CASE REPORT:

UVA/RIBOFLAVIN CROSSLINKING AS TREATMENT FOR CORNEAL MELTING

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ABSTRACT

Purpose: To demonstrate that UVA/riboflavin crosslinking (CXL) can stop corneal melting in therapy resistant infectious corneal ulceration.

Methods: We will present a case report on a 70-year-old female patient referred for severe infectious ulcerative keratitis caused by Pseudomonas aeruginosa. After intensive treatment with fortified antibiotics, corneal melting developed. CXL was performed to avoid imminent corneal perforation.

Results: The CXL treatment was successful: the corneal melting was stopped and the lesion cicatrized, thereby avoiding emergency keratoplasty.

Conclusion: This case report highlights that CXL may be a valuable addition to our therapeutic armamentarium in the treatment of corneal melts.

KEY WORDS

Infectious Keratitis, corneal ulcer, corneal melting, corneal crosslinking.

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INTRODUCTION

Bacterial ulcerative keratitis may have a devastating impact on ocular tissue and is a sight threatening condition. Corneal ulceration leads to activation of proteolytic enzymes that digest human collagen thereby facilitating corneal melting and perforation. Once melting has developed, treatment options are limited and often surgery is the only therapeutic option.

The UVA/riboflavin crosslinking (CXL) procedure was introduced by Wollensak, Spoerl and Seiler in 2003 to stabilize progressive keratoconus by improving the biomechanical characteristics of the stroma (1). Spoerl has shown that CXL enhances corneal stromal resistance against enzymatic digestion by pepsin and collagenase (2). Based on pre-clinical research, Schnitzler in 2000 hypothesized that CXL could have a beneficial effect in cases of melting. He treated 4 patients with corneal ulceration and melting by CXL. He was able to stop the melting process in 3 of the patients and so avoided emergency keratoplasty (3).

Iseli used CXL successfully to treat 5 cases of infectious melting resistant to conservative treatment. He hypothesized that the combination of the anti-collagenase effect of CXL and the antimicrobial effect of the UV light might act synergistically to protect corneas from the damage caused by infection. It is known that UV irradiation has a double anti-microbial action: it causes irreversible damage to the RNA and DNA of micro-organisms thereby preventing them from replicating. UV irradiation and free oxygen radicals interfere with cell membrane integrity leading to direct destruction of bacteria (4).

We will report on the successful use of CXL in a patient suffering from infectious ulcerative keratitis with extensive corneal melting.

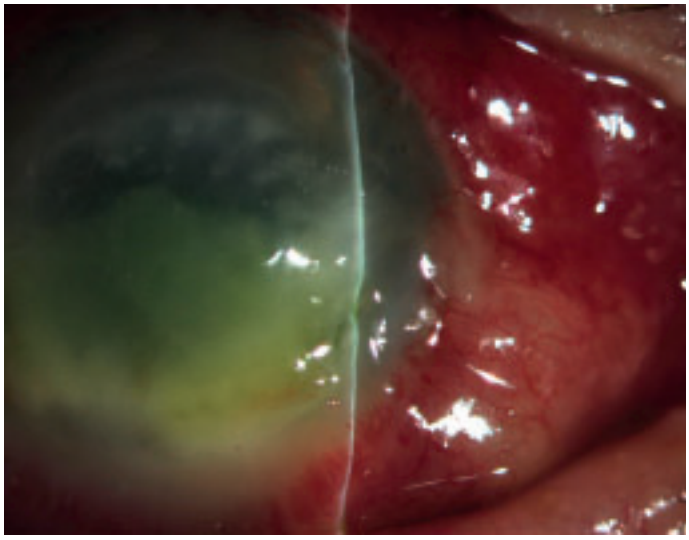

Fig. 1: shows the extensive infiltration and melting of the inferonasal cornea before the CXL treatment.

CASE REPORT

A 70 years old female patient was referred for severe infectious ulcerative keratitis in the right eye after being treated with a subconjunctival injection of long-acting corticosteroids for a recurrent uveitis.

