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Autologous Retinal Transplant in Refractory Macular Holes

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Abstract

Purpose: To report the structural and functional outcomes of autologous neurosensory retinal transplant for closure of refractory macular holes (MHs) and to highlight the long-term follow-up findings. **Methods:** Nine eyes of 9 patients with full-thickness MH refractory to previous vitrectomy with internal limiting membrane (ILM) peeling and tamponade underwent pars plana vitrectomy, autologous retinal transplant with short-term perfluoro-n-octane heavy liquid, followed by gas tamponade. Patients were followed for 12.7 ± 10 months (range, 3-32 months). **Results:** Optical coherence tomography showed complete anatomic closure of the MH in 8 of 9 eyes (89%). Restoration of the outer retina and integration of the neurosensory retinal flap were noted in 5 eyes. The mean corrected Snellen visual acuity (VA) was 20/1600 and improved postoperatively to 20/200. The logMAR VA improved postoperatively from 1.9 ± 0.2 (range, 1.3-2) to 1.0 ± 0.3 (range, 0.59-1.3). Three grafts developed epiretinal membranes and were observed. Graft shrinkage over time was noted in 1 patient. One patient with a chronic large MH and previous panretinal photocoagulation (PRP) had a successful transplant from retinal tissue that had undergone PRP. One eye developed retinal detachment with proliferative vitreoretinopathy (PVR) that was managed with scleral buckle, PVR peeling, and silicone oil tamponade. This was followed by a successful repeat autologous retinal transplant from the detached nasal retina and nasal 120 degrees retinectomy. **Conclusions:** Autologous retinal transplant for large refractory MHs provides anatomic closure and safely improves VA.

Keywords

autologous retinal transplant, refractory macular hole, inner limiting membrane

Introduction

Surgical techniques for the repair of macular holes (MHs) have evolved considerably since the 1990s. Vitrectomy with gas tamponade was the first reported surgical approach to MH closure. This technique sought to eliminate anterior-posterior traction at the vitreoretinal interface, a well-studied hallmark of MH pathophysiology. However, it proved to be effective only for relatively small-to-moderate-sized MHs, with reports of MH persistence and recurrence after surgery. Removal of the internal limiting membrane (ILM) was later developed to help release any residual traction from the cortical vitreous after vitrectomy.[1] Although the success rates have improved with ILM peeling, limited options remain for refractory cases, including repeat fluid–gas exchange,[2] endotamponade with silicone oil (SO),[3] radial relaxing retinotomies on the MH margin,[4] reverse ILM flap,[5,6] application of subretinal fluid,[7] and autologous retinal transplant.[8,9]

Promising results have been seen since the advent of autologous retinal transplant both in terms of anatomic graft integration and postoperative visual acuity (VA). The efficacy of neurosensory autologous retinal transplant has been studied in patients with full-thickness MHs refractory to at least 1 vitrectomy with ILM removal and tamponade.[8] Approximately 90% of cases (36/41) achieved anatomic closure, while vision improved in 36% of those cases. The presence or absence of visual improvement was found to be largely influenced by baseline MH size as well as the presence or absence of macular edema and reconstruction of the ellipsoid zone.[8,10] Autologous retinal transplant has also been used as a first-line surgical option for primary MH cases.[11]

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In a review of 7 patients with a primary chronic large MH with a minimum hole diameter more than 600 μm and a basal diameter of more than 1000 μm, autologous retinal transplant resulted in MH closure in all 7 eyes. Most patients reported significant visual improvement. More than 1 year after surgery, the graft was still present in all 7 treated MHs, suggesting that autologous retinal transplant can last for an extended period of time. The study also showed improved VA after 1 year. Moysidis et al[9] reported an 85.7% closure rate for primary MH repairs and an 88% closure rate for refractory MHs with autologous retinal transplant. A significant percentage of both primary and refractory cases had improvement in VA, while 17% of patients in the primary MH group gained at least 5 lines of VA compared with 25% of refractory cases.[9]

In the current study, we seek to add to the growing collection of data on the use of autologous retinal transplant for MH repair. We describe the anatomic and functional outcomes of this surgical technique in a subset of patients with refractory MHs. Furthermore, the long-term follow-up findings and complications in these patients are highlighted.

Methods

Data including surgical techniques, anatomic outcomes, and functional outcomes were collected. Institutional review board (IRB) exemption from Western Michigan University (IRB# WMed-2023-1072) was obtained. The study protocols were in accordance with the Health Insurance Portability and Accountability Act of 1996, and the research adhered to the tenets of the Declaration of Helsinki for research involving human subjects. The VA was measured using the Snellen charts and converted to logMAR for statistical analysis. Preoperative and intraoperative variables were assessed, including the basal MH diameter, axial length, lens status, harvest site, tamponade agent, and intraoperative and postoperative complications. Optical coherence tomography (OCT) was performed at various time points using a commercially available spectral-domain OCT device (Spectralis OCT, Heidelberg Engineering), the inbuilt caliper tool of which was used to measure the basal diameter of the MH. Widefield fundus photography (Optos) was performed when available.

