



Sterile Infiltrates after Corneal Collagen Cross Linking

Kashviya Suri BA^{1*}, Joseph Mootz MD², Isha Cheela DO², Jules Winokurb MD MBA²

¹Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York

²Northwell Ophthalmology Department, New Hyde Park, New York

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*Corresponding Author

Kashviya Suri BA

E-mail: ksuri@northwell.edu

Introduction

In 2016, corneal collagen cross linking (CXL) was approved by the United States Food and Drug Administration (FDA) to halt the progression of keratectasia and keratoconus.¹ This minimally invasive procedure relies on the application of riboflavin (vitamin B2) and ultraviolet A (UVA) light to the cornea to generate free radicals, which in turn induce new covalent bond formation and cross linking of stromal collagen to restore thickness and rigidity to the cornea.² The antimicrobial properties of riboflavin and UVA have enabled the application of this procedure to the management of chemical corneal burns, bullous keratopathy, as well as infective and ulcerative keratitis.³ CXL remains relatively safe with a low complication rate.¹ Adverse effects most commonly reported are mild and include pain, photophobia, keratoconjunctivitis sicca, and corneal edema, but more severe complications such as corneal melting and infectious or sterile keratitis have also been reported.¹ Herein, we describe three cases of sterile corneal infiltrates following standardized Epi-Off Corneal Collagen Cross Linking per the Dresden protocol for the management of keratoconus.⁴

Case Reports

Note that these procedures were performed using the FDA-approved KXL system (Avedro inc., Waltham, MA) and riboflavin 5'-phosphate ophthalmic solution (Photrex Viscous; Avedro Inc. Waltham, MA). The central 9.0 mm of corneal epithelium was removed using an Amoils brush. Isotonic topical riboflavin 5'-phosphate in 20% dextran ophthalmic solution was applied every two minutes for 30 minutes and then irradiated with UVA light (irradiance of 3 mW/cm²) while continuing to instill riboflavin 5'-phosphate ophthalmic solution every two minutes for 30 minutes, using a total of 5.4 J/cm² total energy. At the end of the procedure, a therapeutic contact lens was placed (Alcon Air Optix Day and Night, Fort Worth, TX) and ofloxacin 0.3% and prednisolone 1%

were instilled and prescribed four times per day. While therapeutic contact lenses were intended to be placed for one week, they were removed immediately upon recognition of stromal infiltrates in each case.

Case A: A 23-year-old female with bilateral keratoconus and best corrected visual acuity (BCVA) 20/50 in the right eye (OD) and 20/70 in the left eye (OS) underwent CXL OS with no complications. Her central corneal thickness prior to CXL was 477 μm on the right (OD) and 454 μm on the left (OS) (Table 1). Two months later, CXL OD was performed without complications, using the same standard procedure and postoperative protocol. On the postoperative day 2, the patient experienced more blurry vision and photophobia. On examination, the cornea had a circular area of edema and haze with two focal stromal infiltrates (Figure 1A). The overlying epithelium was intact, and there was no anterior chamber inflammation. The infiltrates were suspected to be either bacterial or reactive. The bandage contact lens was removed, and bacterial cultures were obtained. Topical cyclopentolate 1% drops three times daily, 1000 mg valacyclovir tablet three times daily, and moxifloxacin 0.5% every two hours were initiated. Bacterial cultures resulted in no growth throughout the course of her treatment.

The negative cultures, in combination with lack of improvement on antibiotics, raised suspicion for a sterile etiology. The patient thus continued topical prednisolone 1% 4 times a day and 20 mg of oral prednisone three times daily was added to her regimen on postoperative day 4. On postoperative day 7, she began tapering the 20 mg oral prednisone to twice a day, followed by a decrease to once a day on postoperative day 13 and discontinuation after postoperative day 20. Antibiotics and antivirals were also discontinued on postoperative day 20. Over the course of 1-month post-procedure the infiltrates consolidated gradually, leaving behind a 1 mm stromal scar outside the visual axis, while the associated stromal haze was markedly improved and the corneal edema resolved (Figure 1B). The BCVA was 20/60 OD at 8 months post-procedure and has remained stable since.