The previous ophthalmic history is not well known: she suffered from glaucoma which was treated by performing a trabeculectomy in 1988. Corneal edema and uveitis were mentioned in a report in 2007. The problems were limited to the right eye.

The patient presented at the emergency department of our hospital with a history of pain and hyperemia of the right eye since 1 week. The symptoms had worsened after the subconjunctival injection of corticosteroids.

At the first examination, the right eye had only light perception. The left eye's best corrected visual acuity was 0.9. The right eye showed pronounced ciliary and conjunctival injection. There was diffuse corneal edema with an inferior corneal ulceration. Evaluation of the anterior chamber was impossible due to the corneal edema. B-scan ultrasonography of the right eye showed an attached retina and some mild anterior vitreous opacification in an otherwise echographically empty vitreous body. The ocular tension was elevated on digital evaluation. Examination of the left eye proved completely normal.

The patient was hospitalized for intensive treatment consisting of a topical fortified antibiotic regimen of tobramycin and vancomycin every

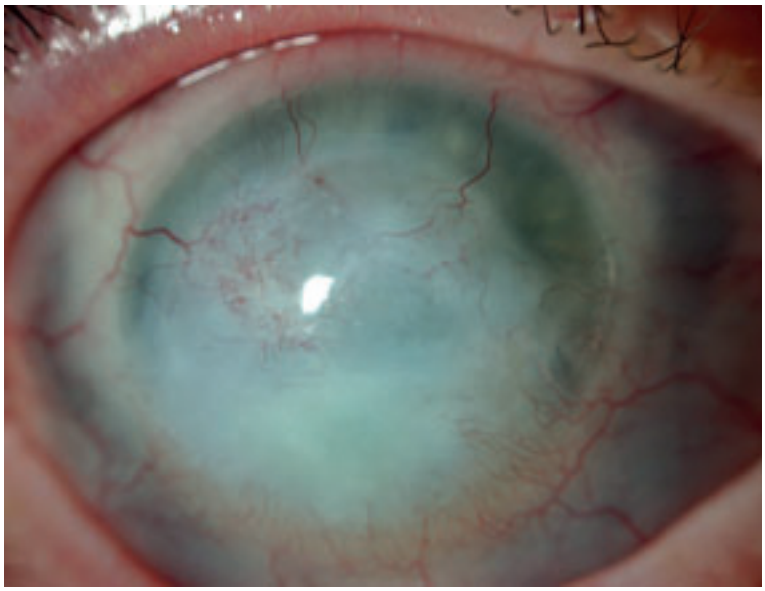

Fig. 2: illustrates vascularization and scar formation of the cornea after the CXL treatment.

hour combined with fluorometholon 4 times a day and atropine 2 times a day as a treatment of anterior uveitis and systemic acetazolamide 250mg 4 times a day to treat the elevated intraocular pressure.

Corneal scraping revealed a tobramycin sensitive Pseudomonas aeruginosa. PCR was performed on an anterior chamber tap but proved to be negative for viral antigens.

In the course of the following 10 days of intensive treatment, the pain persisted and the ulceration increased in size. The dosage of fortified antibiotics had been tapered to avoid undesired toxic side-effects. Therapy was changed to unpreserved fluoroquinolone eye drops and intensive lubrification with autologous serum drops. Unfortunately no signs of healing of the ulcer could be observed after 14 days of treatment. On the contrary, progression of corneal melting did occur bearing the risk of corneal perforation (figure 1). At this point, we decided to treat the patient with CXL to try to stop the corneal melting and avoid emergency keratoplasty.

After instillation of oxybuprocaine, the edge of the corneal ulcer was scraped with a sterile blade and this material was immediately sent to the microbiology lab. Photosensitizing drops containing 0.1% riboflavin in dextran 20% (Peschke Meditrade, Switzerland) were applied on the cornea, once every 3 minutes for 30 minutes. Radiant energy for the CXL treatment was UVA 365 nm 3mW/cm^2 for 30 minutes using the VEGA crosslinker light source (VEGA C.B.M. X-Linker®, Ofta hi-tech, Italy), while instillation of riboflavin was continued. After the CXL treatment, topical medication consisted of unpreserved fluoroquinolone eye drops 4 times a day and intensive lubrification with autologous serum drops every hour.