Surgical Technique

Three-port 23-gauge pars plana vitrectomy (Stellaris Elite, Bausch + Lomb) was performed with retrobulbar anesthesia using monitored anesthesia care. All procedures were performed unimanually with either the vertical scissors or the vitrector in one hand and the light pipe in the other. Indocyanine green dye solution (25 mg indocyanine green in 20 mL 5% dextrose plus water solution) was delivered to the retinal surface around the MH to confirm the status of the ILM. A neurosensory retinal graft was selected choosing a donor site between the arcades and the equator (posterior). The surgeon (T.A.) chose to harvest from various sectors: superonasal, superior, inferotemporal, inferonasal, and nasal. The size of the graft was at the discretion of the surgeon and was recorded as a multiple of the optic disc (eg, 1 disc diameter, 2 disc diameters, etc). In most cases, barrier endolaser treatment was delivered in multiple rows around the graft harvest site, along with endodiathermy to cauterize blood vessels at the edges of the graft site. The graft itself was harvested from healthy retinal tissue within the barrier zone of the endolaser ensuring that the edges of the graft were not affected by laser or diathermy. However, in 1 case, the graft was harvested from previously laser-treated retinal tissue because the patient had heavy 360-degree panretinal photocoagulation (PRP). The graft was cut using vertical scissors (Pinnacle 360, Synergetics). Perfluoro-n-octane (PFO, Alcon) was injected up to the equator level to secure the transplant during the final stages of harvesting the graft and during the transfer of the graft to its intended site, at the MH, using a finesse flex loop (Alcon). End-grasping forceps (Alcon) were used to hold the edge of the graft, if required. The finesse flex loop was used to gently tuck the graft into the MH space under PFO, which was left in the eye for 5 to 7 days as a short-term tamponade. This was followed by PFO–air exchange and diluted gas (sulfur hexafluoride or perfluoropropane) as the tamponade agent. The patients were positioned face down postoperatively for 1 week except when perfluorocarbon was used as tamponade, in which case patients were positioned supine for 5 to 7 days. The surgical technique is further described in the Supplemental Video.

The primary study outcome evaluated was anatomic MH closure after the retinal-free flap, confirmed by OCT. Secondary outcomes were measured using OCT, including VA at various time points and restoration of the outer retinal bands' external limiting membrane (ELM) and ellipsoid zone (EZ). These were evaluated during all follow-up visits using the Spectralis OCT (Heidelberg Engineering). Microperimetry was not used as an outcome because it was not available at our facility. However, the patients' subjective visual outcomes were documented. Mean values are ± SD.

Results

Nine eyes of 9 patients with full-thickness MHs refractory to previous vitrectomy with ILM peeling and tamponade were included in the study. The mean basal diameter of the MH was 1454.8 ± 562.8 μm. The mean axial length was 24.1 ± 2.0 mm (22.3-27.8 mm), and the mean corrected basal diameter of the MH was 1483 ± 666 μm (950-2964 μm).[12] The mean age at the time of surgery was 66 ± 9 years (6 women, 3 men). Two of the 9 eyes had high myopia (< –6.00 diopters, axial length > 26.5 mm). Patients' preoperative demographic and anatomic characteristics are summarized in Table 1.

Patients were followed for a mean of 12.7 ± 10 months (range, 3-32 months). Complete anatomic closure of the MH, defined as "no detectable gap between tissues" on OCT, was achieved in 8 of 9 eyes (89%). Postoperative neurosensory retinal flap dislocation and loss noted in 3 patients, 2 of whom underwent successful repeat autologous retinal transplant and 1 who declined any further attempts at autologous retinal transplant; hence, the MH

Table 1. Preoperative Characteristics of Eyes With Large Refractory Macular Holes Undergoing Autologous Retinal Transplant (n = 9).

