

Research Article

Rapid Healing with ReGeneraTing Agent (RGTA) of a Refractory Post Surgical Corneal Ulcer

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ABSTRACT

Purpose: Corneal ulcer, especially in the context of neurotrophic keratopathy is a potentially challenging and sight threatening condition. We present a case of refractory post-surgical ulcer with decreased corneal sensitivity, successfully treated with RGTA (Cacicol[®]).

Methods: A 95 years-old man underwent eyelid surgery for basocellular carcinoma. Because of a secondary eyelid malocclusion, a band keratopathy developed, leading visual acuity to 3/10. Two EDTA scratching surgeries were performed in order to improve vision. But six weeks after the last surgery, a partial loss of sensitivity associated with an epithelial defect (1,5 mm *2,5 mm) and deep stromal ulcer (with stromal edema all around and temporal neovascularization) was still present despite an intensive treatment with artificial tears, vitamine A ointment, antibiotic drops, 24-hours bandage with a topical antibiotic cream: oxytetracyclin- polymyxin and hydrocortisone (Terracortril[®]). For this refractory corneal ulcer with neurotrophic keratitis, we then decided to stop this treatment and to replace it by RGTA 1*/48hours and artificial tears 5*/day.

Results: While it did not respond to previous topical treatments for six weeks, this post-surgical ulcer with decreased corneal sensitivity and exposed cornea, responded quickly to RGTA drops. After one week, the size of the ulcer was a fifth from its original size. It took fifteen days to completely close the ulcer.

Conclusion: The healing of corneal ulcers especially when the corneal sensitivity is involved with a consequent neurotrophic keratitis is a challenge. Several steps are necessary: to stop topical toxic treatment, to find and to treat causes of the ulcer and then apply and alternative treatment. In some cases, RGTA drops can quickly help.

Introduction

The cornea is one of the most innervated tissue in the human body. This innervation is essential to assure corneal sensation and to provide trophic factors for the maintenance of the integrity, function and structure of the cornea [1].

However, there is a potentially sight threatening condition in

which there is an innervation impairment: neurotrophic keratopathy. By definition, neurotrophic keratopathy refers to a condition where epitheliopathy leading to epithelial defect with or without stromal ulceration is associated with reduced or absent corneal sensations.

The common causes of neurotrophic keratopathy are: corneal herpes infections, ocular surface thermal and chemical burns, contact lenses misuses and cranial neurosurgery, systemic condition as

diabetes mellitus, ocular problem as abuse of topical anaesthetics, ocular surgery [2].

According to Mackie's classification, the treatment of neurotrophic keratopathy is different depending on the stage. The first step consists of stopping topic drops that can be toxic, lubricating with artificial drops. Vitamin A creme, collagenase inhibitors, prophylactic topical antibiotic or therapeutic lenses can also be used.

The step further in severe cases consists of oral doxycycline, autologous serum, amniotic membrane transplantation, tarsorrhaphy, even conjunctival flap [1,3].

A next progress has been reached recently by using a new matrix-regenerating agent (RGTA). It is a biopolymer designed to mimic heparan sulfates bound to corneal extracellular matrix proteins, protecting them from proteolysis and enabling growth factors and cytokines to act on the injured site [1].

Several studies showed the usefulness of RGTA treatment in the cases of neurotrophic keratopathy, as Aifa et al. [4] and Guerra et al. [1].

Case Presentation

We present a case of A 95 years-old man, with a two years history of neurotrophic keratitis in the right eye, the left eye was strongly injured in a car accident in the 1960's, the eyeball was saved but without any visual function. The patient presented an end-stage renal failure, hypertension in a context of renal artery stenosis. His grandfather and father passed out after a myocardial infarction at the age of thirty.

In 2016, an eyelid surgery (right eye) was realized to remove a basocellular carcinoma, leading to an eyelid malocclusion. The patient developed a band keratopathy (visual acuity 3/10), and two EDTA scrapping surgeries were performed to improve his visual acuity.

After the second surgery, a loss of part corneal sensitivity and an epithelial defect with deep stromal ulcer persisted, and did not respond to treatment (artificial tears, vitamin A ointment, antibiotic drops, 24-hours bandage with a topical antibiotic crème for six weeks. Visual acuity was then 1/10.

During his first visit in the emergency unit of our eye clinic, he was applying an ointment containing hydrocortisone, oxytetracyclin and polymyxin (Terracortril *). The main complain consisted in eye discomfort, decreased vision to counting fingers. The treatment was Terracortril* ointment 3*/day in the right eye.

