American Journal of Surgery Case Reports

Case Report

Autologous Retinal Transplant: Functional Success despite Graft Displacement

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Abstract

Purpose: Report outcomes of one autologous retinal transplant.

Participants: A 68-year-old woman with large macular hole.

Methods: Autologous retinal transplant was performed for a large macular hole. Follow-up monitoring with imaging.

Main outcome measures: Tomographic closure and best corrected visual acuity.

Results: Three month follow-up showed full-thickness anatomical closure, and the patient presented a remarkable visual function recovery. Optic coherence tomography showed early graft displacement.

Conclusion: Severe macular holes may undergo autologous retinal transplant. Despite graft displacement in our patient, functional outcomes were better than average, which may raise discussion on where to position the retinal graft.

Introduction

An idiopathic Macular Hole (MH) is characterized by full-thickness anatomic disruption in the foveal retina and leads to loss of central vision, metamorphopsia and a central scotoma [1]. The formation of a macular hole typically evolves over a period of weeks to months through the clinically defined stages and usually arises from vitreomacular interface adhesions [2].

Macular hole surgery results depend on hole's dimension and surgery's timeliness. Current vitreoretinal surgical techniques with Internal Limiting Membrane (ILM) peeling and inverted flap allow primary closure rates exceeding 90% [3,4].

The International Vitreomacular Traction Study (IVTS) Group has recently updated the classification scheme of vitreomacular traction and macular holes based on Optic Coherence Tomography (OCT) findings, where the MH's narrowest diameter is used to determine MH grading; A 400 µm or higher cutoff is used to describe large MHs [5].

Success rate decreases when Pars Plana Vitrectomy (PPV) with ILM peeling is used for large or extra-large MHs (>600 µm), and surgical success was found to have a strong correlation to the Basal Linear Diameter (BLD) ≤ 1200 µm [6].

When MH closure failure is foreseeable or when treatment fails despite previous surgery, other techniques may be suitable to achieve hole closure and these patients may be addressed with bandage techniques such as Autologous Retinal Transplant (ART) or Human Amniotic Membrane (hAM) plugs to accomplish complete anatomical closure [5,6]. Nevertheless, anatomical and functional outcomes in such patients are often unpredictable [5,7].

In this case report, we discuss the role of ART technique and graft's placement for cell signalling migration to achieve full MH closure and functional success.

Case Presentation

A 68-year-old female presented to the ophthalmology clinic with a 12-month history of decreased vision in her left eye due to a large dimension MH.

At presentation, her Best Corrected Visual Acuity (BCVA) was 20/630 on the left eye and 20/20 on the right eye. Bilateral slit-lamp examination was unremarkable on the anterior segment, but left eye fundus examination revealed a large full-thickness disruption on the central macula, with a wide tissue defect, exposing the retinal pigment epithelium with concomitant peri-foveal greyish colour, suggesting the presence of sub-retinal fluid. Pre-operative OCT confirmed a full-thickness macular hole measuring 676 µm on the innermost layers and presenting a 1190 µm in the widest diameter, corresponding to this MH's BLD (Figure 1 and 2). This classified under the modified-Gass scale as a grade 4 MH and as a large Full-Thickness Macular Hole (FTMH) without Vitreo-Macular Traction (VMT) according to the IVTS group classification [5].

An elective three-port 23-gauge pars plana vitrectomy was performed with extensive ILM peeling. An ART free flap graft was harvested in the mid-periphery neurosensory retina, outside the supero-temporal vascular arcade. This graft was subsequently placed over the macular hole and held in place with 20% Sulfur Hexafluoride (SF6) endotamponade.

The patient was closely monitored full ophthalmologic evaluation every 2 weeks for the first month and every 8 weeks subsequently for 6

Citation: Matos DB, José P, Ferreira JT, Faria MY, Marques-Neves C. Autologous Retinal Transplant: Functional Success despite Graft Displacement. Am J Surg Case Rep. 2023;4(4):1066.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Apr 19th, 2023

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months. The patient did not complain of negative or positive scotomas and subjectively referred the vision was improving. The BCVA was recorded on the 1-month follow-up visit (20/400), 3-month visit (20/160) and on the 5-month visit (20/80). Follow-up included OCT scans on every visit upon SF6 endotamponade reabsorption. The first OCT possible was performed at the 3-month post-operative visit and showed autologous retinal graft migration to the inferior macula, therefore not overlying the macular hole location (Figure 3).

