Ring-Shaped Corneal Stromal Opacities after Corneal Cross-linking with Riboflavin and Ultraviolet A Irradiation for Keratoconus

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ABSTRACT
A 32-year-old female patient with progressive keratoconus in her right eye was treated with simultaneous customized photoreactive keratoctomy (PRK) and corneal cross-linking (CXL) with riboflavin and Ultraviolet A (UVA) irradiation. Ten days after the procedure, the patient was presented with foreign body sensation, mild ring-shaped corneal infiltration with vascularization at the limbus and Trantas dots at slit-lamp examination along with conjunctival injection and papillary reaction. One month postoperatively, the conjunctival injection decreased but the limbus vascularization and circular infiltration remained. Five months postoperatively, there were no subjective complaints and slit-lamp examination revealed circular pseudogerontoxon more dense superiorly. Best corrected visual acuity (BCVA) remained 20/20 and corneal topography remained stable. Ring-shaped intrastromal corneal infiltrate could appear after simultaneous PRK-CXL for progressive keratoconus without interfering with the stiffening effect of the procedure.

Keywords: Cross-linking complications, Keratoconus, Ring-shaped opacities.

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INTRODUCTION
Corneal collagen cross-linking (CXL) with photosensitizer riboflavin and ultraviolet A (UVA) irradiation is a new technique for stabilizing progressive keratoconus and iatrogenic keratectasia after laser in situ keratomileusis. This procedure stimulates formation of intrafibrillar and interfibrillar covalent bonds by photosensitized oxidation, which results in increased biomechanical stability and increased rigidity of cornea. Other treatment modalities available for keratoconus include rigid gas permeable (RGP) contact lenses, implantation of intrastromal corneal rings segments (INTACS), lamellar and penetratin keratoplasty. Several combined procedures have been proposed to optimize the CXL outcomes, such as conductive keratoplasty or implantation of Intacs followed by CXL but it seems that the most effective is the combination of customized photorefractive keratectomy (PRK) followed by CXL. Several adverse events have been reported in the literature following corneal CXL including bacterial keratitis, herpetic keratitis and keratitis from acanthamoeba and pseudomonas. The most common complication after simultaneous PRK-CXL is the formation of posterior linear corneal stromal haze.

We present a patient with pseudogerontoxon after corneal collagen CXL with riboflavin and UVA irradiation for keratoconus treatment.
Corneal CXL was conducted under sterile conditions. The right eye was anesthetized with proparacaine 0.5% (Alcaine). A 6.5 mm diameter of the corneal epithelium was removed by transepithelial phototherapeutic keratectomy (t-PTK) at intended 50 µm. PRK was performed in a 5 mm diameter with attempted correction 0 to 2.50 × 51. Both PTK and PRK were performed with the same excimer laser Allegretto wave 400 Hz (WaveLight Laser Technologie AG). After PRK, riboflavin was instilled (0.1% solution 10 mg riboflavin-5-phosphate in 10 mL dextran-T-500 20% solution) repeatedly every 3 minutes for approximately 30 minutes. Penetration of the cornea and presence of riboflavin in the anterior chamber (riboflavin shielding) was monitored by slit-lamp examination. UVA irradiation was performed using an optical system (UV-X illumination system version 1000) with a light source consisting of an array of UV diodes (365 nm) with a potentiometer in series to allow regulation of voltage. Before treatment, an intended irradiance of 3.0 mW/cm² (5.4 J/cm² surface dose) was calibrated using a UV light meter at a working distance of 1.0 cm. Irradiance was performed for 30 minutes, corresponding to a dose of 5.4 J/cm². During treatment, the riboflavin solution was applied every 5 minutes to saturate the cornea with riboflavin and drops of physiological salt solution were applied every 2 minutes to moisten the cornea. After treatment, a bandage contact lens was placed and topical antibiotic/corticosteroid drops tobramycin-dexamethasone (TobraDex, Alcon Laboratories, Inc) were instilled. The procedure was uneventful.

The patient was examined daily until the epithelium was healed completely. On the fourth day, the bandage contact lens was removed. Postoperative medication included diclofenac sodium 0.1% (Denacol; Novartis, Hellas, Athens, Greece) for 2 days as well as antibiotic/corticosteroid (tobramycin/dexamethasone) drops (TobraDex; Alcon Laboratories, Inc) four times daily and antibiotic ofloxacin (Exocin, Allergan Inc., Irvin, USA) drops 4 times daily until the removal of the bandage contact lens. After the removal of the contact lens, patient was prescribed corticosteroid drops (fluorometholone 0.1%; Falcon Pharmaceuticals, Ltd, Fort Worth, Texas, USA), tapering for the next 20 days. Patient was encouraged to use artificial tears (sodium hyaluronate, preservative free) at least six times per day for 6 months postoperatively.

On the 10th day postoperatively, the patient started to complain of a foreign body sensation along with redness in her treated eye. Slit-lamp examination showed conjunctival injection, mild edema and papillary reaction. At the periphery of the cornea signs consisted of a stromal ring-shaped infiltration with intact epithelium above it, a zone of clear cornea between the infiltrate and the limbus, vascularization, more prominent superiorly and Trantas dots (Fig. 1). The central cornea was clear and the anterior chamber had no reaction. The UVA was 20/32 and the BCVA 20/20 with +1.25 –1.25×120°. The left, untreated eye had no signs of inflammation. Because of the peripheral location of the corneal stromal infiltrate, an immune etiology was suspected and no corneal scrapings were performed.