Characteristics	Value
Age at time of surgery, years, mean ± SD (range, 50-79)	66 ± 9.1
Sex, n (%)	
Female	6 (66.7)
Male	3 (33.3)
Follow-up, mean ± SD (months)	12.8 ± 10.1
Visual acuity, mean ± SD (logMAR)	
Preoperative visual acuity	1.9 ± 0.2
Postoperative visual acuity	1.0 ± 0.3
Baseline measurements, mean ± SD	
Basal diameter of the macular hole (μm)	1454.8 ± 562.8
Mean axial length of the eye (mm)	24.1 ± 2.0
Corrected basal diameter (μm)	1483.0 ± 666.4
Lens status at baseline	
Phakic, n (%)	5 (55.6)
Pseudophakic, n (%)	4 (44.4)
Coexisting ocular morbidities	N/A
High myopia (< –6.00 diopters, axial length >26.5 mm), n (%)	2 (22.2)

remained open. The mean corrected VA (logMAR) improved from 1.9 ± 0.2 (range, 1.3-2.0) to 1.0 ± 0.3 (range, 0.59-1.3) at the final postoperative visit. Correspondingly, Snellen VA improved from approximately 20/1600 (20/400-20/2000) to 20/200 (20/80-20/400). In the 8 eyes in which the MH was closed (89%), the VA improved by 1 logMAR unit; in the 1 eye where the MH remained open (11%), the VA improved by 0.3 logMAR units. The preoperative and final postoperative improvement in logMAR VA was statistically significant (Wilcoxon matched-pair signed rank test, $P = .0039$). Although 4 of 9 eyes (44%) were pseudophakic at baseline, 6 of 9 (67%) were pseudophakic at final follow-up, with cataract surgery performed later after MH repair.

As seen on postoperative OCT images, none of the eyes had an inverted retinal transplant placed. Three grafts developed an epiretinal membrane (ERM) over the graft (Figure 1), which did not cause worsening of vision and were observed. Graft shrinkage over time was noted in 1 patient (Figure 2). A chronic MH in a highly myopic patient was closed with an undersized graft and remnant nasal thinning was noted (Figure 3).

A chronic large MH in a patient with diabetes and a history including PRP had a successful transplantation from retinal tissue that had also undergone PRP (Figure 4). Retained PFO droplets were noted within the retina tissue around the transplant (off-center) and were observed. At the 3-month follow-up visit, 2 eyes had developed inner retinal cystic changes of the transplant tissue. These eyes were observed and improved spontaneously. A woman in our cohort with a history of breast cancer underwent successful retinal transplant with full closure of the MH, and the vision improved from count fingers to 20/100+ (Figure 5). Unfortunately, 3 months after surgery she developed complications from metastatic breast cancer and respiratory failure and passed away while remaining phakic.

One highly myopic patient (axial length 26.64 mm) with a large MH (basal diameter of 2670 μm; corrected to 2964 μm) underwent autologous retinal transplant, but the transplant was displaced and subsequently lost; hence, the MH remained open. The patient's vision improved from 20/400 to 20/200 after cataract surgery, and no further surgical interventions were pursued.

Retinal detachment (RD) with proliferative vitreoretinopathy (PVR) developed in 1 patient and was initially managed with scleral buckle, PVR peeling, and SO tamponade. The MH remained open, and the nasal retina detached with progressive PVR. The MH was successfully closed with further PVR peeling and autologous retinal transplant from the detached nasal retina, followed by nasal 120 degrees retinectomy and SO infusion (Figure 6).

Postoperatively, there were no cases with intraocular inflammation, endophthalmitis, suprachoroidal hemorrhage, or choroidal neovascularization at the graft site or harvest site. Fluorescein angiography (FA) was performed in 6 of 8 patients (in which the autologous retinal transplant had succeeded). Evidence of vascularization within the graft was noted in 4 grafts but was not directly correlated with VA improvement.

Conclusions

Our technique of autologous retinal transplant for refractory MHs involves 2 consecutive procedures, with specific positioning requirements after each. The risks, recovery process, and the slow visual improvement must be discussed at length before consenting highly motivated patients for the retinal transplant procedures. There is certainly a surgical learning curve in the way the neurosensory transplant is harvested and separated from the underlying retinal pigment epithelium (RPE). In our cohort, the retinal transplant was harvested posterior to the equator level due to easy surgical accessibility and because the neurosensory retina gets thinner anteriorly.[13–15]

Gravitational forces, immiscibility with bodily fluids, and the ability to transport oxygen make short-term tamponade with PFO ideal. Its use for 5 to 7 days helps maintain the graft position and improves oxygenation.[16] Although some authors have described inflammatory reactions after short or midterm use,[17] this was not seen in our study. To avoid subretinal entrapment, PFO must be carefully injected, directing the jet away from the MH and the harvest site. Furthermore, meticulous PFO–air exchange should be completed before infusion of gas in the second procedure.

