a removed ILM flap showing spherical vacuoles considered to be silicon oil inside macrophages. Moreover, hyperreflective foci observed in our patient's OCT may confirm the presence of activated macrophages and microglia, as suggested by several studies.[20]

Finally, the use of silicon oil tamponade in High Myopes might enhance the sequestration of inflammatory cells within the macular interface. This is due to insufficient retinal contact surface compared to emmetropic eyes, especially at the staphyloma, which is left in contact with the aqueous meniscus in all the positions except the standing one.[21]

Interestingly, the other 8 cases operated in our institution; including cases 3, 4, and 5, benefitted from the same MLI ILM flap technique with gas tamponade and did not experience proliferative gliosis. This suggests the central role of silicon oil in this process. However, their final BCVA ranged between 20/200 and 20/80, suggesting an equivalent visual outcome.

In conclusion, the development of the MLI ILM flap techniques has revolutionized the management of concurrent MH with RRD. However, these can be associated with proliferative gliosis, especially in complicated cases with high myopia, preoperative PVR and inflammation, and silicon oil tamponade. In high-risk cases, we recommend reducing ocular inflammation, peeling all PVR membranes, trimming the MLI ILM flap edges, and using long-acting gases if possible, instead of silicon oil tamponade. A larger cohort study with histological examination may be necessary to elucidate this phenomenon.

3. Patient consent

• Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Submission declaration

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CRediT authorship contribution statement

Yassine Malek: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Conceptualization. **Shamil Louaya:** Validation, Supervision, Resources, Project administration, Methodology.

Declaration of competing interest

None.

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