Slit lamp examination: a large epithelial defect 1.5mm x2.5 mm with a deep stromal ulcer and stromal edema around the ulcer and temporal neovascularization. Corneal epithelium was diffusely irregular. The upper eyelid did not cover the entire cornea which induced a temporal exposition of the conjunctiva with local hyperhemia and slight part of the temporal cornea. The tear break up time was 4 seconds. An ectropion of the inferior eyelid was also observed (Figure 1).

The cornea sensitivity was present in both eyes but slightly decreased in the right eye. The method used to evaluate corneal sensitivity was by taking a tissue, and testing subjectively each quarter of the cornea in both eyes.

Treatment was: arrest of oxytetracyclin and polymyxin

(Terracortril) and topical treatment RGTA (Cacicol) 1*/48 hours and artificial tears Thealoz Duo 5*/day.

A photograph was taken at each control, to evaluate the healing process (Figures 2-6).

It took fifteen days to close the cornea, but it remained a stromal edema that was in the visual axis. The visual acuity was then 1/20. Softacor was added 2*/day to decrease inflammation, reduce the



Figure 1: Day 1. Large neovascularized deep stromal ulcer with epithelial defect 1.5mm x2.5 mm surrounded by stromal edema

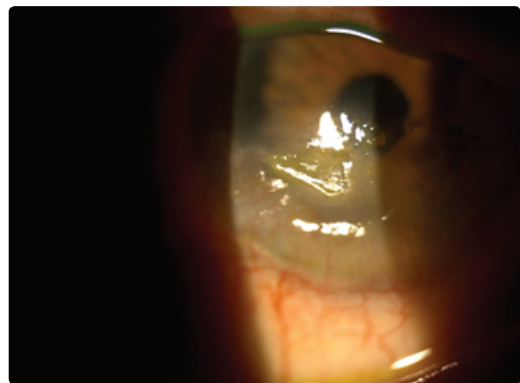


Figure 2: Day 2. Ulcer size had decreased to 1 mm x 1.8 mm

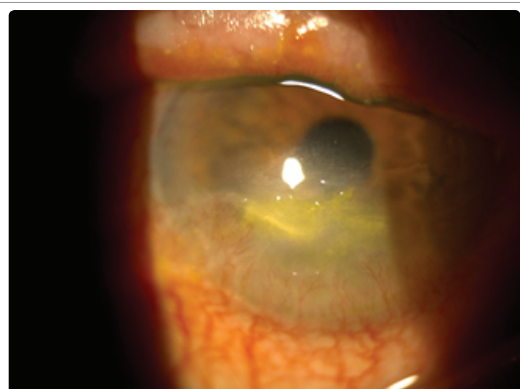


Figure 3: Day 4. Ulcer size is 0.5mm x 1.5mm, still surrounded by slight corneal edema.

neovascularization in front of the ancient ulcer, so decrease the stromal edema (Figure 7).

Finally, after twenty days of treatment of Cacicol and Softacor, the ulcer was closed, and the inflammation decreased (Figure 8).