Postoperative OCT scans in 5 patients showed integration of the neurosensory retinal flap with the surrounding tissue. This finding aligns with reports suggesting that transplanted retinal photoreceptors can directly synapse with host bipolar cells, thereby promoting retinal integration.[18] Additionally, Müller glia isolated from the peripheral retina may serve as a source for cells exhibiting properties of rod photoreceptors.[19–21] Johnsen et al[19] showed that while neural stem cells in Müller glia remain quiescent in the adult human peripheral retina, they can become activated after retinal injury, as seen

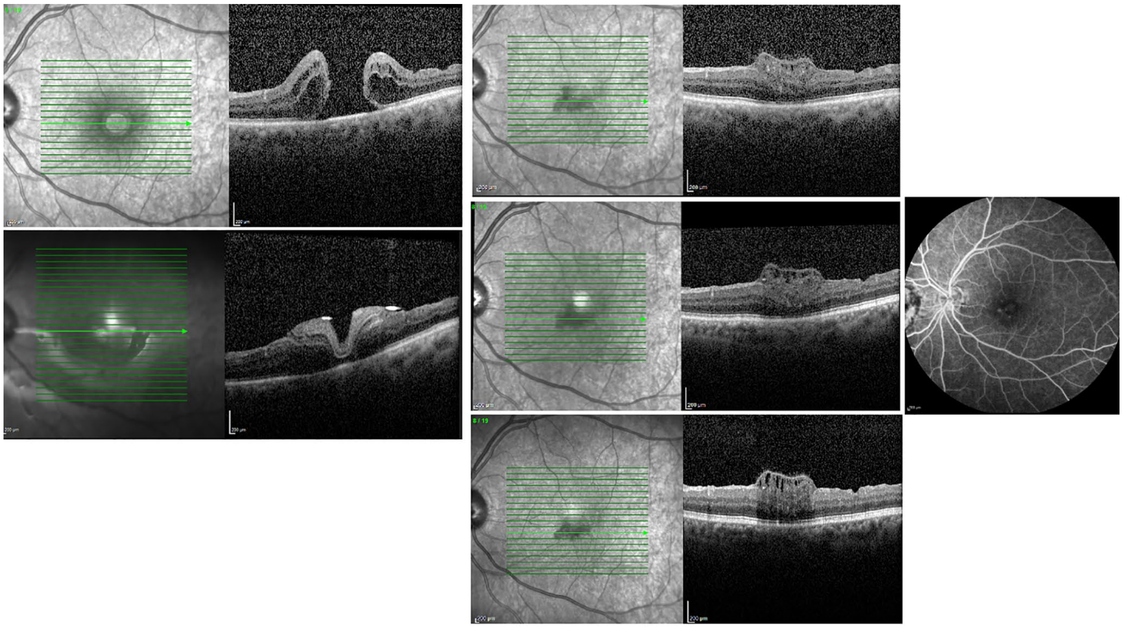

Figure 1. Sequential preoperative optical coherence tomography scans (upper left) and up to 18 months after an autologous retinal transplant (right) in a refractory full-thickness macular hole that failed previous internal limiting membrane peeling and gas tamponade. Preoperative visual acuity was counting fingers. One day postoperatively (lower left), the neurosensory retinal transplant is in good position under the perfluoro-n-octane. At 9, 13, and 18 postoperative months (middle), there is restoration of the ellipsoid zone within the transplant in addition to an epiretinal membrane and cystoid changes within the inner retina of the transplant, and the vision is stable around 20/80. Fluorescein angiography at 13 postoperative months (right) shows evidence of vascularization within the graft.

