Cross-Linking Pack Plus Plasma in the Mycotic Corneal Ulcer Case Report

Leopoldo Garduño Vieyra  Raúl Rúa Martínez  Bruno Flores Escobar
Clínica Oftalmología Garduño, Edif, Plaza Delta, Mexico City, Mexico

Keywords
Fungal keratitis · Fusarium · Cross-linking pack · Plasma · Surgical management

Abstract
Fungal keratitis is a complication of refractive surgery that, if not treated in time, can lead to blindness. Given the lack of effective topical treatments for fungal ulcers, surgical treatment is necessary. The least invasive procedure is a cross-linking pack, although it has limitations when the fungus has penetrated the deep layers of the cornea. In this case report, a patient that presented a typical case of fungal corneal ulcer with hand motion perception, on the fourth day after surgery, is described. Given the nonresponse to topical antifungal treatment, plasma treatment was performed prior to cross-linking. Plasma acts by nonmechanical debridement of the ulcer, reducing the fungal colonies and allowing better penetration of riboflavin. After 6 months, the cornea remained transparent, without haze, and the patient achieved 20/25 vision.

Introduction
The first report of fungal keratitis was described by Leber in 1879 in a patient with a corneal ulcer caused by Aspergillus [1]. Fungal keratitis is an ulcerative-type infection of the cornea caused by fungi. An ulcer must exist because fungi are not capable of penetrating an intact corneal epithelium. These fungi proliferate and penetrate the cornea through persistent corneal abrasion [1]. The most common fungi in keratitis are Fusarium, Aspergillus, and Candida albicans [2].
The incidence of fungal keratitis following refractive surgery is relatively low compared to bacterial or viral keratitis. The incidence of infectious keratitis after photorefractive keratectomy is reported to be between 0.02 and 0.2%, being more common than in laser in situ keratomileusis [3].

With the increasing popularity of refractive surgery, it is normal that complications associated with the procedure, such as infectious keratitis, also increase [4]. The conventional pattern in these cases is early diagnosis and aggressive medical treatment. Notably, the drugs used in this therapy are not available in all countries and patients can also present toxic keratopathy [5]. Furthermore, antifungal agents are fungistatic but not fungicidal. Topical natamycin is the treatment of choice [1].

Penetrating keratoplasty has been reserved for cases in which there is no favorable response to the use of medical therapy and that already show severe stromal damage (melting) with risk of perforation [5]. Cross-linking treatment has recently emerged as a therapeutic option previous to performing keratoplasty. Numerous studies demonstrate the efficacy of ultraviolet light for the inactivation of microorganisms [5–8].

Cross-linking treatment with ultraviolet light and riboflavin has been used since the 1990s for the treatment of corneal ectasia. Its use was later expanded and proved effective in stabilizing melting in corneal ulcers and incipient infectious keratitis [6–8].

To achieve better results for the treatment of this pathology, new procedures are being sought that will act in a more direct and effective manner. The use of plasma technology in ophthalmology has been reported for more than 10 years [9].

**Case Report**

A male patient came to our office to undergo refractive surgery in order to stop wearing glasses. At the initial consultation, he presented uncorrected visual acuity of 20/200 in his right eye (OD) and 20/200 in his left eye (OS). Slit-lamp examination revealed an unaltered anterior segment. The fundus was also unaltered. Refraction was OD −3.00 diopters and OS −3.00 diopters. Corneal topographies were performed which confirmed that the patient did not present with any other pathology and was a candidate for surgery in both eyes. Pachymetry results showed OD 556 microns and OS 548 microns.

Based on the above, photorefractive keratectomy was proposed. Prior to performing the surgery, the patient and a family member signed a written consent to perform the procedure. The surgery was uneventful. Therapeutic bandage lenses were put on. The patient was prescribed 0.5% moxifloxacin eye drops (one drop every 3 h for 8 days) and 3% trehalose (one drop every 4 h for 1 month).

Four days after surgery, the patient came to the emergency room reporting discomfort, severe eye pain, and decreased vision in his right eye. The visual acuity of the OD showed hand motion perception, while the OS was at 20/25.

Slit lamp examination of the OD detected photophobia, marked conjunctival hyperemia, contact lens in place, anterior stromal liquefaction (corneal melting) 9 mm in diameter on ablation with irregular borders, and feathery ramifications. The OS examination was within normal limits, contact lens in place, epithelialization in 80%, and no signs of infection. A sample was taken and sent for a Sabouraud glucose neopeptone agar culture. After 24 h, the laboratory report reported hyphae.

