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Case Report

Microbial Keratitis following Self-Retained Cryopreserved Amniotic Membrane

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Keywords
Cryopreserved amniotic membrane · Microbial keratitis · PROKERA · Mixed fungal and bacterial keratitis

Abstract
The aim of this study was to report a severe case of mixed fungal and bacterial microbial keratitis following implantation of a self-retained cryopreserved amniotic membrane, PROKERA® SLIM (Bio-Tissue, Inc) in a patient with history of neurotrophic ulcer secondary to herpetic epithelial keratitis. Despite maximally tolerated topical and systemic therapy, the patient's eye continued to deteriorate and eventually required evisceration. PROKERA implantation might be associated with severe recalcitrant microbial keratitis. Caution is urged when considering implantation especially in monocular patients.

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Introduction

Amniotic membrane transplantation (AMT) is used for various indications including persistent epithelial defect (PED) and neurotrophic ulcers [1]. However, AMT is a costly procedure because it requires an operating room. Hence, products such as PROKERA (Bio-Tissue® Inc., Maimi, FL, USA) were introduced which is a single sheet of cryopreserved amniotic membrane (AM) that can be delivered as an in-office procedure. Hence, the anti-inflammatory action of the AM begins immediately [2]. The antimicrobial and anti-inflammatory effects of

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PROKERA make it a suitable indication for severe microbial keratitis [3]. This report presents an unusual case of severe microbial keratitis following PROKERA insertion in a patient with neurotrophic ulcers secondary to herpetic epithelial keratitis.

Case Report/Case Presentation

A 74-year-old male, diabetic, who had undergone bilateral cataract extraction and filtration surgery 3 years ago for primary open angle glaucoma presented with pain and decreased vision OD. The patient had a history of recurrent epithelial erosions and neurotrophic corneal ulcer secondary to herpetic epithelial keratitis OD with frequent ER visits. At presentation, the patient was using topical ganciclovir 0.15% ointment (Virgan; Thea Pharmaceuticals), carboxymethylcellulose 0.5% drops (Refresh Plus, Allergan) QID, polyacrylic acid 2 mg/g gel (Viscotears; Bausch & Lomb) at bedtime, topical timolol 0.5% (Timoptol; Mundi Pharma), and dorzolamide 2% (Xola; Jamjoom Pharma). On examination, the corrected vision was 20/125, through pinhole OD and 20/30 OS. The intraocular pressures were within normal limits, bilaterally. The right eye had a corneal epithelial defect with epithelial edema without infiltrate. Fundus examination indicated a healthy disc with a cup: disc ratio of 0.4 OD and significant optic disc cupping and notching OS.

We initiated aggressive topical treatment with autologous 20% serum BSS eye drops, intensive lubricants, moxifloxacin 0.5% (Vigamox; Alcon) QID, NaCl 5% (Apisal; API) QID, and ganciclovir 0.15% ointment TID. Bandage contact lens placement was unsuccessful. Four weeks later, a linear epithelial defect remained with thick rolled epithelial edges. A PROKERA® SLIM (Bio-Tissue, Inc) AM was delivered using sterile technique in the minor treatment room after cleansing the eye with 5% povidone-iodine and continued the previous medical treatment.

Routine culture of transport media of the PROKERA was negative. The patient showed initial improvement with decrease in the size of his epithelial defect (shown in Fig. 1). Eight weeks after PROKERA insertion, the epithelial defect had significantly become larger despite patient's compliance with the treatment. The medical therapy was changed to gatifloxacin 0.3% (Tymer; Jamjoom) QID and erythromycin 0.5% ointment (Ophthalmolosa, Cusi) at bedtime. Ptosis was induced by Botox (Botox; Allergan) injection to help heal the epithelial defect. The patient was assessed regularly thereafter.

