

CASE REPORT

Diffuse Sterile Corneal Infiltration: An Unusual Complication Post Collagen Cross-linkage

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ABSTRACT

Purpose: Presenting the course of visually disabling corneal infiltration post uneventful collagen cross-linking (CXL) in a 23 years old male with bilateral keratoconus.

Methods: A 23 years old male with bilateral keratoconus underwent cross-linking of left eye with indigenous 0.1% riboflavin dye and 370 nm ultraviolet A irradiation. This patient had an uneventful successful cross-linking performed in right eye 6 months prior with good recovery of vision to LogMAR 0.2 (6/9 Snellen).

Results: Patient developed diminution of vision, along with redness of eye, photophobia and watering on 3rd day after uneventful cross-linkage. Examination revealed very poor vision; diffuse corneal clouding with multiple superficial stromal infiltrates and incomplete corneal epithelization. A provisional diagnosis of infective keratitis was made, *in situ* bandage contact lens (BCL) removed and subjected to culture. Intensive fortified topical antibiotics were initiated and steroids withheld. After complete corneal re-epithelization on 6th day, the infiltrations did not decrease in either intensity or number. Response to antibiotics being inadequate, an immune etiology was suspected and full strength topical steroids reinstated which resulted in slow resolution of infiltration over a 10 weeks period. Last follow-up at 9 months post-CXL, revealed a diffuse stromal haze with unaided visual acuity of LogMAR 0.8 6/36 and best-corrected visual acuity (BCVA) of 0.3 (6/12) with use of a rigid gas permeable lens.

Conclusion: Sterile infiltration post-CXL requiring intense topical steroids is a rare complication of CXL and needs to be differentiated from infective keratitis.

Keywords: Cross-linkage, Keratoconus, Sterile infiltrate.

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INTRODUCTION

Persistent corneal haze is among the most common complications post cross-linking (CXL) while endothelial damage, postoperative infection/ulcer, peripheral sterile infiltrates and herpes reactivation are more dreaded albeit rarer complications.^{1,2}

Corneal haze following collagen CXL, unlike photorefractive keratectomy (PRK) typically extends into anterior stroma to approximately 60% depth (absolute depth of 300 μ m) and has a reticulated subepithelial appearance.³ An ongoing debate attempts to resolve this stromal haze being a normal offshoot of CXL procedure because of its frequency or label it as a complication.⁴ This haze is attributed to back scatter and reflected light, which decreases corneal transparency.⁵ Repopulation by activated keratocytes may contribute, in addition to stromal swelling pressure changes,⁶ proteoglycan-collagen interactions,⁷ and glycosaminoglycan hydration.⁸ This haze has been documented to peak at 1 month, plateau between 1 and 3 months and decline thereafter, to completely regress by 6 months to 1 year post-CXL. Older age, grade III or IV keratoconus (according to Krumeich's classification) and preoperative reticular pattern of stromal microstriae observed preoperatively by *in vivo* confocal microscopy are considered risk factors for corneal haze.²

Debridement of corneal epithelium theoretically exposes cornea to microbial infection and infective keratitis is a potential risk post-CXL. Reports of keratitis during first few days post-CXL have incriminated *Staphylococcus epidermidis*, *Escherichia coli* and *acanthamoeba* post-contamination of eye with tap water.⁹⁻¹¹ Poor hygiene has been responsible for polymicrobial keratitis due to *Streptococcus salivarius*, *Streptococcus oralis*, and coagulase negative *Staphylococcus*.¹² The usual etiology is contact with microbial agent during early postoperative period rather than intraoperative as ultraviolet (UV) light used during surgery is destructive to microbes. Antimicrobial activity of UV light is due to generation of free radicals, resulting in increased collagen resistance to digesting enzymes produced by pathogenic bacteria/fungi. In addition, UV light with wavelengths of 315 to 380 nm inhibits microbial growth. This antimicrobial effect of CXL has been employed

to treat infective keratitis cases with proven efficacy against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, methicillin-resistant *S. aureus* (MRSA), multidrug-resistant *P. aeruginosa*, drug-resistant *Streptococcus pneumoniae*, but not against *Candida albicans*.