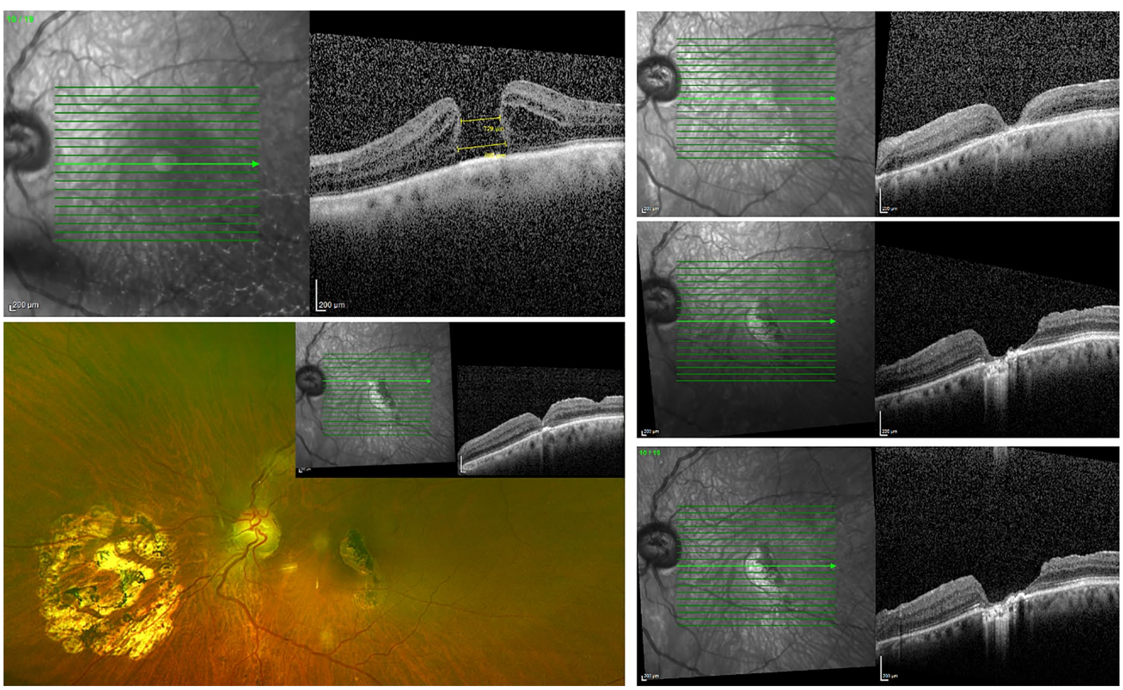

Figure 2. Sequential preoperative optical coherence tomography scans (upper left) and up to 31 months after an autologous retinal transplant in a refractory full-thickness MH that failed previous internal limiting membrane peeling and gas tamponade. Preoperative visual acuity (VA) was counting fingers. At 3 postoperative weeks (upper right), the VA was 20/400 and the hole was closed. At 22 months (right middle and lower), there is thinning and atrophy of the retinal flap with retinal pigment epithelium (RPE) migration, and the vision is stable around 20/200. Optos fundus imaging (lower left) shows the RPE pigmentary changes within and around the neurosensory retinal transplant.

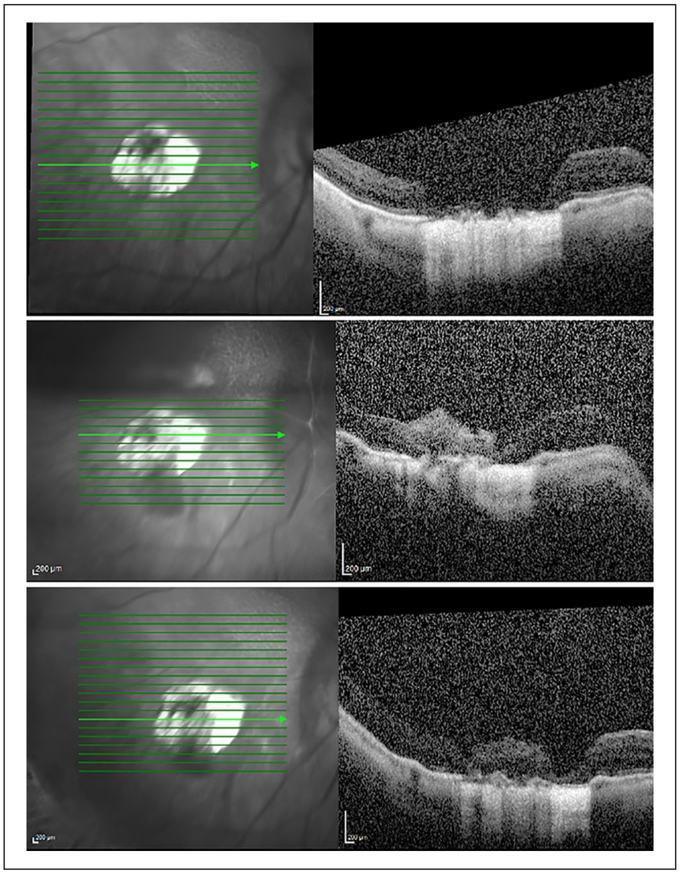

Figure 3. A highly myopic woman (axial length of 27.76 mm) with a large macular hole (MH) (basal diameter of 1700 µm; corrected to 1966.3 µm) (upper). Sequential optical coherence tomography scans at 2 weeks (middle) and at 5 months (lower) after an autologous retinal transplant in a chronic full-thickness MH that failed previous internal limiting membrane peeling and gas tamponade. Preoperative visual acuity (VA) was counting fingers. At 2 weeks and 5 months postoperatively, the VA was 20/400 and the hole is closed with an undersized graft and remnant nasal thinning, which can affect the transplant tissue's potential for synaptogenesis with the papillomacular bundle.

in PVR. The process of harvesting retinal transplants can also stimulate this activation. Nevertheless, the behavior and functional contribution of these rod photoreceptors within the macula warrant further investigations.