The patient was treated with natamycin eye drops (one drop every 4 h), and a daily exam was performed, three consecutive days. As there was no improvement in the condition and the corneal melting persisted, it was decided to perform cross-linking pack surgery plus plasma. Once again, prior to performing the surgery, a written consent was obtained from the
patient and a family member to perform the procedure. Plasma was used to evaporate mycotic colonies using a plasma arc, without needing tissue debridement or manipulation with mechanical instruments (shown in Fig. 1).

The cross-linking pack plasma procedure is described below:

- Asepsis and antisepsis
- Tetracaine drops, as local anesthesia, were applied
- Superficial drying with a merocel sponge
- Sweeping of the affected corneal surface with a plasma arc (Plasma Pen)
- Coating with isotonic riboflavin every 5 min for 30 min and irradiation with ultraviolet light type A 3 mW/cm² and 365 nm for 40 min
- Applying chloramphenicol ointment and occlusion for 24 h

The plasma equipment used on this patient was the Plasma Pen Liss KC6 (Kiyalaser). This equipment had been used previously for eye surgeries [10].

Twenty-four hours after performing the procedure, there was a decrease in eye pain and epithelialization was observed from the periphery toward the center. The treatment with 3% trehalose (one drop every 2 h) and chloramphenicol (one drop every 3 h) was maintained. It was decided to discontinue natamycin and continue with chloramphenicol due to the degree of corneal toxicity. After 48 h, there was notable improvement in the cornea, melting began to disappear, the cornea was restructured, and corneal epithelialization continued. The laboratory findings reported Fusarium (shown in Fig. 2).

The patient returned for consultation 5 days after surgery (cross-linking pack plus plasma) showing corneal epithelialization of 50%, a decrease in corneal melting, and considerable stromal restructuring with moderate corneal edema. On day 7, the restructuring of the corneal stroma and epithelialization were noticeable in 80%. On day 10, there was corneal restructuring, epithelialization in 90%, and anterior edema. On day 12, there were total stromal restructuring and 100% epithelialization with slight epithelial edema. At the third week, there was complete epithelialization and grade 2 haze was observed. Treatment with 3% trehalose (one drop every 4 h) and glycerol (one drop every 2 h) was maintained for 1 month.

On the fourth postoperative week (cross-linking pack plus plasma), the patient presented a visual acuity of 20/70 without correction and without signs of haze or infection and refraction of OD +2.00 diopters and OS −0.50 diopters (shown in Fig. 3). After 6 months, visual acuity without correction was OD 20/25 and OS 20/20. The corneas remained transparent and haze-free, and pachymetry results showed OD 506 microns and OS 548 microns. The final refraction was OD +0.75 diopters and OS −0.50 diopters.
Discussion

Among the patient’s risk factors for fungal keratitis, were a history of eye surgery, the use of topical antibacterials, and contact lenses [1]. Fusarium and Aspergillus are the most common fungi isolated from patients with fungal keratitis. The laboratory studies determined this patient was positive for Fusarium. This is a highly penetrating fungus capable of diffusing into the corneal stroma and even penetrating Descemet's membrane and accessing the anterior chamber [1].

Surgical treatment options are considered once medical treatment has been unsuccessful. In these patients, surgery sometimes does not guarantee vision recovery, leaving them with visual deficiencies and even blindness [1]. The goal of surgery is to control the infection and the integrity of the eyeball. Surgical options include corneal scaling, debridement, conjunctival resurfacing, lamellar keratoplasty, and therapeutic penetrating keratoplasty [1].

The photoactivated chromophore treatment with cross-linking in corneal keratitis (CXL-PACK) has a high degree of antimicrobial effectiveness, reported to be as high as 88% [6]. This treatment continues to be the gold standard for this pathology. The CXL-PACK technique was first described by Spörl in 1997, but the antimicrobial properties of riboflavin in combination with UV light have been known since 1965 [7]. In this patient, the Dresden protocol for CXL-PACK was performed [8]. Plasma was applied first, in order to perform nonmechanical debridement of the ulcerated area.

It has been shown that ultraviolet light alters the DNA and RNA sequences, inactivating a large number of microorganisms by suppressing replication of the pathogen [2, 5]. Moreover, riboflavin penetrates the stroma, enhancing this effect. Additionally, the use of cross-linking
increases collagen resistance against digestive enzymes. The microorganisms are also inactivated by the free radicals produced during the treatment [2, 5].