Sterile corneal infiltrates are a rare complication with only four documented reports in literature.¹³⁻¹⁶ Reason for sterile corneal stromal infiltrates is attributed to enhanced cell-mediated immunity to *Staphylococcal antigens* deposited at high concentrations in areas of static tear pooling beneath the bandage contact lens (BCL).¹⁷

Another complication noted has been both development and reactivation of herpetic keratitis and iritis.¹⁷ Ultraviolet light is hypothesized to be a potent stimulus to trigger/induce reactivation of latent herpes simplex virus (HSV) infections even in patients with no prior history of clinical infection. Epithelial/stromal trauma, damage to corneal nerves and use of topical

steroids has been touted to be risk factors. Prophylactic systemic antiviral treatment in patients with history of herpetic disease is thus recommended after cross-linking.

CASE REPORT

A 23 years old male agricultural worker developed painful diminution of vision, with photophobia, redness and watering in left eye within 3 days of an uneventful collagen cross-linking for keratoconus.

Preoperative profile revealed stage II keratoconus as per Amsler-Krumeich classification with K_{max} of 50.7 D and thinnest pachymetry of 507 μ m and best corrected vision of LogMAR 0.2 (6/9 Snellen) with contact lens. (Figs 1 and 2).

Cross-linking had been performed using indigenous 0.1% riboflavin dye, ultraviolet-A (UVA) light irradiation (370 nm) for 30 minutes with Vega CBM X-linker ensuring an irradiance of 3 mW/cm² after epithelial debridement done with 8.0 mm corneal trephine. The dye application had been done at 5 minutes interval both prior to and during irradiation. Patient was discharged after application of bandage contact lens (PureVision, Bausch and Lomb) and eye patched for 24 hours. Subsequently, topical low dose steroid (loteprednol etabonate 0.5% and tobramycin sulfate 0.3% combination) was instituted on 4 hourly basis along with tear substitutes. In addition systemic anti-inflammatory analgesic combination was prescribed on twice a day (BD) dosing for 3 days.

On examination of the acute red eye, vision was documented as of counting fingers with accurate projection of rays in left eye and 6/9 in right eye. Left eye revealed diffuse conjunctival hyperemia in addition