Rod bipolar cell dendrites can exhibit ectopic synaptogenesis when their preferred contacts are absent.[20] Horizontal and rod bipolar cell processes have the capacity to extend into the outer nuclear layer, forming ectopic synapses with photoreceptors, especially after photoreceptor degeneration resulting from RD.[21–23] These studies provide valuable insights into the mechanisms behind graft integration and the subsequent enhancement in visual function, offering a promising avenue for further exploration into the field of retinal regeneration.

Graft shrinkage over time was observed in 1 of our patients (Figure 2), underscoring the importance of oversizing the graft.[24,25] This patient had a history of glaucoma with preexisting retinal nerve fiber layer thinning, which may have contributed to the observed graft shrinkage. A small area of thinning at the nasal part of the graft was identified in 1 patient with a refractory chronic large MH (Figure 3). Therefore, intraoperative OCT can further refine this technique, confirming full closure of the MH,[26] especially along the nasal edge. This would allow for better synaptogenesis along the papillomacular bundle and subsequently better visual outcome. Future studies should explore the potential relationship between glaucoma and autologous retinal transplant graft survival.

With time, an ERM can develop within the graft in some patients.[27,28] In our study, 3 grafts developed an ERM that did not cause worsening of vision and were observed (Figure 1). Although the grafts were carefully and gently teased into the MH, it is possible that touching the inner surface of the graft with the Finesse Flex Loop (Alcon) or the ILM forceps could have triggered proliferation, resulting in development of an ERM. Such risks may be mitigated by gentle graft manipulation and minimal contact with surgical equipment surfaces. The complication profile in our case series is in line with the reported literature.[8,9,29]

One of the patients in our cohort, a man with diabetes and a chronic large MH who had undergone PRP, proved the concept that it was possible to harvest the transplant from scarred retina tissue previously treated with PRP (Figure 4). Technically, it was easier to harvest the graft from the previously laser-treated inferotemporal arcade retina tissue. It is hypothesized that laser photocoagulation may create scarring at the RPE-choroid level, potentially facilitating separation of the neurosensory retina from the underlying RPE.

FA clearly demonstrated vascularization within the graft in 4 of our cases, and the transplant tissue developed inner retinal cystoid changes in 4 eyes, which were observed and improved. Last, and although not used in our study, OCT angiography could provide valuable insights into the graft at the superficial and deep vascular plexus.[24]

Our study has a number of limitations. First, our sample size is relatively small. However, these are all complex refractory MHs that have previously failed ILM peeling and tamponade and then underwent autologous retinal transplant by a single surgeon. Second, missing minimal linear diameter measurements for some patients precluded its inclusion. Although important for guiding surgical approaches and study comparisons, we relied on basal diameter because it was consistently available.[30] Third, there was variability in the follow-up duration. In addition, microperimetry to provide fixation stability data in the 2- and 4-degree field was not available to measure visual performance before and after autologous retinal transplant.

In conclusion, autologous retinal transplant represents a surgical approach for large refractory MHs and provides a reasonable rate of anatomic closure and a safe technique to improve VA. Further research is needed to elucidate the mechanisms behind graft integration and patient-specific factors affecting outcomes. It is important to highlight the long-term follow-up findings in these cases to improve the surgical technique, including reasonable oversizing of the graft, minimal manipulation of the neurosensory retinal transplant tissue, and management of PVR when it occurs. Our findings contribute to the growing literature on autologous retinal transplant as a promising avenue for the management of challenging MH cases.

