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Pseudomonas Keratitis in a Neurotrophic Cornea Ulcer Successfully Treated with Topical Antibiotics, Deep Anterior Lamellar Keratoplasty and Human Amniotic Membrane Transplantation

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Abstract

An 80-years old man came to our attention with severe infection keratitis in his left eye. The patient presented a history of recurrent herpetic keratopathy, leading to severe corneal hypoesthesia and persistent neurotrophic ulceration in affected eye. Slit lamp examination revealed a large paracentral corneal ulcer with stromal melting and hypopyon. Corneal scraping was positive for P. aeruginosa sensitive to ceftazidime. Fortified topical antibiotics led to rapid resolution of the infection. However AS-OCT showed a severe stromal thinning. We performed a no stitch triple-layered human amniotic membrane transplantation (AMT) by using fibrin glue, followed by the application of a scleral contact lens, to reduce inflammation and to prepare the ocular surface for the subsequent deep anterior lamellar keratoplasty (DALK). A few days later, due to persistent corneal thinning, we proceeded with DALK, combined with AMT and with the application of a scleral contact lens. The sequential application of fortified antibiotics, trilaminar AMT, and subsequent DALK and AMT allowed a successful infection control, effective modulation of inflammation, and restoration of corneal structural integrity.

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Introduction

Neurotrophic ulcer is a degenerative condition affecting corneal epithelium and stroma, primarily caused by damage to the trigeminal nerve that innervates the cornea [1]. Corneal nerves transduce a variety of sensations, including pain, mechanoreception, and temperature which regulate tear production and the blink. Corneal nerve additionally supports corneal healing through the production of trophic factors, such as nerve growth factor (NGF) [2].

Persistently altered corneal sensitivity can trigger a chain reaction, including reduced or imbalanced production of trophic factors, subsequent dysfunction of the lacrimal functional unit (LFU), and impaired corneal repair. If let untreated, these changes may result in epithelial persistent damage and visual impairment [2].

Conventional treatment of neurotrophic corneal ulcers can be either medical or surgical, depending on the severity of the condition, and often involves a combination of approaches. In clinical practice, medical therapy includes intensive lubrication with frequent use of preservative-free artificial eye drops, contact lenses, blood derived products, punctum plugs, topical recombinant nerve growth factor. Surgical approaches such as fibrin glue, cyanoacrylate, amniotic membrane transplantation (AMT) and tarsorrhaphy are reserved for more severe cases [3,4].

Amniotic membrane (AM) is the innermost layer of the placenta and comprises three layers: epithelium, basement membrane, and avascular stroma. AMT has been successfully used to treat neurotrophic corneal ulcers by providing mechanical protection, releasing growth factors, and supporting epithelial cell adhesion and proliferation [5].

Bacterial superinfection is a potential complication of neurotrophic keratitis requiring initial empiric broad-spectrum antibiotic therapy, subsequently refined according to microbiological culture results [6]. The main pathogens responsible for superinfection are Gram-positive bacteria

such as *Staphylococcus aureus* and Gram-negative bacteria such as *Pseudomonas aeruginosa* [7].

Pseudomonas aeruginosa is a gram-negative opportunistic pathogen organism that is a leading cause of infection keratitis worldwide. Infection keratitis from Pseudomonas aeruginosa is commonly linked to contact lens use, but it can also be associated with ocular trauma, ocular surgery and compromised ocular surface. P. aeruginosa can cause severe infectious keratitis that may rapidly progress to corneal melting and perforation [8].

Case Presentation

An 80-years old man came to our attention complaining a decreased visual acuity, conjunctival hyperemia, and mucopurulent discharge in the left eye, without associated pain.

The patient presented a history of recurrent herpetic keratopathy started 20 years ago, leading to profound corneal hypoesthesia, tested by using Cochet-Bonnet aesthesiometer, and chronic neurotrophic ulceration in affected eye.

Best-corrected visual acuity (BCVA) in the left eye was light perception.

Slit lamp examination showed: chemosis, marked conjunctival hyperemia, roundish paracentral corneal ulcer measuring 6 mm in diameter, with stromal infiltrates, edema and signs of corneal melting. Additionally, there was tyndall and hypopyon (2.5 mm), regular pupil, dense cataract (Figure 1).