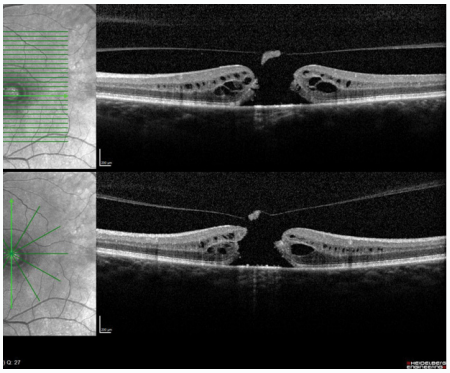

Figure 1: Pre-operative OCT horizontal and vertical scans showing large macular hole with overlying operculum. Intra-retinal fluid is also visible in the macular hole edges.

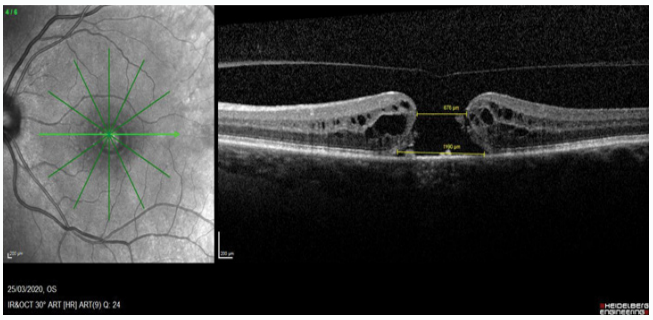

Figure 2: Pre-operative OCT horizontal scan- yellow calipers measuring full-thickness macular hole (innermost length: 676 µm; BLD: 1190 µm).

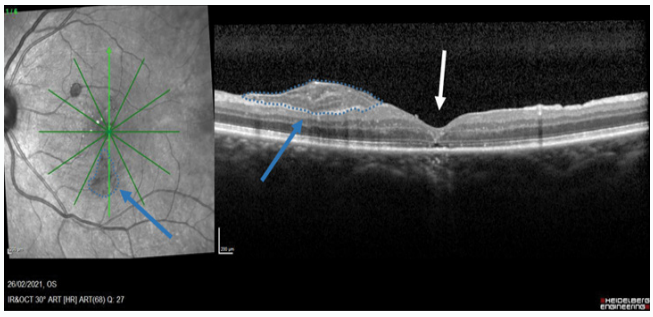

Figure 3: Three-month post-operative follow-up OCT vertical scan showing full-thickness anatomic macular hole closure (white arrow) and inferior autologous retinal graft displacement (blue arrows).

The BCVA improved a total of 40 letters from 20/630 to 20/80, between the pre-operative status and the 5-month follow-up visit, remaining stable thereafter. This represents a remarkable outcome given the pre-operative dimensions of the MH. FTMH closure was achieved, despite graft displacement and graft's incorporation in the outer retinal layers of the inferior macula.

Methods

Patient evaluation

Pre-operatively, the patient underwent complete ophthalmological evaluation, including assessment of BCVA, Goldmann® tonometry, slit lamp biomicroscopy, standard fundus dilated ophthalmic examination, colour fundus photography and serial OCT, with a spectral-domain OCT device (Spectralis HRA OCT; Heidelberg Engineering®, Heidelberg, Germany). The patient received sequential follow-up every 2 weeks for the first month and every 8 weeks thereafter, with the same ancillary exams as performed in the pre-operative evaluation.

Surgical intervention

An elective three-port 25-gauge PPV (Constellation® coupled to Advanced UltraVit® vitrector; Alcon, Fort Worth, TX) was performed under a combined peribulbar and sub-tenon anaesthesia. A 25-gauge chandelier endoilluminator was used to maintain image quality during bimanual manoeuvres. A BIOM®5 microscope system (OCULUS® Surgical, Inc., FL, USA) was coupled with a surgical microscope (Zeiss® OPML Lumera T) to provide intraoperative fundus visualization. All materials coupled to Constellation device were acquired through Alcon®, Fort Worth, TX, unless otherwise specified.

After a core vitrectomy, Membrane Blue Dual® (MBD) dye was used to confirm the presence of internal limiting membrane, which was peeled extensively with a Grieshaber® ILM forceps until the temporal retina vascular arcades, according to the protocol described by the multicenter international collaborative study group on macular holes case series report [8].