The use of cross-linking is reported in the treatment of Acanthamoeba keratitis resistant to medical therapy, with satisfactory results. After one session, the disappearance of symptoms, elimination of the epithelial defect, and total reduction of the stromal infiltration were achieved [5].

González Castellanos et al. [2] state that the use of CXL reduces the severity and intensity of Fusarium in keratitis. However, he also explains that in patients with deep corneal abscesses who do not respond to conventional treatment, photodynamic therapy may not be sufficient and corneal perforations may occur.

Sometimes, CXL is not effective for treating these cases. For the patient presented, CXL could have been used alone. However, with the goal of reducing the number of fungal colonies and favoring greater depth penetration of riboflavin, the Plasma Pen was used. This increases the effectiveness of the treatment.

The plasma energy works by ablating the tissue. The plasma arc that is generated also creates a wall around the ulcer, and the temperature generated does not extend beyond the ulcerated area; therefore, it does not affect nearby structures.

**Conclusions**

Using plasma before performing cross-linking constitutes a novel technique that allows for a more effective treatment. Plasma works by reducing the number of pathogenic colonies while ensuring better penetration of riboflavin to deeper layers.
Statement of Ethics

This case report was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study does not include any information which may reveal the patient’s identity. This study was reviewed and approved by the Ethics Committee of the Clínica Oftalmología Garduño on March 2021 and written on the approval reference number 202103001. A written informed consent to publish on October 2021 was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received.

Author Contributions

Dr. Leopoldo Garduño Vieyra: he is the main doctor. He performed all surgeries. He participated in the writing of the manuscript. Dr. Raúl Rúa Martínez: he is the second staff doctor. He performed the postoperative follow-up of the patient. He wrote the manuscript. Dr. Bruno Flores Escobar: he performed the preoperative consultation and studies of the patient. He participated in the writing of the manuscript.

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.

References

1 Castano G, Elnahry AG, Mada PK. Fungal keratitis. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2022 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493192/
2 González Castellanos JC, Osaba M, Reviglio V, Canchi MT, Cuyén Arrigone M, Reviglio VE. Early treatment of bilateral fungal keratitis with corneal cross-linking as adjuvant therapy. Vol. 6. Oxford Medical Case Reports; 2020. p. 169–71.
3 Albathi L, Alshabebb R. Bipolaris keratitis following photorefractive keratectomy: case report. Int J Surg Case Rep. 2021;79:372–4.
4 Kouyoumdjian GA, Forstot SL, Durairaj VD, Damiano RE. Infectious keratitis after laser refractive surgery. Ophthalmology. 2001;108(7):1266–8.
5 Garduño-Vieyra L, González-Sanchez CR, Hernandez-Da Mota Sergio E. Ultraviolet-A light and riboflavin therapy for Acanthamoeba keratitis: a case report. Case Rep Ophthalmol. 2011;2(2):291–5.
6 Garduño Vieyra L, De la Fuente-Batta I, Hernández-Da Mota SE, Zavala-Martinez MT. Photoactivated chromophore with crosslinking as treatment for Acanthamoeba keratitis. Rev Gabana Oftalmol. 2020 Jun;33(2):e824. http://scielo.sldcu/scielo.php?script=sci_arttext&pid=S0864-21762020000200016&lng=es&nlp=todero&beginpage=1&endpage=824 Epub 01-Jun-2020.
7 Balparda K, Mejia-Turizo JC, Herrera-Chalarca T. Simultaneous noncentered photoactivated chromophore for keratitis-corneal collagen cross-linking and penetrating keratoplasty for treatment of severe marginal fusarium spp. Keratitis: a description of a new surgical technique. Case Rep Ophthalmol Med. 2017;2017:6987896.
8 Garduño-Vieyra L. Crosslinking en infecciones PACK-CXL. En: Garduño-Vieyra L, Rivera-Abril LA, editors. El universo del Crosslinking bases y tratamientos de vanguardia. 1st ed. Ciudad de México: Grupo Percano de Editoras Asociadas; 2019. p. 111–22.

9 Roy H, Singh D, Fugo RJ. Ocular applications of the Fugo Blade. 1st ed. Philadelphia: Lippin Cott Williams and Wilkins; 2011.

10 Garduño Vieyra L, Rúa Martínez R, Muñoz Cornejo V, López Portillo HB. Trabeculoplasty new surgical technique in the treatment of glaucoma pilot report. J Ophthalmol. 2021. (Ukraine): Article in press.