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Amniotic Membrane Transplantation: A Good Treatment Option for Refractory Neurotrophic Keratitis

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Neurotrophic keratitis is a degenerative disease of the corneal epithelium resulting from impaired corneal innervation, possibly leading to perforation. In this report, we present a case with a history of herpetic keratitis, who developed a difficult neurotrophic ulcer despite 10 days of topical lubricant therapy and oral doxycycline. Amniotic membrane transplantation can be considered an effective alternative for treating persistent and progressive neurotrophic corneal ulcers.

Keywords: Amniotic membrane transplantation; neurotrophic keratitis; combination of graft and patch.

1. INTRODUCTION

Neurotrophic keratitis (NK) is a rare degenerative corneal disease caused by impairment of trigeminal innervation leading to corneal epithelial breakdown, impairment of healing, and development of corneal ulceration, melting, and perforation [1-3]. The distinctive feature of NK is a decrease or absence of corneal sensation [2,3]. Impairment of corneal trigeminal innervation causes morphological and metabolic epithelial disruption and leads to development of recurrent or persistent epithelial ulcers [3].

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The most common causes of neurotrophic keratopathy include herpetic infection (Simplex or Zoster), intracranial space-occupying lesions, and/or neurosurgical procedures that damage the trigeminal ophthalmic branch, chemical burns, physical injuries, corneal dystrophies, chronic use of topical medications, diabetes mellitus, tumours affecting the trigeminal ganglion or sensory routes, radiation, and anterior segment surgeries [1,3-5].

Pharmacological treatment options for NK are limited. Topical lubricants such as preservative-free artificial tears, new osmoprotective formulas and recently topical dexapanthenol may help improve the corneal surface healing in mild to moderate NK [6]. Amniotic membrane transplantation (AMT) is a surgical option for ocular surface reconstruction in the management of refractory neurotrophic corneal ulcers. AMT is relatively easy to perform, and is effective in promoting corneal epithelial healing, reducing ocular surface inflammation and neovascularization. Multilayer AMT has been proposed for treating deep neurotrophic corneal ulcers [7].

We report a patient with a history of herpetic keratitis, who developed a difficult neurotrophic ulcer despite 10 days of topical lubricant therapy and oral doxycycline.

2. CASE REPORT

A 73-year-old man presented with redness, blurred vision, and foreign body sensation in his left eye. He had been treated with topical antibiotics and artificial tears for this condition over the last four months. His past history was insignificant except cataract surgery six months ago. It was an uneventful phacoemulsification surgery in both eyes, at another institution.

At the time of admission, his visual acuity was counting fingers in the left eye and his best-corrected visual acuity (BCVA) in the fellow eye was 20/20. Slit-lamp biomicroscopy revealed a paracentral deepcorneal ulcer, approximately 4 x 7 mm wide (clinical stage 3 according to Mackie) [8], with hazy borders and surrounding stromal edema (Fig. 1). A corneal sensitivity test using a cotton thread revealed decreased sensation in the inferior and paracentral areas of the left cornea compared to the other locations in the left cornea and to all the locations in the right cornea. Polymerase chain reaction (PCR) was performed on the corneal scraping samples of his to test for the presence of herpes simplex virus 1 (HSV1), HSV2, and varicella zoster virus genomes.

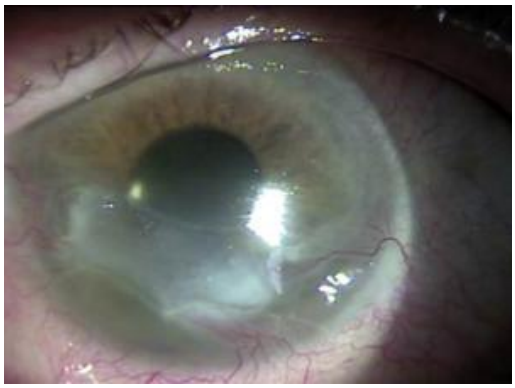

Fig. 1. Diffuse slit-lamp view of patient showing the area of deep corneal ulcer, stromal melting and signs of ocular inflammation (Stage 3 neurotrophic keratitis)

PCR was positive for Herpes Simplex virus type I. A diagnosis of herpetic keratitis was made on the basis of corneal hypoesthesia, the clinical appearance of the corneal lesion and positive PCR. Treatment was started with oral acyclovir 400 mg (Aklovir®; Sandoz, Turkey) 5 times daily, 100 mg of oral doxycycline (Monodox®; Deva, Turkey) twice a day, topical fucidic acid (Fucithalmic®; Abdi Ibrahim, Turkey) as lubricant ointmet (Terramycine®; Pfizer, Turkey) twice a day and preservative-free artificial tears (Tears Naturale Free®, Alcon, USA) drops 4 times a day. The ulcer was not much different despite the above therapy (Fig. 2). Therefore, amniotic membrane transplantation (AMT) was performed on the 10^{th} day of admission.

