

Multi-layered amniotic membrane transplantation for the management of corneal ulcers during the Covid pandemic

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This study was done to assess the outcome of multilayer amniotic membrane transplantation (AMT) for severe progressive fungal keratitis & perforated corneal ulcers. With the COVID-19 pandemic-related lockdown and unavailability of donor corneas, multi-layered AMT was done in these cases. We hereby report nine such cases, all of which showed reduced inflammation, resolution of infiltrates, good epithelisation and no recurrence of infection. None needed TPK in subsequent weeks of follow-up. With palliative treatment of AMT, eyes with vision-threatening keratitis can be salvaged, till the availability of donor corneas.

Keywords: Multilayer amniotic membrane transplantation, COVID-19, Fungal keratitis

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Introduction

Fungal keratitis is the most common cause of infective keratitis and comprises at least 50% of all culture-positive cases in India.[1]. Various modalities of treatment are antifungal drops, Intrastromal injections of antifungal drugs for deep-seated ulcers, [2]. cyanoacrylate glue and a bandage contact lens for small perforations. [3]. In non-responding large ulcers, Therapeutic Keratoplasty (TPK) is currently considered the most effective method, for the elimination of infection & salvaging the eye.

With Coronavirus disease 2019 (COVID-19) spreading all across the globe, many countries, including India faced a lockdown. As per the Government notifications, all activities of the eye bank were halted and no donor corneas were available even for emergency procedures. In the past, many studies have proved that Amniotic membrane (AM), because of its special biological properties like lack of immunogenicity, promotion of epithelisation, inhibition of stromal inflammation, stabilisation of stromal thickness can help to heal corneal perforations and deep ulcers. [4,5]. So we thought of treating cases of very progressive corneal ulcers with increasing infiltrates, ulcers approaching limbus, impending perforations and perforated ulcers, with multi-layered AM Transplantation (AMT). We present a series of nine cases which were salvaged with this technique.

Materials and Methods

This is a retrospective case series of very severe & progressive fungal ulcers, that presented to our cornea OPD from April 2020 – September 2020. All the cases, except one, had a history of vegetative trauma. All cases were previously given a mixed regimen of topical anti-bacterial & antifungals for a minimum of two weeks (one case) to two months (eight cases), before being referred to our hospital. The diagnosis was based on clinical features, smear and or culture of corneal scrapings. Three were positive for fungus on KOH. Two were large perforated ulcers with near total corneal melt & in one case Glue & BCL had been done. Of the remaining three cases, one posted perforation central ectatic cicatrix, the other was graft infection with impending perforation & third was of unknown etiology, with suspected endophthalmitis.

Technique

All cases were done by two cornea surgeons, (SJ, HJ) under peribulbar anaesthesia with supplementary intravenous sedation whenever required. Cryopreserved AM was washed with Balanced Salt Solution three times, to reduce any possibility of contamination.[6]. Excision of the infected cornea leaving behind a rim of the healthy noninfected cornea was done. Exudates on & behind the iris were removed carefully, sacrificing infiltrate-laden non-viable iris, if needed. A core vitrectomy was done if needed. The amniotic membrane was cut into appropriate, sized pieces & multiple layers (3-4) were placed onto the ulcer bed, with fibrin glue between each layer. Then a piece of AM was trimmed to adequately cover the ulcer bed, placed epithelial side up & sutured with 10-0 nylon interrupted sutures. Lastly, a large piece of AM was used to cover the entire cornea and secured with interrupted sutures placed (Sandwich Technique) and BCL was placed [7].

Postoperatively, patients were continued on topical antifungals, prophylactic antibiotics, antiglaucoma & tear substitute drops.

At each postoperative visit, the following were monitored: 1) Epithelisation 2) Localisation of the infiltrates (location, size, depth) 3) Resolution of infection 4) Need for TPK

Results

Two cases (cases 1&5) with central corneal perforation & pseudocornea, healed well within 6-8 weeks, later after 3- 4 months, optical Penetrating Keratoplasty (P.K.) was done for them.

[Fig.1-3] with good visual recovery.