Ten weeks after PROKERA insertion, the patient presented to the emergency room with severe pain, a total epithelial defect with large stromal infiltrate over the superior half of the cornea and a 2-mm hypopyon. The infiltrate extended to more than 50% of stromal thickness, sparing the limbus and sclera. Clinical examination and B-scan ultrasound did not show any signs of endophthalmitis. The patient was diagnosed with PROKERA-related microbial keratitis.

The patient was admitted to the hospital, and corneal scrapings were performed after withholding antibiotics for 6 h. The PROKERA was removed and sent for microbial testing. Topical fortified broad-spectrum antibiotics were prescribed as follows: cefazolin 50 mg/mL QH alternating with ceftazidime 50 mg/mL around the clock. The clinical condition remained unchanged for the following 7 days. After 7 days, corneal scraping cultures came back positive for *Aspergillus fumigatus* and B hemolytic streptococci (*Streptococcus mitis/oralis*) sensitive to penicillin, ceftriaxone, and clindamycin. PROKERA culture was also positive for *A. fumigatus*. Topical voriconazole 1% QH was added to the medical regimen. The condition did not improve prompting initiation of oral valacyclovir (Valtrex; GlaxoSmithKline) 500 mg TID, voriconazole (VFEND, Pfizer) 20 mg BID, topical natamycin 5% every Q2H, and ganciclovir 0.15% ointment five times daily. Additionally, a dose of intrastromal amphotericin B 0.15% and

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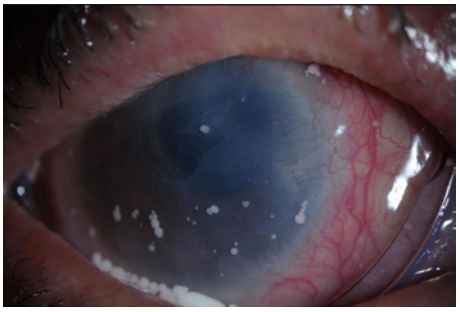

Fig. 1. Slit-lamp corneal photo showing epithelial defect under PROKERA 1 week after insertion.

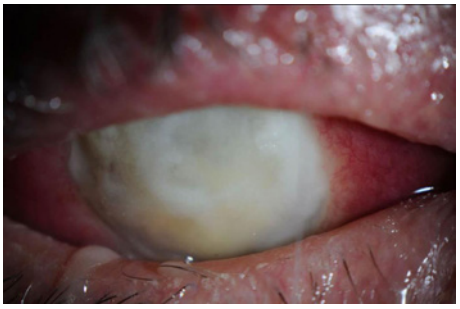

Fig. 2. Slit-lamp photo of total corneal infiltrate with melting and endophthalmitis.

subconjunctival antibiotic was delivered. The disease progressed with an aggressive course. Two weeks after admission, a corneal melt developed with a large infiltrate extending to the limbus (shown in Fig. 2). The patient complained of severe ocular pain and developed clinical signs of endophthalmitis including decreased vision to light perception with poor projection and lid swelling.

Ultrasonography indicated retinochoroidal thickening and a choroidal detachment. A vitreoretinal consult was ordered, and vitreous aspirate showed a thick black fluid. Intravitreal antibiotics and antifungal were prescribed as follows; amphotericin B 5 μg/0.1 mL, vancomycin 1 mg/0.1 mL, and ceftazidime 2.25 mg/0.1 mL. Due to the poor visual potential and the risk of the infection spreading to the orbit and central nervous system, an evisceration was performed by an oculoplastic specialist.

Discussion/Conclusion

PEDs are a common sequelae of corneal HSV infections, and medical therapy usually fails. AMT has a good therapeutic effect on PED secondary to HSV keratitis [4]. Self-retained cryopreserved AM is effective for treating many ocular surface conditions, including PEDs [5]. The use of PROKERA facilitates early and easy intervention with comparable efficacy [2]. However, cases of early and late (after 30 days)-onset postoperative microbial infections can occur (Table 1) [6–8].