On the day after the procedure, slit-lamp examination showed neovascularisation of the cornea growing towards the edge of the ulcer. From the second day onwards, corneal edema decreased and the epithelial defect gradually healed. The patient reported significant reduction of pain.

Microbiological culture of the corneal scraping for bacteria, virus and fungi could not identify any micro-organisms. Four days post crosslinking the patient could be discharged. Topical therapy was continued with ofloxacin 4 times a day and tropicamide 4 times a day. Figure 2 shows the eye one month after crosslinking: the cornea had completely cicatrized with vascular ingrowth but at least an emergency keratoplasty had been avoided. The patient was happy with this result.

DISCUSSION

This case report describes a chronically diseased eye with a protracted and complicated history of anterior segment disease. The patient presented with an acute infectious ulceration, caused by a culture proven Pseudomonas aeruginosa. The condition of the cornea worsened despite the use of fortified antibiotics, possibly because of the toxic side-effects of the topical antibiotics. A breakdown of the normal defence and repair mechanisms in this eye with longstanding disease is even more pro-

bable. Limbal stem cell deficiency was later confirmed by impression cytology. As the corneal melting developed, emergency keratoplasty “à chaud” seemed to be the only solution. The major drawbacks of emergency keratoplasty however are an increased risk of reinfection and rejection. The peripheral location of the melting in this case would have required a large or eccentric graft, further increasing the risk of rejection. A more conservative approach was warranted. The optimistic reports of Schnitzler and Iseli on the use of CXL for the treatment of corneal melts encouraged us to apply this treatment to our patient (3,4).

Riboflavin/UVA CXL has been initially developed by Wollensak, Spoerl and Seiler for the treatment of progressive keratoconus (1). UVA irradiation with concomitant administration of riboflavin solution as a photosensitizer creates free radicals that lead to physical crosslinking of the corneal collagen fibers, a process that leads to strengthening of the corneal stroma. The results of the pilot study have been confirmed by several larger clinical trials that show crosslinking to be a safe and effective procedure halting the progression of keratoconus (5-7).

Spoerl has shown in vitro that CXL leads to an increased resistance of the stroma against enzymatic digestion by pepsin, trypsin and collagenase. Collagenases and other metalloproteinases play an important role in the pathogenesis of corneal ulceration, eventually leading to tissue melting and perforation. The stabilizing biochemical effect can be explained by the changes of the tertiary structure of the collagen fibrils induced by CXL preventing access of the proteolytic enzymes to their specific cleavage sites by steric hindrance (2).

Additionally, UV light and oxygen radicals may have an antimicrobial effect: the UV irradiation causes irreversible damage to the RNA and DNA of viruses, bacteria, and parasites preventing them from replicating. The oxygen radicals interfere with cell membrane integrity. Recently Martins, Schrier and Makdoumi have tested the in vitro antimicrobial efficacy of riboflavin and ultraviolet light on bacterial and fungal isolates (8-10). All three authors concluded from their experiments that the combination of riboflavin and UV A, as used in CXL, can achieve a very effective eradication of different types of common corneal pathogens. These laboratory findings encourage the use of CXL as an alternative treatment for infectious keratitis. Very recently two reports have been published describing the successful treatment of infectious ulceration in one case of contact lens related ulceration and in a second case of E. Coli keratitis (11,12). In both cases CXL was performed after failure of the conventional treatment with antibiotics. It is possible that in the near future CXL could be used as a primary therapy for infectious ulceration of the cornea, avoiding problems of bacterial resistance to antibiotic treatment, antibiotic related toxicity, long periods of ocular morbidity and hospitalisation. In the meantime our case report confirms previous findings that CXL is a valuable addition to our therapeutic armamentarium in the treatment of corneal melts.

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