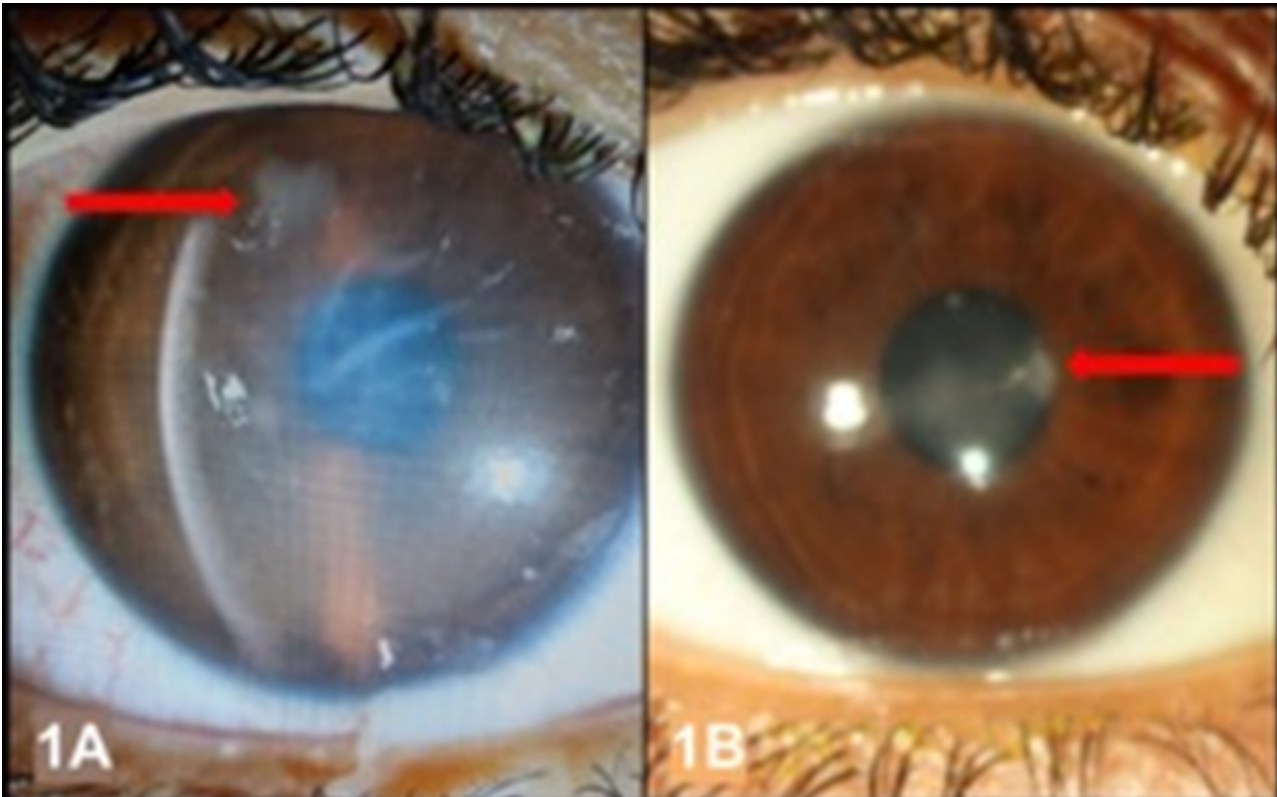


Figure 1. A. Case A. Slit lamp photographs at postoperative day 4. B. Slit lamp photograph on postoperative day 25.

Case B: A 22-year-old male with keratoconus and BCVA 20/30- OD and 20/20- OS elected to have CXL to prevent progression. His central corneal thickness was 405 μm OD and 440 μm OS (Table 1). CXL was performed without complication OD. On postoperative day 1, the patient presented with a central epithelial defect with anterior stromal haze in OD. On postoperative day 6, two discrete infiltrates were noted (Figure 2A). The overlying epithelium was intact, and no anterior chamber inflammation was identified. There was a concern for the presence of corneal infiltrates. The bandage contact lens was removed. Moxifloxacin 0.5% every 2 hours was started with a plan to transition to increased steroids if the infiltrates did not improve within 24-48 hours. On postoperative day 8, the patient reported worsening vision, and moxifloxacin 0.5% drops were reduced to four times daily, while topical prednisolone dosing was increased to every 2 hours due to growing concern for sterile infiltrates. A response to the steroids was observed, and oral prednisone was initiated on postoperative day 11, at a dose of 20 mg three times daily, tapering to twice a day after one week of use and to once a day after two weeks of use. Antibiotics were discontinued on postoperative day 20. By postoperative month 1, the infiltrates had resolved, leaving mild residual stromal scarring (Figure 2B). The BCVA returned to baseline at 20/30- OD. The cornea was not cultured given infiltrate size <2 mm, midperipheral location, and absence of pain or photophobia.