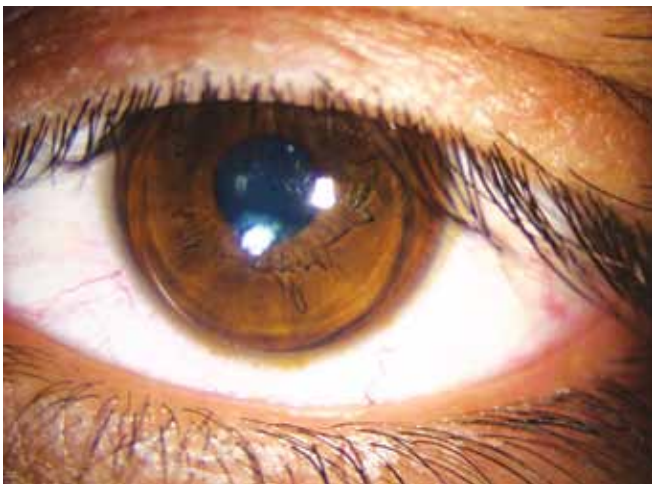


Fig. 1: Pre-CXL left eye fitted with RGP lens

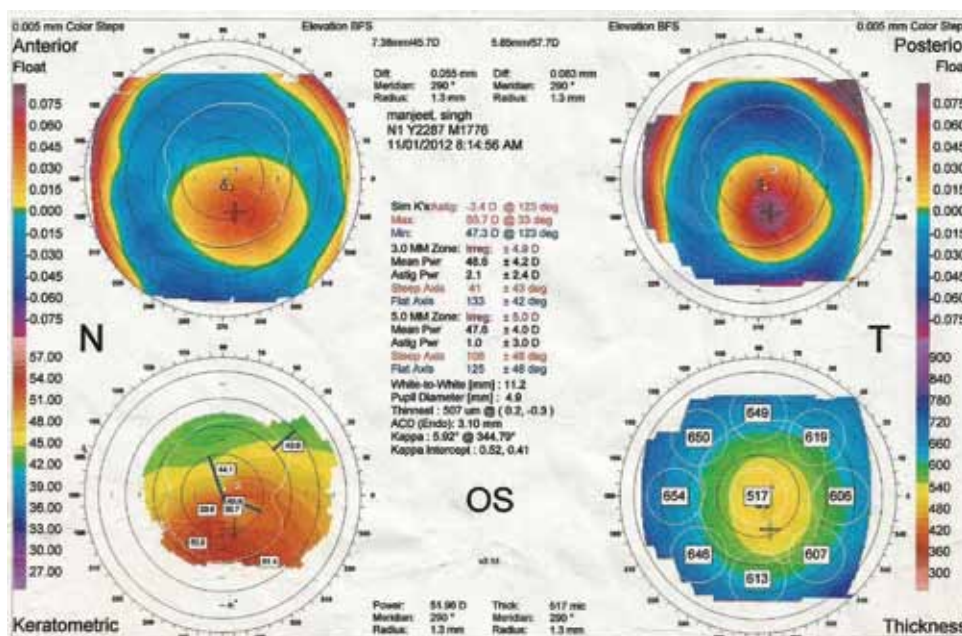


Fig. 2: Pre-CXL Orbscan



Fig. 3: At presentation (day 3), markedly congested eye with multiple superficial infiltrates and incomplete epithelization

to circumcorneal congestion, diffuse corneal clouding, multiple superficial stromal infiltrates (approximately 30 in number), with incomplete corneal epithelization (Fig. 3). Anterior chamber and posterior segment details could not be appreciated but no hypopyon was present. Intraocular pressure recorded by noncontact tonometer

was 16 mm Hg. Provisional diagnosis of infective keratitis was made and microbiological smears taken from corneal scraping. Bandage contact lens was removed, cut into pieces and subjected to bacterial and fungal cultures. A CXL procedure of the right eye performed 6 months prior with similar technique and equipment had healed uneventfully with best-corrected visual acuity (BCVA) of 6/9 over a 6 months follow-up.

Patient was started on fortified 5% vancomycin, 5% ceftazidime eye drops 2 hourly along with cycloplegics, lubricants and prior prescribed topical low dose steroids were withheld. Cultures of BCL and conjunctival swab reported sterile and re-epithelization of cornea occurred by 6th day resulting in symptomatic relief of pain. Response to antibiotics being inadequate an immune etiology was suspected and full strength topical steroids (1% prednisolone acetate) reinstated on 7th day and topical antibiotic frequency reduced.

This therapy resulted in slow resolution of infiltrations over a 10 weeks period, extent and depth being documented with anterior segment optical coherence tomography (ASOCT) (Fig. 4). This improvement