The fundus was poorly visualizable and thus a B-scan ultrasonography (ECO-B) was performed, showing no signs of vitreitis.

Cornea optical coherence tomography (AS-OCT) was performed with Optovue® (software version: 2018,1,0,37).

We immediately performed corneal scrape, and we started fortified antibiotics: topical vancomycin 5% and ceftazidime 5% eye drops every 5 minutes for two hours and then alternated every hour.

Within 24 hours, both the hypopyon and anterior chamber inflammation (Tyndall) were resolved. Microbiological culture from the corneal scraping tested positive for *Pseudomonas aeruginosa*, which was sensitive to ceftazidime.

We continued only ceftazidime therapy 8 times a day and checked daily the patient for other six days and finally slit lamp examination showed no signs of restarting infection.

Figure 1: Slit lamp examinations showing chemosis, marked conjunctival hyperemia, roundish paracentral corneal ulcer measuring 6 mm in diameter, with stromal infiltrates, edema and signs of corneal melting, hypopyon (2.5 mm), regular pupil, dense cataract

Figure 2: Slit lamp examination showing the scleral contact lens and triple layer amniotic membrane transplantation.

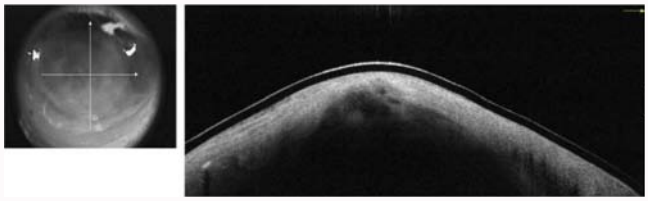

Figure 3: AS-OCT showed stromal thinning even after AMT.

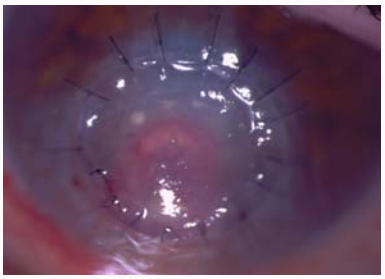

Figure 4: Slit lamp examination showing DALK graft and AMT opposed to the recipient stroma, interrupted sutures in place, mild corneal edema, anterior chamber formed with internal corneal blood coating.

AS-OCT revealed critically reduced stromal thickness. Given the risk of perforation and to promote ocular surface healing, we performed an AMT to reduce inflammation and to prepare the ocular surface for a future deep anterior lamellar keratoplasty (DALK).

The informed consent was explained and then signed by the patient. Topical anesthesia with oxybuprocaine chlorhydrate 4% was performed. In surgical room, periocular tissues disinfection was performed with iodopovidone solution at 10% concentration for 5 minutes. A sterile drape and eyelid speculum were applied. The cornea was dried accurately using sponges, and three layers of human amniotic membrane were transplanted by using fibrin glue (TISSEEL®). The first layer (5 × 5 mm) was epithelium down, the second one (6 × 6) was epithelium up, and the last one (7 × 7 mm) was epithelium down. A scleral hydrogel contact lens (Regenera® eyepharma, diameter 16.5 mm, ionic material G-72 HW H2O 72%) was applied to protect the graft and to promote the epithelial healing (Figure 2).

We monitored the patient daily for four days. Conjunctival hyperemia significantly decreased; however, AS-OCT confirmed persistent extreme corneal thinning (Figure 3).

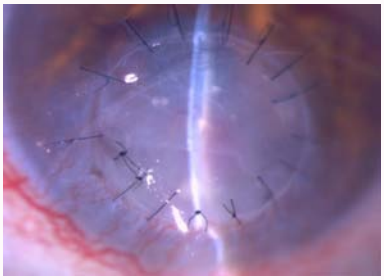

Figure 5: Slit lamp examination showing decentered LAC, DALK graft well apposed, interrupted sutures in place, reduction of blood coating and of corneal edema, regular anterior chamber.