In eye with neurotrophic ulcer, the base of the ulcer was debrided with a microsponge and fine forceps, and the poorly adherent epithelium adjacent to the edge of the ulcer was removed up to the area where the epithelium became adherent. Then, multilayer fresh amniotic membrane was performed using combination of graft and patch technique (also called the sandwich technique) on the deep corneal ulceration with epithelium side up and the mesenchymal surface in contact with the recipient eye, and fitted to fill up the ulcer and cover the defect by trimming off the excess edges (Fig. 3). AMT was secured using 10/0 monofilament nylon sutures. A bandage contact lens was applied on top of the membrane until the membrane started to dissolve. The patient received topical prednisolon acetate 1% (Pred

Forte®; Abdi Ibrahim, Turkey) and ofloxacin 0.3% (Exocin®; Abdi Ibrahim, Turkey) ophthalmic solution four times daily for one week. Topical steroid was gradually decreased and topical antibiotic was stopped after contact lenses removal. Four weeks postoperatively, a membrane completely dissolved revealing a fully restored stromal thickness with no epithelial defect. Regular follow-up visits were scheduled every two months, and after three years of follow-up there was no corneal ulcer recurrence. On slit-lamp examination a residual stromal haze was noted, and superficial vascularization was observed across the paracentral cornea over the amniotic membrane site (Fig. 4). The final best corrected visual acuity of 20/200 was achieved.

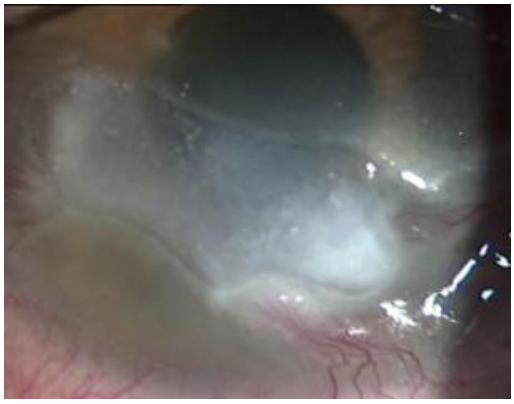

Fig. 2. Corneal neurotrophic ulcers after medical treatment. Patient who was nonresponsive to medical treatment. Appearance at 10 days after topical medical treatment revealed wide persisten epithelial defect and stromal melting

3. DISCUSSION

Corneal healing is a complex process involving complex cellular interaction and various molecules (proteases, growth factors, and epithelial and stromal cytokines) [7,9]. Corneal neurotrophic ulcers, particularly in patients with total corneal anesthesia, are among the most difficult ophthalmological conditions to treat, and may potentially result in blindness.If the process cannot be reversed on time, it may progress toward corneal perforation or total de novo vascularization [10,11].

The treatment is based on artificial tears and the withdrawal of preserved eye drops or other types of epitheliotoxic topical medicines. Osmoprotectant compatible solutes including erythritol, glycerol, trehalose, taurine, L-carnitine may be use for protecting ocular epithelial cells [12]. If one of an osmoprotective formula is successful, one would expect this to reduce inflammation and additional cell damage. Also, tetracyclines (doxycycline and minocycline) can protect the cornea against proteolytic degradation. They inhibit matrix metallo-proteinases by mechanisms independent of their antimicrobial properties, primarily through restriction of the gene expression of neutrophil collagenase and epithelial gelatinase, suppression of α1-antitrypsin degradation, and scavenging of reactive oxygen species. Recently, the antiangiogenic property of doxycycline has received increasing attention, particularly in ocular angiogenesis [13].

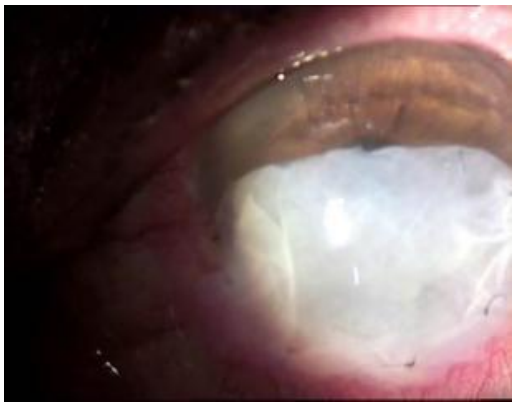

Fig. 3. Fresh amniotic membrane transplantation was performed over the deep neurotrophic corneal ulcer and covered as combination of graft and patch technique