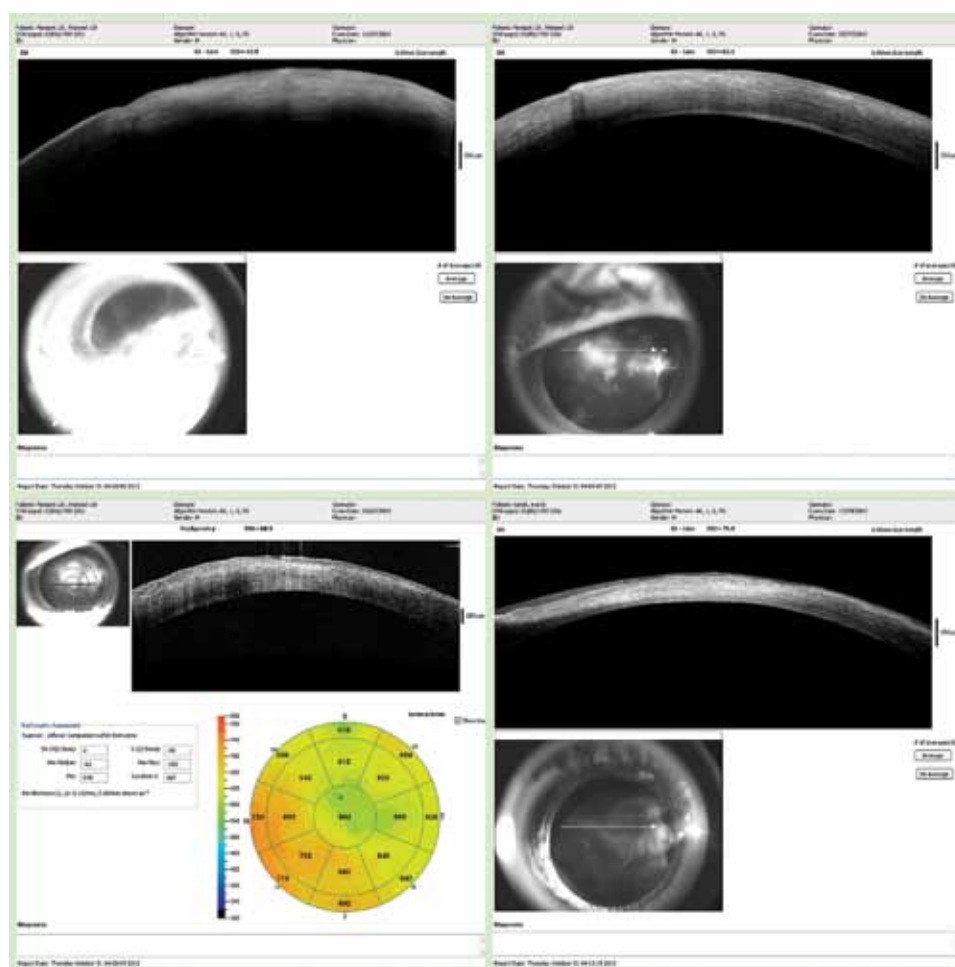


Fig. 4: Left-right anterior segment optical coherence tomography showing re-epithelization followed by resolution of infiltrates with residual diffuse stromal haze over 3 months period

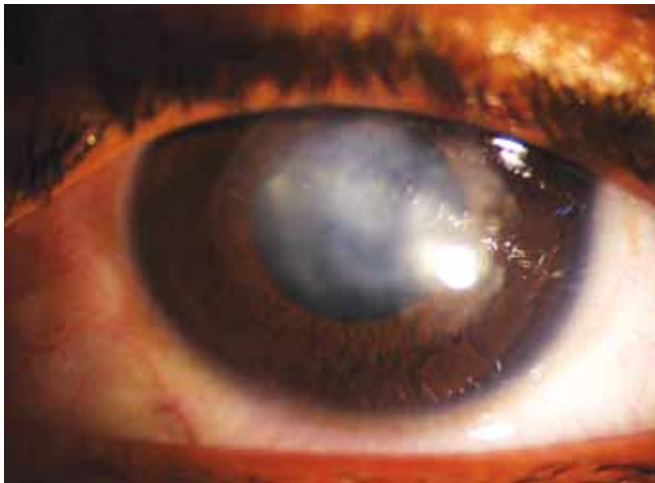


Fig. 5: Three months post-CXL; diffuse residual stromal haze

continued and infiltrates merged resulting in diffuse stromal haze by end of 3 months with an unaided visual acuity of 6/36 and BCVA of 6/12 with RGP lens (Fig. 5). The steroids were subsequently weaned over a 1 month period. Last follow-up of 9 months, revealed a diffuse stromal haze with unaided visual acuity of LogMAR 0.8 (6/36 Snellen) and BCVA of LogMAR 0.3 (6/12 Snellen) with an RGP lens (Fig. 6).

Throughout the use of steroids, intraocular pressure of patient remained in low teens.

DISCUSSION

Collagen cross-linking with riboflavin-UVA is a safe and effective surgical procedure for cases of keratoconus with minimal reported complications. Microbial keratitis, a dreaded complication, is fortunately rare in occurrence with most patients presenting within 1 week. This early keratitis despite being sterile in culture responds to intensive antimicrobials with final visual acuity being variable depending on the extent of haze.¹⁸

Sterile corneal infiltrates manifesting in early post-operative period present a diagnostic dilemma as the presentation is similar to microbial keratitis from which they need to be differentiated. A series of cases of sterile peripheral infiltrates within first week of CXL were reported by Ghanem RC who hypothesized phototoxic effect on corneal stroma to trigger alteration of antigenicity of native stromal proteins resulting in cornea recognizing these altered proteins as nonself and mounting immune responses.¹⁵ Isolated few reports of sterile infiltration have incriminated individual hypersensitivity reaction to riboflavin or UVA light as the probable cause.¹⁶ Lam FC in a retrospective study suggested thinner and steeper corneas to be at an increased risk of developing these sterile lesions. Visual outcomes of this complication depend on timely recognition and intervention.¹⁶



Fig. 6: Nine months post-CXL with RGP lens *in situ*

CONCLUSION

This case highlights sterile infiltrates as a rare but disabling complication of collagen cross-linkage. These sterile infiltrates require intense topical steroids and needs to be differentiated from infective keratitis. Caution needs to be exercised while using steroids on a long-term basis to prevent complications of corneal thinning and steroid responsive glaucoma.

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