The fluorometholone 0.1% drops were discontinued and fucidic acid viscous eye drops twice daily along with chloramphenicol/dexamethasone eyedrops four times daily (with tapering a drop per week), were prescribed.

One month postoperatively, there was a significant decrease in conjunctival injection and edema, with no Trantas dots visible. There was however, a mild circular infiltration and vascularization at limbus. Central cornea in diameter of 7 mm was still clear. BCVA was not decreased. Keratometry readings at her right eye were K1: 46.08 D at 130° and K2: 45.10 D at 40° (Galilei dual Scheimpflug imaging, Zimmer Ophthalmics, Port, Switzerland). The patient was advised to continue with therapy as prescribed.

Three months after the procedure there was still the circular limbal infiltration present with more discernable infiltration lines superiorly. The infiltration was documented by anterior segment optical coherence tomography (AS-OCT). Cyclosporine 0.05% ophthalmic emulsion two times daily was started along with chloramphenicol/dexamethasone eye drops four times daily.

On a 5-month follow-up, the patient had no subjective complains. Her visual acuity remained stable. Keratometry readings at her right eye were K1: 44.72 D at 138° and K2: 44.02 D at 32° (Galilei dual Scheimpflug imaging, Zimmer Ophthalmics, Port, Switzerland) with evident corneal flattening and corneal astigmatism reduction. Slit-lamp examination showed presence of complete circular pseudogerontoxon, more dense superiorly (Fig. 2). The

**Fig. 1:** Slit-lamp examination on the 10th postoperative day showing a stromal ring-shaped infiltration with intact epithelium above it, a zone of clear cornea between the infiltrate and the limbus.
Peripheral corneal stromal infiltrates could be attributed to an infection, blepharitis-related hypersensitivity to Staphylococcus epidermidis, Mooren’s ulcer, Terrien’s marginal degeneration and peripheral ulcerative keratitis associated with autoimmune or collagen vascular disease. There have been reports of sterile peripheral corneal stromal infiltrates after photorefractive keratectomy, phototherapeutic keratectomy, laser in situ keratomileusis with the flap being created with a microkeratome or the femtosecond laser and laser-assisted subepithelial keratectomy. They all appeared as early postoperative complication unilaterally or bilaterally and tended to disappear after topical antibiotic and steroid drops along with systemic steroid treatment without corneal scarring, affection of the visual acuity, subjective symptoms and with no recurrence.18

Sterile corneal stromal infiltrates and melting have been described after the CXL procedure and probably occur as a result of enhanced cell-mediated immunity to staphylococcal antigens deposited at high concentrations in areas of static tear pooling.19

Our case may represent a variant of syndromes related to staphylococcal antigen deposition in areas of static tear pooling beneath the bandage contact lens. However, the patient’s history of seasonal allergic rhinitis could also explain predisposition to ocular immune response similar to vernal keratoconjunctivitis, triggered by the riboflavin or UVA irradiation.

At a recent publication20 the authors reported the appearance of bilateral ring-shaped corneal stromal opacities after CXL for progressive keratoconus which appeared on the first postoperative day and slowly resolved during the following 6 months. Thirty-two months postoperatively the corneal topography revealed corneal flattening and good visual acuity was preserved. The incident could be attributed to the corneal wounding from the CXL with riboflavin which alters cornea’s cellularity for until 36 months after the operation.

Pseudogerontoxon is a rare clinical entity usually associated with vernal keratoconjunctivitis. It represents peripheral corneal lipid deposits due to increased vascular permeability caused by corneal allergic inflammation. To our best knowledge this is the first reported case of complete pseudogerontoxon after CXL treatment with no previous history of any type allergic keratoconjunctivitis.

Corneal CXL probably represents the future treatment of corneal ectatic disorders as it may minimize the percentage of patients who need penetrating keratoplasty.

**DISCUSSION**

Corneal collagen CXL by riboflavin and UVA is a new method for the treatment of progressive keratoconus. It has been shown to effectively increase the biomechanical strength of the cornea and to stop or even reverse the progression of keratoconus. The simultaneous PRK-CXL procedure seems to be safe and effective treatment for progressive keratoconus providing improved and stable visual outcome.

Since, CXL represents a relative new surgical technique, it is vital to inform the scientific community about its possible complications or adverse events. Microbial keratitis after CXL has been reported mainly due to the epithelial defect and the use of bandage contact lens, including infection of Pseudomonas aeruginosa, Escherichia coli, acanthamoeba, Streptococcus salivarius, Streptococcus oralis and coagulase-negative Staphylococcus. All these incidents resulted in residual corneal opacities of different severity. In some cases the corneal transplantation was performed in order to control the infection and improve visual outcome of the patients.10-13 A case of herpetic keratitis with iritis even in patients with no previous history of herpetic disease has been reported in the literature.14 Furthermore, induction of diffuse lamellar keratitis after CXL in a patient with post laser in situ keratomileusis ectasia has been recorded.15 Another two potential complications of the technique seem to be the reduction of the corneal endothelial cells in patients with central corneal thickness below 400 µm and the appearance of posterior linear stromal haze formation after simultaneous PRK-CXL which gradually becomes less dense and moves anteriorly over a 1 year follow-up period.16,17
The role of the UV light on the immune mechanisms of the cornea warrant further investigation. More studies of rare complications of corneal CXL treatment are necessary in order to establish appropriate patient selection, technique performance and improve success rates. Since, the exact pathogenesis of this complication remains unclear, it is vital to be differentiated from an infectious keratitis because the management of the patients is completely different.

REFERENCES


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