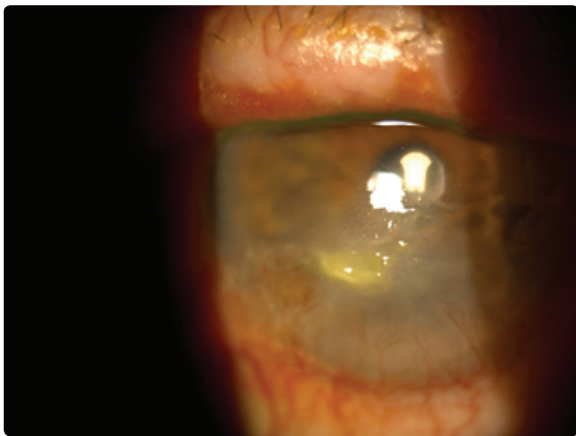


Figure 4: Day 6. Ulcer size is 0.5mm x 1.3mm

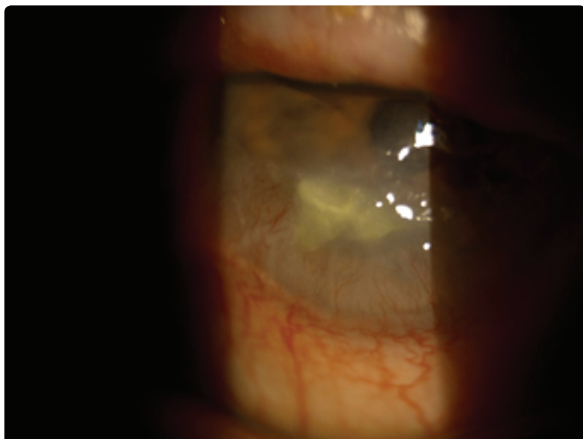


Figure 5: Day 8. Ulcer size was 0.5mm x 1.0mm



Figure 6: Day 11. Ulcer size was 0.5mm x 0.5mm

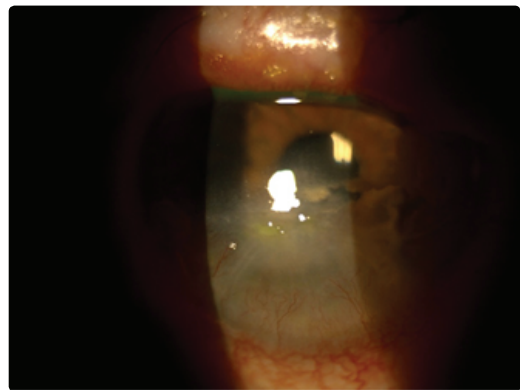


Figure 7: Day 15. Healed ulcer, cornea is completely closed but it remained as light stromal edema and neovascularization

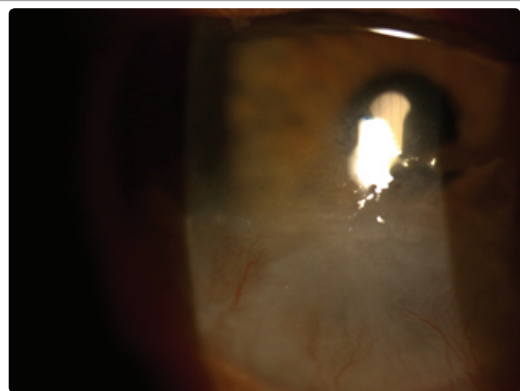


Figure 8: Day 20. Healed corneal ulcer with no epithelial defect, decreased inflammation and neovessels

Discussion

In this case, postsurgical ulcer with a decreased corneal sensitivity and exposed cornea, responded quickly RGTA drops (Cacicol) while it did not respond to previous topical treatments for six weeks.

Indeed, the patient was known for an end-stage renal failure, which is a risk factor to develop band keratopathy [5]. When eyelid surgery was realized to remove the basocellular carcinoma, the fragile balance of the cornea surface was broken and a band keratopathy showed up.

Corneal scrapping after EDTA application was necessary, because off the visual discomfort, but this was the trigger of the neurotrophic keratitis. The case was a stage 3 (severe) in the Mackie's classification [2].

Autologous serum has been considered, but the patient presented an anemia, in the frame of his end-stage renal failure, which represents a contraindication [6].

Amniotic membrane transplantation, even tarsorrhaphy were proposed, but the patient refused any surgery.

RGTA drops (Cacicol) were applied every other, and thealoz duo tears were applied 5*/day. All the others topic treatments were stopped.

Within 24 hours, the erosion surface was already decreasing, and the depth of the stroma melting diminished too.

As shown on the pictures, the healing occurred very quickly, and the initial neurotrophic ulcer was closed within 15 days.

RGTA drops may be effective in the treatment of neurotrophic ulcer by replacing heparin sulphates in degraded extracellular matrix. It would then reconstitute the cellular microenvironment and protect the growth factors within the injured epithelium. The molecule of Cacicol is designed to specifically bind extracellular matrix proteins and growth factors, protecting them from proteolysis [1].

The therapeutic interest of this regenerator agent was first described by Papy-Garcia, et al. in 2005 and initially used to treat skin healing after burns. Indeed, this kind of molecule can work in every body tissue containing some extracellular matrix.

A soft topical corticosteroid, unpreserved hydrocortisone (3.35 mg/ml) (Softacor) was added, after the ulcer closure, and a decrease of inflammation and neovascularization could be obtained in 5 days.

Currently, the indications for the Softacor use are: to treat allergic conjunctivitis, moderate dryness [7]. In this case, Softacor was chosen thanks to its absence of preservative substance and low penetration in the cornea.

Conclusion

The healing of corneal ulcers especially when the corneal sensitivity is abolished, with a consequent neurotrophic keratitis is a challenge.

Several steps are necessary, removing of the topical toxic treatment, find and treat causes of the ulcer and then apply an

alternative treatment: several steps are possible, RGTA drops can quickly help in some patients. The cleaning of the surface ulcer to remove surface debris microfilm can improve the contact of RGTA with the stroma and improves its effects.

RGTA (Cacicol) was found to be a good therapeutic option in this case, allowing us to close the ulcer very quickly, without using surgery.

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