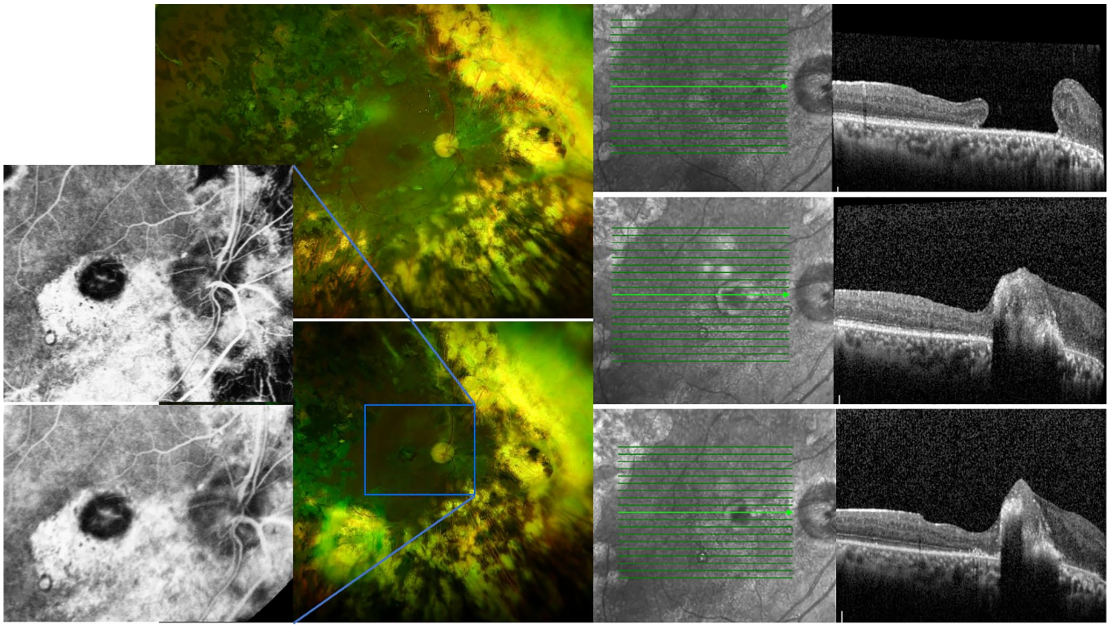

Figure 4. Optos fundus and optical coherence tomography images before (upper right) and 3 months and 7 months after (middle and lower right) an autologous neurosensory retinal transplant in a man with diabetes and a chronic large macular hole previously treated with heavy panretinal photocoagulation (PRP), showing successful transplantation from retinal tissue that had been treated with PRP along the inferotemporal arcade. Perfluoro-n-octane droplets were noted within the retina tissue around the transplant (off center). Fluorescein angiography images obtained preoperatively (upper left) and at 7 months postoperatively (lower left) show evidence of vascularization within the graft at 1:00 and 2:09 clock hours.

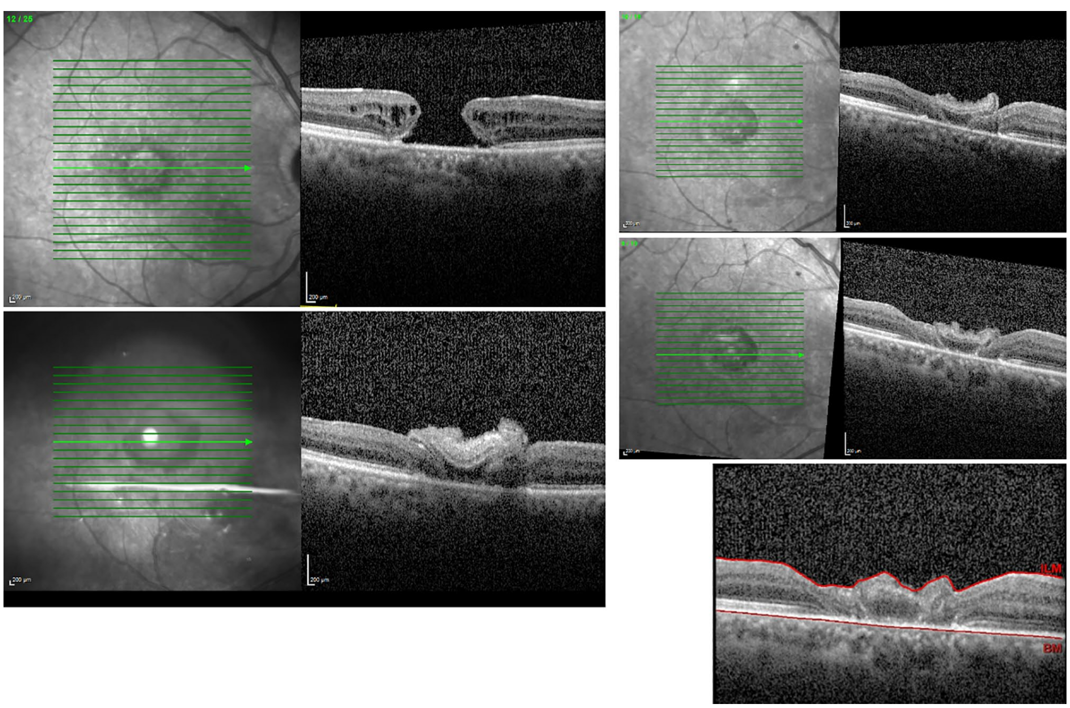

Figure 5. Sequential optical coherence tomography scans preoperatively and up to 3 months after an autologous retinal transplant in a refractory full-thickness macular hole. The preoperative visual acuity (VA) was counting fingers (upper left). At 1 postoperative day (lower left), the neurosensory retinal transplant is in good position under the perfluoro-n-octane. At 2 and 3 weeks, then 2.5 months postoperatively (right; upper, middle, and lower), there is gradual and progressive restoration of the outer retinal bands within the transplant tissue. No further follow-up was available after 3 months due to the patient's death from stage 4 breast cancer complications.