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Figure 1 – Case 1

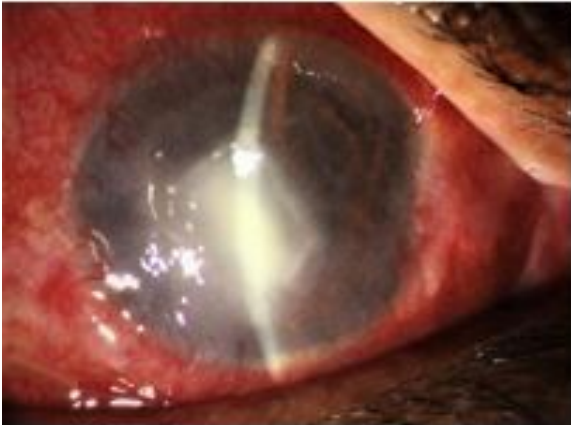


Figure 1A: Perforated fungal ulcer- Aspergillus



Figure 1B: Post-Multi-layered AMG

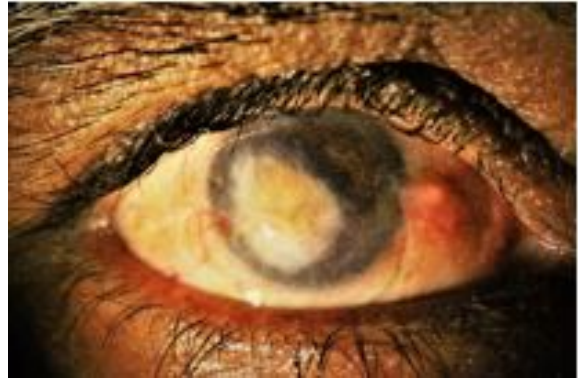


Figure 1C: Post healing- adherent leucoma



Figure 1D: Post-Optical Keratoplasty

Figure 2 – Case 5



Figure 2A: Perforated fungal ulcer

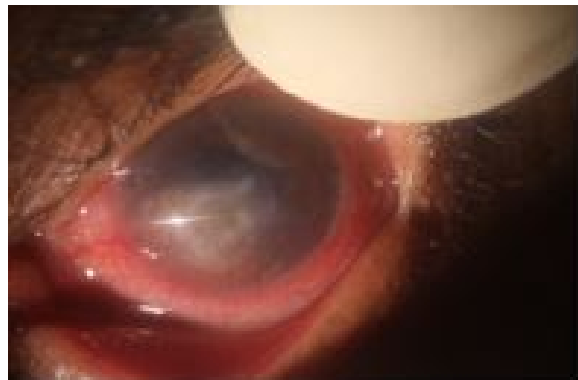


Figure 2B: Post multi-layered AMG



Figure 2C:Post Optical PK

In four cases with large perforations & near total corneal melt, resolution of keratitis with globe integrity was achieved.

(Case 2,3,7,8) (Figures 3A and B)



Figure 3A:Perforated fungal ulcer with near-total corneal melt



Figure 3B: Post-AMG, healing of melt with irregular scarring

Table 1-Clinical findings & outcome of AMT in case series of 9 patients

Serial no	Onset(weeks)	Morphology of lesion	Smear & culture	Prior treatment	Post AMG course
1	5 weeks	Central corneal ulcer with deep stromal infiltrates, Hypopyon	KOH-septate fungus CULTURE-Aspergillus	6 intrastromal voriconazole injections	Resolved with corneal scarring, optical P.K.done later
2	6 weeks	Perforated corneal ulcer with near-total corneal melt	KOH-septate fungus	Topical antifungals & antibiotics	Epithelisation of the lesion, no reinfection, restored anatomical integrity
3	18 days	corneal abscess with impending perforation, 360° choroidal	KOH-septate fungus	Topical antibiotics & antifungals	Epithelisation, resolution of ulcer
4	7 weeks	Deep stromal ulcer with endoexudates, suspected endophthalmitis	KOH negative	Intracameral & intravitreal ceftazidime & voriconazole injections	Epithelisation, resolution of endophthalmitis, no reinfection, Phthisical eye
5	2 weeks	Central ulcer with impending perforation	KOH & Culture negative	3 intrastromal voriconazole injections	Resolved keratitis with corneal scarring.Optical P.K.done later
6	5 weeks	Central progressive ulcer	Not done	Glue BCL did (outside hospital)	Healed with anterior staphyloma formation. Tectonic P.K. done
7	3 weeks	Total corneal melt with IOL extruding out	Not done	Topical antibiotics antifungals	1 week FU- beginning of epithelisation Lost to FU
8	8 weeks	Central ectatic cicatrix with iris incarceration	Not done	Topical antibiotics	Corneal scarring
9	6 weeks	Failed graft with decematocele	Not done	P.K. done twice (outside hospital), Glue BCL done	Resolution of infection.