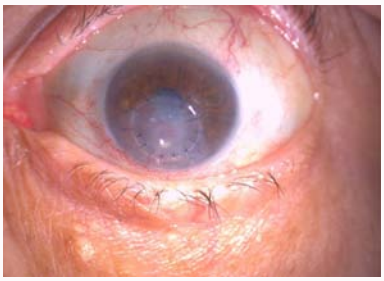

Figure 6: Slit lamp examination showed DALK graft well apposed, interrupted sutures in place, reduction of corneal edema, blood coating resolution and conjunctival redness, anterior chamber formed.

Based on these findings, we proceeded with combined DALK and AMT.

The informed consent was explained and then signed by the patient.

In surgical room, periocular tissues disinfection was performed with iodopovidone solution at 10% concentration for 5 minutes. A sterile drape and eyelid speculum were applied. After measuring the actual diameter of the ulcer (6 mm), the donor graft was manually trephined in the same size, attached to the recipient wound, and sutured into the host bed using 10-0 nylon interrupted suture. The corneal graft was covered with a double layer of AM by using fibrin glue (TISSEEL®). A scleral hydrogel contact lens (Regenera® eyepharma, diameter 16,5 mm, ionic material G-72 HW H2O 72%) was applied to protect the graft (Figure 4).

The patient was visited every 5 days during the first 15 days, and then every 10 days.

At the 10-day follow-up, slit-lamp examination showed a well-apposed DALK graft with interrupted sutures in place. There was a reduction in conjunctival hyperemia, a decrease in corneal edema. Anterior chamber was formed and blood coating was reduced (Figure 5).

The 2-month follow-up showed well integrated DALK graft in recipient stroma, a further reduction in conjunctival hyperemia and corneal edema, the anterior chamber formed and quiet (Figure 6).

Discussion

The pathophysiology of neurotrophic keratitis involves a loss of sensitivity as a result of damage to the trigeminal nerve. One of the main causes of trigeminal nerve damage is infection by HSV (Herpes Simplex Virus). The loss of sub-epithelial and sub-basal plexus density causes hypoesthesia, disrupts the supply of trophic factors necessary for epithelial cell migration, and impairs neural signaling essential for maintaining both the quality and quantity of the tear film [9,10]. Management of neurotrophic keratitis is based on clinical severity, and focuses on promoting corneal healing, restoring nerve function, and preventing complications [4].

In our case, once the bacterial superinfection was resolved with fortified antibiotics, it was necessary to manage the inflammation and the significant corneal thinning. The first AMT was performed to modulate inflammation and to prepare the ocular surface for the following DALK.

There are different AMT techniques: the inlay (or graft) technique, where one or more layers of AM are trimmed to match the size of the corneal defect and placed within the ulcer bed, with the top layer secured to the edges of the lesion; the overlay (or patch) technique, in which an oversized AM sheet is applied to cover the entire cornea and limbal region; and the sandwich technique, which combines both inlay and overlay approaches [11].

AMT can be performed using either a single-layer or multilayer membrane, depending on the size of the ulcer [12]. In our case, a trilaminar graft was chosen due to the wide extent of the lesion. The three layers were arranged according to the "sandwich" technique, with each layer cut in progressively larger dimensions to ensure complete coverage of the defect.

Despite the significant reduction in inflammation achieved within a few days of the initial treatment, a DALK procedure was required due to the extensive size of the ulcer and corneal thinning. We also performed AMT to promote the survival of the DALK graft and ensure its proper integration into the recipient bed.

Furthermore, we think that, at the time of DALK and AMT, to associate a therapy with recombinant human nerve growth factor (rhNGF) could be helpful to promote corneal sensitivity recovery and facilitate graft integration [13]. If rhNGF is not available, blood derived products (diluted autologous serum or PRP eyedrops) could be used instead.

Conclusion

The management of neurotrophic keratitis requires a multimodal approach to promote epithelial healing, reduce inflammation, restore and prevent severe complications such as corneal perforation. In our case report the combined and sequential use of fortified antibiotics, trilaminar AMT, subsequent DALK combined with AMT, showed to be a successful therapeutic strategy.

Of no lesser importance we believe that it is necessary to restore corneal sensitivity to avoid recurrences.

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