To our knowledge, this is the first case of combined fungal and bacterial microbial keratitis following the use of a suture-less, self-retained cryopreserved AM in our region. Microbial transmission from the PROKERA device to the host is unlikely due to the strict manufacturing standards and negative culture results of transport media. The device was inserted under strict sterile conditions; hence, intraoperative transmission is very unlikely.

If soaked with antibiotics prior to implantation, AMs function as slow-release antibiotic reservoirs increasing the antibiotic concentration in the tear film compared to topical

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Table 1. Microbial keratitis after AMT

Case	Age	Gender	Diagnosis	AMT technique	Additional procedure	AMT to MK interval, days	Culture results
1	26	M	VKC, PED with recurrent shield ulcers	Single	Superficial keratectomy	38	*Staphylococcus epidermidis*
2	50	M	CDK, PED with sterile melt and perforation	Single	PKP, ECCE, IOL	55	*Mycobacteria abscessus*
3	70	M	HSV keratitis; PED	Single	Tarsorrhaphy	92	*Staphylococcus epidermidis, Pasteurellahaemolytica*
4	4	M	HSV Keratitis with perforation: PKP <30 days; PED	Double	None	143	*Streptococcus pneumoniae, Haemophilus influenzae*
5	96	M	CDK; MK <30 days; perforation; PED	Single	PKP, lensectomy, vitrectomy	182	*Staphylococcus epidermidis, Streptococcus viridans*
6	57	M	Chemical injury; PKP >30 days; PED	Double	None	209	*Pseudopmonas aeruginosa*
7	69	M	CDK; MK >30 days; PKP >30 days; PED	Single	None	347	*Staphylococcus epidermidis, Corynebacterium diphtheriae*
8	55	F	PBK	Single	Epithelial debridement, anterior stromal puncture	28	*Aspergillus* sp.
9	74	M	Glaucoma, HSV neurotrophic keratitis, recurrent erosions, PED	PROKERA	Upper lid Botox injection	74	*Aspergillus fumigatus, Streptococcus mitis/oralis*

AMT, amniotic membrane transplantation; MK, microbial keratitis; VKC, vernal keratoconjunctivitis; PED, persistent epithelial defect; CDK, climatic droplet keratopathy; HSV, herpes simplex virus; PBK, pseudophakic bullous keratopathy; PKP, penetrating keratoplasty; ECCE, extracapsular cataract extraction; IOL, intraocular lens.

application after 1 and 2 h [9]. However, the possibility of AMs acting as a barrier to penetration of certain antibiotics remains a possibility in our case. The prolonged use of the PROKERA device, exceeding the conventional duration of treatment, in addition to the induced ptosis may have also contributed to the increased risk of infection in our patient.

The long-standing history of diabetes, herpetic eye disease, and neurotrophic keratopathy with PED and impaired immunity makes it the most probable cause for this aggressive and extensive infection. Due to the aggressive nature of fungal keratitis, enucleation is an alternative to evisceration in cases approaching the sclera. Conjunctival flaps or cryotherapy can also be considered [10]. Although a self-retained cryopreserved AM is safe, the risk of microbial infection remains, especially in patients with poor ocular surface and compromised immunity.

Statement of Ethics

This case report was reviewed and approved by the Ethical Committee of the Institutional Review Board at King Khaled Eye Specialist Hospital in Riyadh, Saudi Arabia. An expedited approval was granted, project number: 1767-CR. This work has been conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. This report does not contain any identifying information for the patient. Written informed consent is included with the general hospital's consent which is signed in advance, once the patient starts receiving treatment at the hospital.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Each of the authors has contributed to, read, and approve this manuscript. All authors meet the current ICMJE criteria for authorship. Dr. Rafah Fairaq and Dr. Eman D. AlBalawi were responsible for the literature review and writing of this manuscript. Dr. Samar A. Al-Swailem oversaw the management of this patient in addition to the final review and approval of this manuscript. All authors have read and approved the final manuscript submitted for publication.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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