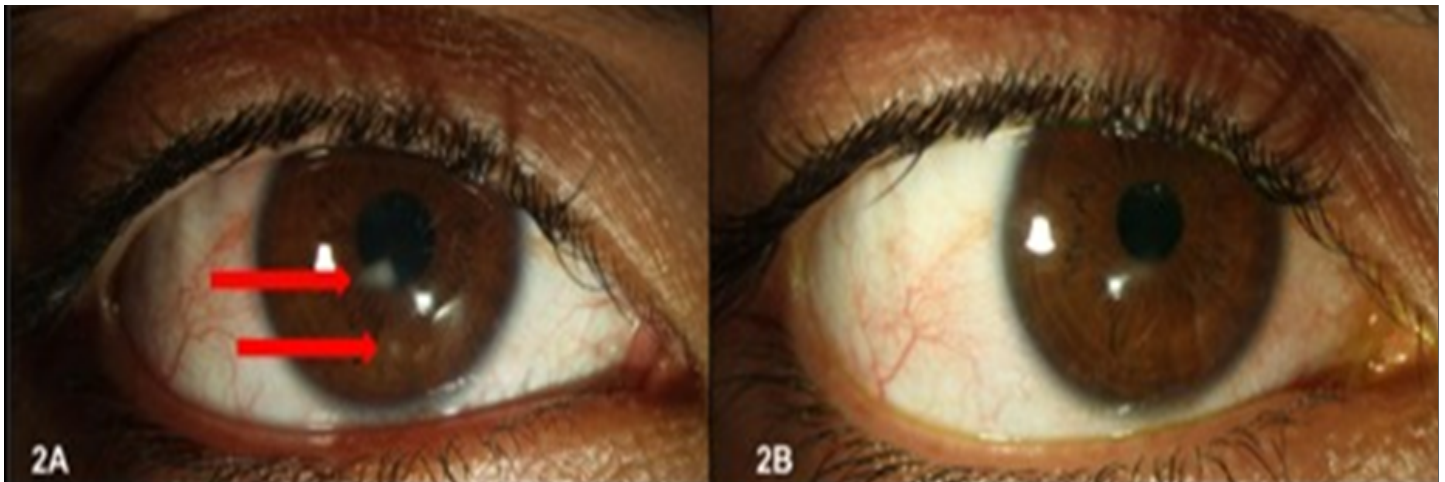


Figure 2. A. Case B slit lamp photographs at postoperative day 6. B. Case B slit lamp photograph at postoperative month 10.

Case C: A 20-year-old male was referred for keratoconus management and elected to undergo CXL OU. Initial BCVA was 20/30 OD and 20/30- OS. Central corneal thickness was 514 μm OD and 502 μm OS (Table 1). CXL OS was performed uneventfully. Over a year later, CXL was performed OD without complication. At postoperative week one, a ring-shaped infiltrate with central cornea edema and discrete superior stromal infiltrate was present OD (Figure 3A). The overlying corneal epithelium was intact, and no anterior chamber inflammation was identified. The bandage contact lens was removed, and bacterial cultures were obtained. A one-week course of fortified tobramycin and vancomycin drops were started to cover possible infectious etiologies. In addition to continuing the topical prednisolone 1% four times a day, 20 mg oral prednisone twice a day was added to address associated corneal inflammation as well as sterile etiologies. Upon completion of the topical tobramycin and vancomycin, 0.5% moxifloxacin four times daily was started, which was ultimately discontinued after four weeks as cultures resulted in no growth. The oral prednisone was tapered down to 10 mg daily after 3 weeks of use (postoperative day 28). Five weeks post-procedure, the stromal haze had improved, although residual scarring contributed to BCVA of 20/400. Topical prednisolone was continued, and topical losartan 0.08% four times daily was added. Five months later, the BCVA improved to 20/70 OD, and the medications were discontinued (Figure 3B).