Figure 4 – Case 6

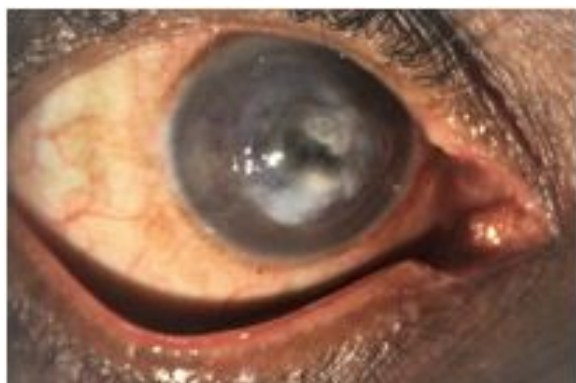


Figure 4A:Corneal ulcer with large descemetocoele

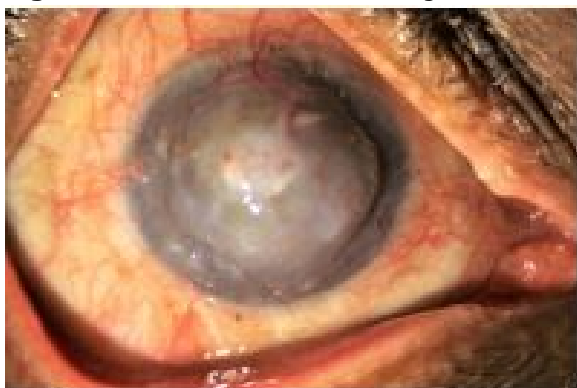


Figure 4B:Post-AMG healed ulcer with anterior staphyloma

One case healed with anterior staphyloma formation later required tectonic P.K. (Case 6) (Figure 4A and B)

In one case with perforation & endophthalmitis, the progression of infection was prevented, but the eye became pre phthisical. Case with graft infection also healed well post AMT, was advised repeat optical PK but refused surgery. The findings of patients are summarized in Table 1.

Discussion

During the COVID-19 pandemic, due to the stoppage of the Hospital Cornea Retrieval Program (HRCP), there was an acute shortage of donor corneas. Hence we resorted to, multilayer AMT for patients with severe keratitis with large perforations. Amniotic membrane (AM), produces various proteinase inhibitors and the stromal matrix has various growth factors like TGF β which contribute to its anti-inflammatory, anti-angiogenic, anti-scarring & pro-regenerative abilities.[4].

AM can reduce tissue damage & promote wound healing. [4]. Although in the past there were concerns about the recurrence of infection with AM transplantation, recent reports show that cryopreserved AM with intrinsic anti-infective properties has been used successfully in the treatment of non-healing corneal ulcers. [7,8]. It has been used in non-healing bacterial ulcers, [9]. also in acanthamoeba & HSV necrotising stromal keratitis.[10,5]. It has been used in Aspergillus, Fusarium & other persistent fungal infections [10,11]. with very low and treatable recurrence of infection even in active fungal keratitis [11]. In our case series too, there was no reinfection. AM is used as a single-layer inlay or overlay, multi-layered inlay or sandwich technique depending on the depth of the ulcer. [7,10].

Add what new this study adds to existing knowledge under the separate heading.

Newer Insights: In many cases reporting the use of AMG for nonhealing ulcers, keratitis was in the form of persistent epithelial defect with early sterile stromal melt.in these cases, a temporary AM as a patch, either sutured or self-retained (PROKERA) resulted in surface healing [7,10]. In contrast, all our cases were infective melts or perforations. So a single-layer AM graft would have melted or dissolved due to overwhelming infection & inflammation. There are reports of the use of AMT for frank infections too, but those were central or paracentral small and superficial ulcers.[8,10]. unlike our series where all cases were severe progressive, limbus reaching or perforated ulcers. AMT has been used quite effectively for bacterial, acanthamoeba & herpes simplex keratitis, [5,7]. but in very few fungal keratitis cases, unlike our series where the majority were fungal. Another difference in the technique of AMG is most case series report the use of a single-layer overlay, or multi-layered inlay technique [8,11,12]. whereas we have used a combination or sandwich technique and method of using several pieces of AM as an inlay with the use of fibrin glue & onlay patch with sutures probably worked like a tectonic patch graft.

As all our cases were very severe keratitis, a single layer of AM would have melted within a few days. The use of multi-layered AM in ulcers with marginal residual stromal tissue, prevented aqueous leak & anterior chamber collapse, whereas, in perforated ulcers, it provided some tectonic support, possibly

By restoring corneal integrity & healing by scar formation [12].

Alternatively, conjunctival flap (CF) has been used by Gunderson & others [13]. in the past for the treatment of chronic ulcers. However, it might not work for large perforated ulcers due to difficulty in dissection, mobilisation, suturing with possible complications, buttonholing, and retraction of the flap & corneal perforation [14].

Conclusion

In our small case series, we achieved the elimination of infection with the restoration of globe integrity. we found that AMT is effective in the resolution of ulcers with the preservation of globe integrity & salvaging the eye when the donor cornea is unavailable. So we recommend the use of cryopreserved AMT in infectious keratitis cases not responding to medical management. It is definitely worth using this technique of multi-layered AMG, to buy time, till donor cornea becomes available. For very large perforations, conjunctival or Tennon's graft may not suffice, so AMT becomes a globe-saving surgery in such cases.

Authors' Contribution: **Shilpa Joshi** performed many cases of these series, maintained proper documentation of follow-up visits, clinical photos etc., helped in compiling the data, wrote the manuscript & revised it many times. **Hema Joshi** operated on some cases of these series. **Ananya Abhyankar** helped in compiling the data and in writing the initial draft of the manuscript. **Col Deshpande** gave some valuable inputs to improve the quality of the manuscript.

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