A mid-periphery retinal area outside the superior temporal arcade for the donor-retina autologous retinal graft was marked with both vascular endodiathermy and an endolaser barricade in a circular manner with an area of around 2 disc-diameters. A small retinal detachment was created with a microneedle and bimanual dissection was performed with Grieshaber® ILM forceps, vertical and curvilinear scissors to harvest a circular, full-thickness autologous neurosensory retinal graft with 1284 µm diameter. The harvested retina was placed over the MH under perfluorocarbon and positioned with a Flexloop® diamond-dust scraper. The diathermy-marked edges were used to check correct surface orientation of the free flap graft, to maintain anatomic positioning. The autologous retinal transplant was held in place with a 20% SF6 endotamponade [9-14].

Results

Pre-operative ancillary exams

Pre-operative OCT confirmed full-thickness macular hole with overlying operculum (Figure 1) measuring 676 µm on the innermost layers and presenting a 1190 µm in the widest diameter (BLD, as shown in Figure 1 and 2). This classifies as a grade 4 MH under the modified Gass scale and is considered a FTMH without VMT according to the IVTS group classification [5].

Post-operative outcomes and ancillary exams

Two different outcomes were evaluated in this case: (i) anatomic closure; and (ii) functional improvement.

Anatomic closure was assessed through serial post-operative OCT evaluations and direct comparison to pre-operative OCT exams. Upon the 3-month post-operative follow-up OCT, a full-thickness anatomic macular hole closure was apparent, despite inferior graft displacement as shown in the vertical scans (Figure 3). The 3-month post-operative OCT also showed that despite retinal

graft displacement, the graft was adherent to the underlying retina with incorporation of the graft's outer-segments into the innermost layers of the receptor retina, encompassing graft structural integrity, indicating perfusion and inclusion in the receptor area (Figure 4). Fundus auto fluorescence in the same post-operative period further confirmed MH full closure, with a mild hipo-autofluorescence pattern surrounding the fovea. The area of the autologous retinal graft presented a mild hipo-autofluorescence signal, probably due to the increased thickness of the inner retinal layers with the graft overlying the retinal pigmented epithelium of such area (Figure 5).

On the functional evaluation, patient's BCVA was assessed throughout the follow-up visits, with a gradual increase from 20/630 pre-operatively to 20/400, 20/160 and 20/80 on the 1-month, 3-month and 5-month follow-up visits. This represents a 40-letter improvement, which represents a remarkable functional improvement given the pre-operative severity of the MH (Figure 6).

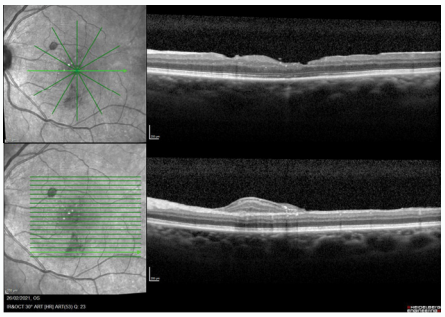

Figure 4: Three-month post-operative follow-up OCT horizontal scan showing full-thickness anatomic macular hole closure with continuous photoreceptor and outer-segment retinal layers (top image) as well as horizontal scan intersecting the displaced autologous retinal graft-outer-segment graft incorporation in the innermost layers of the receptor area.

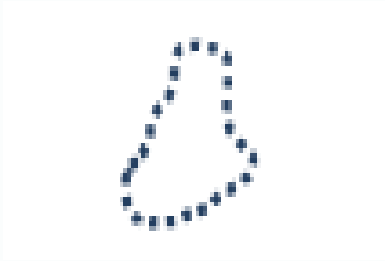

Figure 5: Three-month post-operative Fundus Autofluorescence of the left eye showing complete macular hole closure and autologous retinal graft inferiorly displaced (area dashed in blue). A superior hemorrhage is seen as hypoautofluorescent on the superior macula (white arrow).

Figure 6: Twelve month post-operative evaluation with colour fundus photography, showing complete macular closure.

To further confirm the functionality of the ART cells with objective measurements, a multifocal electroretinography (mf-ERG) was performed on 3-month post-operative evaluation (Figure 7) and demonstrated a P1 wave with an absolute value within the normal range, with a double peak representation on the tridimensional representation.