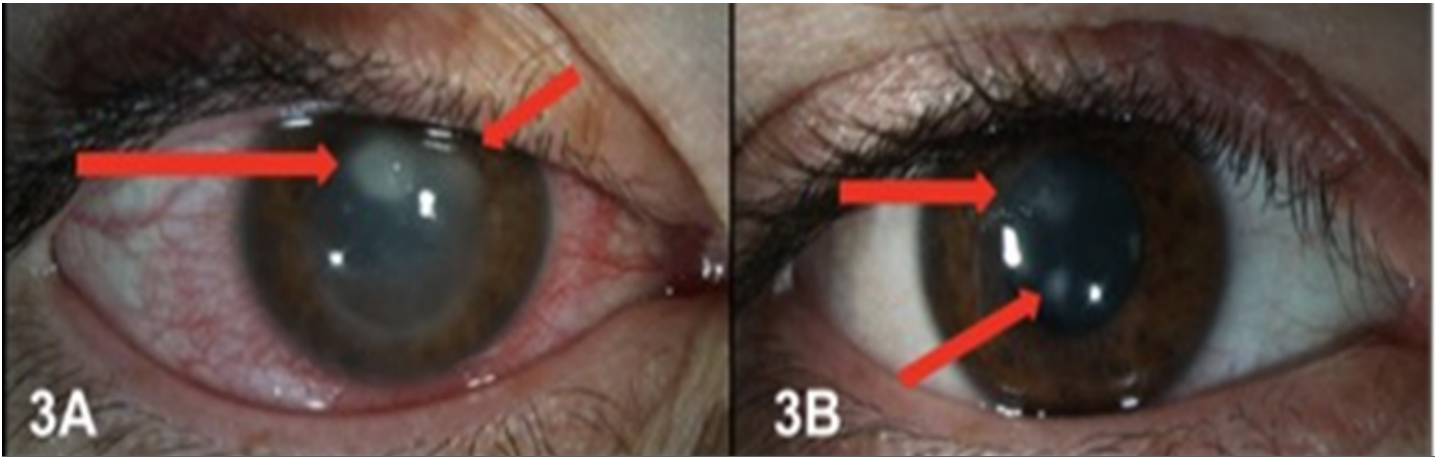


Figure 3. A. Case C slit lamp photograph at postoperative day 8. B. Case C slit lamp photograph at postoperative month 10.

Discussion

Though CXL is reported to have a very low complication rate, adverse outcomes may still arise. Pain, dryness, edema, and photophobia, the most commonly cited adverse outcomes of CXL, can be attributed to the removal and subsequent absence of the corneal epithelium, exposing its corresponding nerve fibers.¹ Persistent epithelial defects, corneal stromal melting, and perforation have also been reported.

Keratitis marks another broad category of consequences following CXL.¹ Corneal epithelial removal and slow regeneration can contribute to an inflammatory process, where sterile or infectious infiltrates may develop. This may lead to stromal scarring and decreased BCVA. Reported causes of infectious keratitis include Gram positive bacteria such as *S. aureus*, Gram negative bacteria such as *E. coli*, as well as fungi, *Acanthamoeba*, and Herpes simplex virus.⁵ In our case series, antibiotic coverage was intensified in all three patients, and Case A also received oral valacyclovir, to address potential infectious sources. None of our cultures resulted in microbial growth, and all patients improved with the addition of oral steroids. Fungal culture and polymerase chain reaction testing for Herpes simplex virus were not performed because the clinical appearance was not suggestive of these organisms (e.g., no feathery infiltrate margins, satellite lesions, or dendritic epithelial changes).

We acknowledge, however, that negative bacterial cultures do not definitively exclude infection. All three patients had been using prophylactic topical ofloxacin since CXL, which may reduce culture yield and fungal, viral, and atypical organisms were not specifically tested for. The diagnosis of sterile keratitis in this series was thus driven by clinical features, inadequate improvement in response to antibiotics, and comparatively stronger temporal response to steroids.

The etiology of sterile keratitis following CXL is not well established, but it has been proposed to reflect an exaggerated immunological response to the riboflavin/UVA application.⁶ The procedure relies on UVA toxicity to keratocytes in the anterior stroma to induce their repopulation. The new keratocytes increase collagen and

extracellular matrix synthesis, strengthening the cornea. An exaggerated immune response may activate the keratocytes to overproduce extracellular matrix, resulting in infiltrates and subsequent scar deposition.⁷

Although infection cannot be fully excluded, sterile infiltrates due to exaggerated immune response appear to be the underlying etiology in all three cases. The patients developed infiltrates on the second, sixth, and eighth days following the CXL procedure, respectively. In all three cases, the epithelium remained intact, and the anterior chamber did not exhibit any inflammatory reaction. Characteristic signs of bacterial, fungal, and viral infections were not observed, and cultures were negative for Cases A and C. Furthermore, a response to antibiotics was not observed in each case, suggesting that the etiology was noninfectious. In conjunction, these clinical features raised suspicion for a sterile keratitis. This prompted an increase in topical prednisolone in Case B, and addition of oral prednisone in all three cases. In response, a marked improvement was observed.

