Sterile keratitis after corneal collagen crosslinking in keratoconus

Erbil Seven, MD, Muhammed Batur, MD, Adnan Çınal, MD, Tekin Yaşar, MD

Sterile keratitis is a rare complication following corneal collagen crosslinking (CXL) treatment. Although some suspected factors in sterile keratitis have been described, the etiology remains unclear. We report 2 sterile keratitis cases after CXL and discuss possible etiology in these cases.

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Keratoconus is a progressive disorder characterized by noninflammatory thinning of corneal stroma.1 Corneal collagen crosslinking (CXL) is a new, noninvasive treatment modality that increases the rigidity of the cornea by about 300% through a combination of a photosensitizing substance (riboflavin) and ultraviolet A (UVA).2 Some complications associated with CXL have been reported; these include diffuse lamellar keratitis, bacterial keratitis, Acanthamoeba keratitis, herpetic keratitis, development of corneal haze, corneal melting, and corneal perforation associated with severe microbial keratitis.3–5 A few cases of sterile keratitis after CXL have been reported,6–10 but the etiology and incidence of this complication have not been studied.

We performed CXL on 4 patients on the same day, and 2 of the patients developed sterile corneal keratitis. We report these 2 sterile keratitis cases and retrospectively review the data of all cases of CXL that have been performed at our clinic.

Surgical Procedure

Under sterile conditions using topical anesthesia with proparacaine hydrochloride 0.5% (Alcaine) and following central 9.0 mm mechanical epithelial debridement, the standard method of CXL was performed. Three drops of a solution containing riboflavin 0.1% and dextran 500 20% were instilled every 3 minutes for approximately 30 minutes. After instillation of the riboflavin solution, the UVA lamp was turned on to irradiate a 9.0 mm diameter of the central cornea. Riboflavin solution was not applied during the irradiation. The UVA (wavelength 370 nm) source was a unique beam-optimized system consisting of 1 UVA diode (UV-X 2000, Iroc Innocross AG). The source was focused on the apex of the cornea at a distance of 50.0 mm to obtain a radiant energy of 9 mW/cm². The cornea was irradiated with the UVA diode for 10 minutes. After treatment, the surface of the eye was washed with 20 mL of a balanced salt solution. A bandage contact lens (Purevision, Bausch & Lomb, Inc.) was placed at the end of surgery.

Following the procedure, topical ofloxacin 0.3% was instilled and a soft bandage contact lens was fitted. Postoperatively, ofloxacin 0.3% and preservative-free lubricant eyedrops (Eyestil) 8 times daily and paracetamol 500 mg tablet 3 times a day were prescribed for 1 week.

The procedure was used in 183 consecutive eyes of 138 cases between January 16, 2013, and October 16, 2015. All procedures were done by 2 surgeons (E.S., M.B.). Four of the patients had surgery on the same day; none wore contact lenses for keratoconus before CXL. Two of them (1.09%) developed sterile keratitis. The data of the 4 same-day surgery cases and of the other 179 eyes are given in Table 1.

CASE REPORTS

Case 1

A 24-year-old woman presented with progressive keratoconus. The patient’s history was unremarkable. Preoperatively,
The corrected distance visual acuity (CDVA) was 20/32 with −0.75 −4.50 × 65 in the right eye and 20/100 with −1.75 −10.00 × 134 in the left eye. The minimum thickness of the cornea was 429 μm and 393 μm, respectively. Other ophthalmic examinations were normal in both eyes.

The CXL procedure was performed uneventfully in the left eye of the patient. Routine prescriptions were given as described above. On postoperative day 2, the patient complained of discomfort, redness, and low visual acuity. The visual acuity was 20/400 in the left eye. On slitlamp examination, a diffuse conjunctival injection and a central corneal epithelial defect 3.0 mm in diameter were seen. In the central corneal stroma, an area 4.0 mm in diameter was hazy; on the outside border of this area, 2 corneal subepithelial infiltrates of different shapes were noted (Figure 1). There were keratic precipitates on the central corneal endothelial surface and anterior chamber cell reaction. The bandage contact lens was in place. Samples were taken for microbiologic study.

With a presumed diagnosis of bacterial infiltration in the left eye, the bandage contact lens was removed. All drugs were stopped; cyclopentolate hydrochloride 1 drop 3 times a day and fortified topical antibiotics consisting of vancomycin (50 mg/mL) and ceftazidime (50 mg/mL) were initiated.

On postoperative day 3, prednisolone sodium phosphate 1.0% 3 times a day was started. On postoperative day 4, there was a significant improvement in symptoms and signs. On postoperative day 5, after the corneal epithelial defect had closed, the dosage of prednisolone was changed to 1 drop an hour. On postoperative day 7, fortified topical antibiotics and cyclopentolate hydrochloride were stopped and moxifloxacin 0.5% (Vigamox) 1 drop 4 times a day was started and the prednisolone sodium phosphate was reduced to 1 drop 12 times a day (or every 2 hours). No colony was isolated from the microbiologic samples. On postoperative day 10, the dosage was changed to moxifloxacin 1 drop 3 times a day and prednisolone sodium phosphate 1 drop 8 times a day.