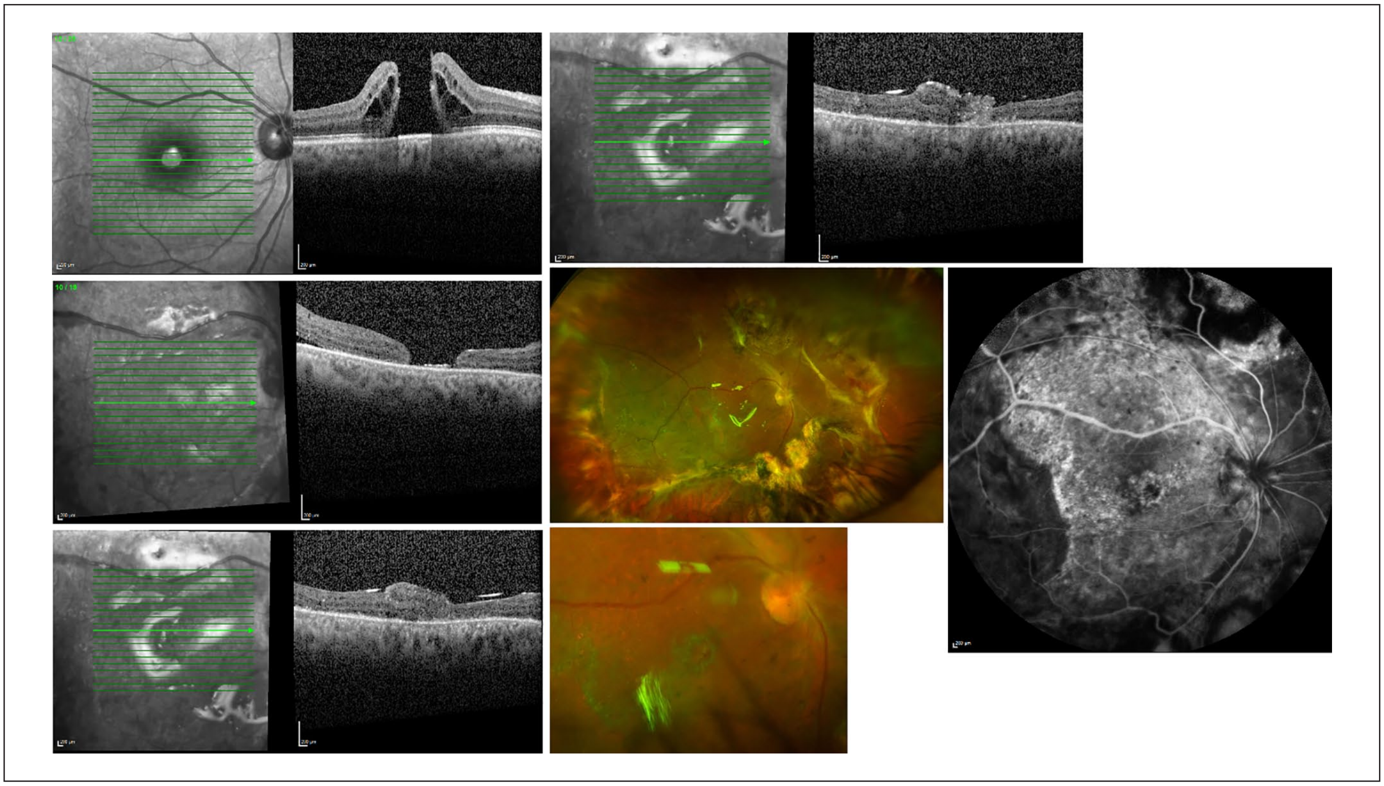

Figure 6. (Left) Preoperative and postoperative optical coherence tomography (OCT) scans after a failed autologous neurosensory retinal flap, where the macular hole (MH) remained open and the eye developed a retinal detachment with proliferative vitreoretinopathy (PVR), both of which were managed with scleral buckle, PVR peeling, and silicone oil (SO) tamponade. (Lower left) OCT of the macula after repeat autologous retinal transplant shows MH closure with the transplant in good position under SO tamponade. (Right) Postoperative OCT and Optos fundus images after additional PVR peeling and repeat autologous retinal transplant from the detached nasal retina successfully closed the MH (note the nasal 120 degrees retinectomy and SO tamponade). Fluorescein angiography imaging (middle, upper and lower) at 3 postoperative months shows evidence of vascularization within the graft.

Ethical Approval

We obtained institutional review board exemption from Western Michigan University (IRB# WMed-2023-1072). The study protocols were in accordance with the Health Insurance Portability and Accountability Act of 1996, and the research adhered to the tenets of the Declaration of Helsinki for research involving human subjects.

Statement of Informed 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.

Declaration of Conflicting Interest

The authors all declare that there is no conflict of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material is available online with this article.

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