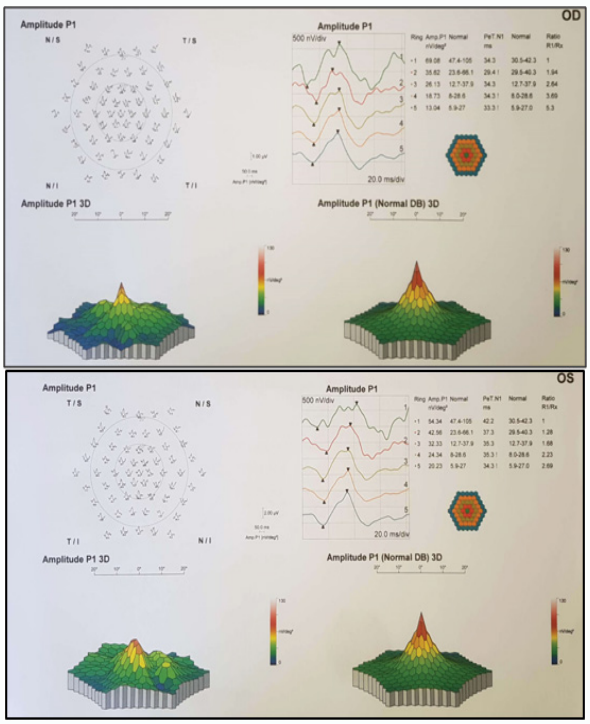

Figure 7: Three-month post-operative multifocal ERG (mf-ERG) showing a double peak on the left tridimensional representation, most likely corresponding to the overlapping retinal layers and autologous graft.

Post-operative complication

Throughout the follow-up, a superior macular post-operative haemorrhage was diagnosed on the 2-week post-operative evaluation, and which resolved spontaneously without further intervention upon the 6-month follow-up. No other intra or post-operative complication was apparent.

Discussion

The early detection of a macular hole is associated with both a higher closure rate after vitrectomy surgery as well as better postoperative visual acuity. Studies report that approximately 90% of macular holes <400 μm can be closed with PPV and inverted ILM flap technique [1]. Large and long standing MHs (>400 μm, or even >650 μm) present a challenge on which technique to choose from the several options available. Since there are currently very few randomized controlled studies addressing this topic, there are still no guidelines to assist in the pre-operative evaluation of patients with large MHs. In this patient, we chose to perform an elective PPV with extensive ILM peeling, according to most literature recommendation but decided to perform an autologous retinal transplant as an assisting technique because this patient's MH presented wide dimensions in both vertical and horizontal axis, therefore presenting foreseeable difficulty in MH closure. In our case report the MH closed, and the patient experienced a remarkable visual improvement, despite ART

graft displacement, which may bring up the discussion on whether it would have closed with a simple PPV coupled with ILM peeling without further techniques, or whether the impact of ART relies the most on molecular and cellular signalling for photoreceptor and outer-layer cell differentiation and migration instead of acting as an anatomical scaffold for MH closure. Neither thesis should be confirmed or rejected based on a single case-report, but this discussion may prove important to address the best positioning for the ART graft implantation.

Regarding functional outcomes, the average LogMAR improvements reported in the literature are between 0.42-0.71 LogMAR [6,9]. In our case report, we achieved a 0.9 LogMAR improvement, although it is not possible to determine whether this difference was caused by graft displacement or due to pre-operative characteristics of the MH, because there still lacks an efficient grading system to predict both anatomical and functional outcomes based on pre-operative MH characteristics.

These outcomes reinforce the question on whether the effective advantages of ART grafts depend on the structural and anatomical scaffolds for MH closure, or whether these scaffold properties may prove deleterious to the functional improvement due to the duplication of retinal layers after MH closure, in which case the graft positioning overlying the macular hole may not necessarily be the best placement option. One important limitation when evaluating these outcomes is the lack of a fluorescein angiography, which was not possible to obtain in this patient.

No intraoperative complication was reported and only a superior macular post-operative haemorrhage was diagnosed on the 2-week post-operative evaluation, whose significance is unknown, and which resolved spontaneously without further intervention upon the 6-month follow-up. Retinal graft displacement was apparent at the 3-month post-operative evaluation on OCT.

Further investigation with case-series and comparative analysis are needed to evaluate the pre-operative factors that influence the outcomes of each closure technique, as well as to determine the ideal positioning autologous retinal transplant grafts under similar pre-operative conditions.

Conclusion

With modern vitreoretinal surgical techniques, MH closure rates after primary surgery exceed 90% [3]. The rational for treatment includes visual loss prevention because early detection of a MH is generally associated with better anatomical and functional outcomes [1].

When MH closure fails or where failure is foreseeable patients may be addressed with other techniques such as ART [5].

Despite autologous retinal graft displacement in this case, MH closure in our patient was still successful with excellent functional outcomes and this outcome should prompt us to question whether the best positioning for ART graft is fully overlying the entire MH or if a near-MH graft positioning without direct overlapping may be beneficial for the final functional results.

Further investigation is needed to determine the best technique to use in the setting of severe macular holes and where to position the ART graft to achieve the best anatomical closure and BCVA functional outcomes.

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