The rationale for addition of oral prednisone (60 mg/day in Cases A and B and 40 mg/day in Case C) was threefold. First, the circular pattern of inflammation seen in Cases A and C was suggestive of involvement of the limbal vasculature, which systemic therapy may reach more effectively than topical drops alone.¹²⁻¹⁴ Second, systemic dosing added anti-inflammatory effect without creating a more burdensome drop regimen and avoided the risks associated with topical steroids on a recently de-epithelialized cornea (e.g. stromal melt). Lastly, the relatively younger age of the patients, coupled with the risk for persistent stromal inflammation leading to visually significant scarring, prompted an intensive management protocol.

We note that systemic steroids carry well-recognized risks and can worsen an unrecognized infection. However, the scant existing literature on sterile infiltrates following CXL demonstrated a similar onset of 2-5 days and emphasized that steroids remain the standard of care.⁸⁻¹¹ We therefore suggest that systemic steroids be considered for extensive or progressing infiltrates that do not adequately respond to topical steroid therapy. We underscore that steroids should also be used only after an appropriate infectious workup.

Risk factors for this phenomenon remain poorly defined, necessitating further reporting on the characteristics of each case.^{8,9} Notably, two of the three cases presented here were second eyes, after an uneventful first eye CXL. Consequently, we hypothesize that there may have been priming of the immune system during the first procedure, such that the second procedure provoked an exaggerated immune response. We emphasize that this is a hypothesis rather than an established mechanism, as no immunologic testing was performed, and three cases cannot establish causation. It is, however, consistent with prior observations. Mangioris et al. suggested that sterile infiltrates after CXL may represent an individual hypersensitivity reaction to riboflavin or UVA light.¹² Koppen et al. described delayed-onset keratitis after CXL that improved rapidly with high-dose steroids, and Ghanem et al. proposed that CXL may alter the antigenicity of native stromal proteins, leading the host to recognize them as foreign.^{13,14} A Type IV delayed hypersensitivity reaction is one plausible pathway, although alternative immune mechanisms cannot be excluded.¹³ Future studies should examine associations between sterile infiltrates after CXL and a history of atopy, allergy, or autoimmune disease, ideally with immunologic

testing. We suggest thorough history taking among patients considering CXL to better elucidate any potential correlation between pre-existing immune system aberrations and this untoward outcome.

Conclusion

Establishing clinical concern for sterile infiltrates after CXL enables more prompt introduction of an enhanced steroid regimen to recover and improve BCVA, reducing the risk of potentially vision-threatening corneal scarring. Clinical features such as an intact overlying epithelium, absence of intraocular inflammation, and inadequate improvement with topical antibiotics may help clinicians recognize a sterile process when cultures remain pending or are negative. Timely escalation of topical steroids, and subsequently systemic steroids in severe cases, may help reduce stromal scarring. However, infection can be difficult to exclude, particularly if prophylactic antibiotics are part of the post-procedure protocol. Given that steroids can worsen unrecognized infection, we underscore that steroid therapy be escalated after appropriate infectious workup, with continued antimicrobial coverage and close follow-up. Larger studies are warranted to identify risk factors and define the optimal treatment algorithm.

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Statement of Ethics

This study was conducted in full accordance with international and institutional ethical standards, and written informed consent was obtained.

Patient Consent and Privacy

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflict of interest to disclose.

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Table 1. Cornea Metrics

Case A:			
OD: Kmax (47.1D)	Pachymetry (477um)	Progression Index: 2.84	<i>**reaction eye</i>
OS: Kmax (54.1D)	Pachymetry (454um)	Progression Index: 2.55	
Case B:			
OD: Kmax (56.8D)	Pachymetry (405um)	Progression Index: 2.16	<i>**reaction eye</i>
OS: Kmax (49.1D)	Pachymetry (440um)	Progression Index: 1.66	
Case C:			
OD: Kmax (54.1D)	Pachymetry (514um)	Progression Index: 1.86	<i>**reaction eye</i>
OS: Kmax (43.1D)	Pachymetry (502um)	Progression Index: 1.85	