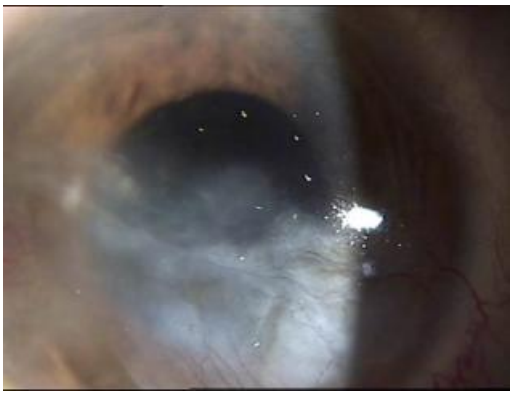

Fig. 4. Twenty-eight days after amniotic membrane transplantation, the membrane dissolved, the corneal and conjunctival surfaces were no longer inflamed, and the deep corneal ulcer completely healed

Autologous serum or amniotic membrane transplantation may also be used in severe cases, but their cost and safety are still under debate [14]. Recently, AMT has been successfully used to treat persistent corneal epithelial defects and ulcers from different causes, and for corneal and conjunctival surface reconstruction for a variety of ocular surface disorders [15,16]. Amniotic membrane can be performed using several different techniques such as graft, patch, and combination. Graft technique, the AM is applied as a permanent basement membrane substitute. In deep defects, e.g. corneal ulceration, multiple layers of AM can be used. Epithelialization of the AM integrates AM into the host tissue. It remains detectable for months, sometimes years, and in defects of the cornea is even colonized by local keratocytes. Patch technique, a large AM is temporarily placed on the surface of the eye as a “natural” patch. Unlike the graft technique, the AM patch typically becomes detached from the surface of the cornea after one to two weeks [17,18]. Sandwich technique is a combination of the two described above and is used mainly in serious disorders of the ocular surface such as deep and extensive corneal ulceration. This method is favored due to its high success rate (65% to 80%), and low rate of recurrence (approx. 20% to 35%) [18,19]. Amniotic membrane may express many antiangiogenic factors, antiinflammatory factors, growth factors, protease inhibitors, and immune molecules to promote the corneal ulcer healing [20,21]. Furthermore, the amniotic membrane can promote migration, adhesion, differentiation of epithelial cell, and prevent epithelial apoptosis. In corneal neurotrophic ulcers, amniotic membrane (AM) can be used to cover the exposed zone and to provide components required for reconstitution of an intact basal membrane. AM-covered surfaces have been shown to induce rapid re-epithelialization (in 2 to 4 weeks) to a smooth and wettable surface and reduce inflammation, vascularization, and scarring, thus allowing successful surface reconstruction [22]. Many researches have noted enhanced healing of wounds with the application of amniotic membrane. Also, using the amniotic membrane as a graft may prevent surface exposure and dryness because of decreased tear and blinking reflex in neurotrophic keratitis [7-9,14,15].

Lee and Tseng [23] first demonstrated the efficacy of AM in treating persistent epithelial defect from various causes while Kruse 24 successfully introduced the use of multilayer AMT for deep corneal ulcer. During a mean follow up period of 18.8 (13.0) months, all but four AMT (13/17, 76.4%) ulcers healed. Epithelialisation took place in 16.6 (9.0) days in these 13 eyes (reviewed by Lee and Tseng). Similarly, Kruse et al. [24] reported who successfully treated with multilayered AMT nine of 11 eyes with neurotrophic corneal ulcers. Prabhasawat et al. [25] transplanted amniotic membrane in 28 eyes with persistent corneal epithelial defect unresponsive to medical treatment including six eyes with limbal deficiency. They reported success rate of 82.1% in all groups with a mean follow-up of 10.9 months. We noted in this case study that ocular surface inflammation was markedly reduced following AMT. In this case, we applied the combination of techniques (sandwich technique) to prolong the durability of the membrane and increase the success rate. We achieved healing of deep corneal ulser using the combination technique (graft and patch). There was no recurrence at the treatment site during the 36-month follow-up period.

In this report, the AM was sutured as a multilayer amniotic membrane to cover the ulcerated area. When used as a combination technique, AM promotes epithelialization over it, and is frequently preserved and may become quite transparent over time. We noted in this case that ocular surface inflammation was markedly reduced following AMT. This finding may be explained in line with some recent studies showing that the stromal matrix of the amniotic membrane excludes inflammatory cells,and contains various forms of protease inhibitors [26]. It is also reported to have suppressed transforming growth factor β (TGF-β) signalling, and proliferation and myofibroblast differentiation of normal human corneal and limbal fibroblasts [27]. Herein, we summarise our experience in using AMT for persistent and progressive neurotrophic corneal ulcers.

4. CONCLUSION

Amniotic membrane transplantation may be considered as an alternative method for treating persistent neurotrophic corneal ulcers and sterile ulceration that are refractory to conventional treatment and before considering treatment by conjunctival flaps or tarsorrhaphy.

CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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