On postoperative day 17, when the epithelial infiltrates were almost completely resolved, moxifloxacin and prednisolone drops were discontinued. Loteprednol etabonate 0.5% (Lotemax) 1 drop 4 times a day was started for 10 weeks and tapered to 1 drop twice a day and discontinued at 3 months. Two months later, the CDVA was 20/50 in the left eye and slitlamp examination showed a mild stromal scar overlying the pupil entrance (Figure 2).

**Case 2**

A 13-year-old girl presented with progressive keratoconus. The patient had no history of contact lens use, allergy,
herpetic keratitis, dry eye, or autoimmune disease. Preoper-
atively, the CDVA was 20/20 with $\frac{-3.50}{-1.75} \times 28$ in the
right eye and 20/20 with $\frac{-3.50}{-1.75} \times 154$ in the left eye.
The minimum thickness of the cornea was 474 µm and
475 µm, respectively. Other ophthalmic examinations were
normal in both eyes.

The CXL procedure was performed uneventfully in the
right eye. Routine prescriptions were given as described
above. On postoperative day 2, the patient complained of
discomfort, redness, and low visual acuity in the right eye.
The uncorrected distance visual acuity was finger counting
at 10 cm. On slitlamp examination, a diffuse conjunctival in-
jection was seen. In the central corneal stroma, a round area
4.0 mm in diameter in the central corneal stroma was hazy;
on the outside border of this area were 7 round subepithelial
infiltrates located in a circular manner. A 2.5 mm hypopyon,
keratic precipitates at the central corneal endothelial surface,
and anterior chamber cell reaction were found in the anterior
chamber (Figure 3). The bandage contact lens was in place.
Samples for microbiologic study were taken. Fluorescein
staining showed no epithelial defect on the cornea. On con-
focal corneal microscopy, changes suggestive of sterile kera-
titis were seen.

With a presumed diagnosis of bacterial infiltration in the
right eye, the bandage contact lens was removed, all drugs
were stopped, and cyclopentolate hydrochloride 1 drop
3 times a day and fortified topical antibiotics consisting of
vancomycin (50 mg/mL) and ceftazidime (50 mg/mL)
each hour were started. On postoperative day 3, prednisol-
one sodium phosphate 1.0% (Predforte) each hour was
added to the antibiotic treatment. On postoperative day 5,
significant improvement in symptoms and signs was seen
and the CDVA was recorded as 20/400. Fortified topical an-
tibiotics and cyclopentolate hydrochloride were stopped,
and moxifloxacin 0.5% 1 drop 4 times a day was started;
the prednisolone sodium phosphate was reduced to 12 times
a day on postoperative day 7. No colony was isolated from
the microbiologic samples.

On postoperative day 17, with the epithelial infiltrates
almost completely resolved, the moxifloxacin and prednis-
olone eyedrops were discontinued. Loteprednol etabonate
0.5% 1 drop 4 times a day was started for 10 weeks and
tapered to twice a day and discontinued at 3 months.
Three months later, the CDVA was 20/20 with $\frac{-3.50}{-1.75} \times 25$ and slitlamp examination showed a mild stromal scar corresponding to previous infiltration areas (Figure 4).

**DISCUSSION**

Sterile keratitis is a rare inflammation of the cornea
and may be seen after corneal procedures such as radial keratotomy and laser in situ keratomileusis. There have been a few reports of sterile keratitis after CXL and a case series. The etiology of sterile keratitis is not clearly understood. One study has suggested
that sterile stromal infiltrates result from cell-
mediated immunity to staphylococcal antigens.3

The incidence of sterile keratitis following CXL is re-
ported as 2.7% and 0.97% in 2 retrospective studies
and 7.6% in a prospective study. In our retrospective
study, the incidence was 1.09%. Finding lower inci-
dence rates in retrospective studies suggests that
some mild sterile keratitis cases might be overlooked
or misinterpreted with overlapping epithelial defects.

Sterile infiltrates are seen 2 to 5 days after CXL. Hypoxia, allergies, topical nonsteroidal antiinflam-
matory drugs, alcohol used for epithelial debride-
ment, and overdose of UVA have been suspected as
etiologic factors.4 However, Lam et al.9 also propose
thin corneas and high corneal curvature as factors in
sterile keratitis development. Our results did not sup-
port their conclusion.

As can be seen in Table 1, our first and third cases
developed sterile keratitis, but the second and fourth
cases did not. We think this order may exclude chemi-
cal contamination or unexpected harmful effect of
surgical equipment as factors in the development of
sterile keratitis.

We observed 2 sterile keratitis cases with very dra-
matic presentations similar to that of bacterial keratitis

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**Figure 3.** Case 2: Appearance on postoperative day 2.

**Figure 4.** Case 2: Appearance at 2 months.
after CXL. We believe 1 of these (Case 2) is the first reported case that had a 2.5 mm hypopyon. These dramatic presentations alerted us, and we started treatment with antibiotics for microbial keratitis. Because of the ineffectiveness of antibiotic therapy, a corticosteroid was added to the treatment. After that, the clinical picture improved.

We could not make statistical comparisons between normal and sterile keratitis cases because of the small number of keratitis cases. Moreover, no remarkable difference was observed between normal and sterile keratitis cases in sex, age, central corneal pachymetry, eye laterality, preoperative keratometry values, and keratometry value differences. Two surgeons used the same procedure in all cases in the same operating room.

In conclusion, our results suggest there may be systemic and immunologic mechanisms in the development of sterile keratitis. Studies dealing with systemic factors are needed to clarify the etiology of sterile keratitis after CXL.

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