Case Report

Recurrent Peripheral Stromal Keratitis Following Corneal Collagen Cross-linking: A Case Report

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Abstract

Purpose: Corneal collagen cross-linking (CXL) has become the standard initial intervention in eyes with progressive keratoconus (KC) that have not undergone keratoplasty. The prolonged exposure of the de-epithelialized cornea predisposes it to adverse complications, such as microbial keratitis and melting. Herein, we report a case of bilateral recurrent peripheral stromal keratitis following CXL.

Case Report: We present a 29-year-old woman who complained of ocular redness and discomfort in both eyes for 4 months, and had undergone bilateral CXL 10 months before. The best spectacle corrected visual acuity (BSCVA) was 60/200 in the right and 80/200 in the left eye. Both eyes showed moderate conjunctival hyperemia, dilation, and engorgement of the perilimbal episcleral vessels. There was a peripheral corneal stromal infiltration with thinning, and an overlying epithelial defect in the right eye with a lucid interval from the limbus. She was treated with lubricating eye drops and ointments and topical corticosteroids every 4 hours for 2 weeks then slowly tapered off. Afterwards, she experienced multiple recurrences in both eyes, which were successfully managed with topical corticosteroids and lubricants. After 2 years, her BSCVA was 20/30 with −3.00-5.50 * 90 in the right eye and 20/40 with −4.00-4.50 * 90 in the left.

Conclusion: Although CXL is a safe method, studies with longer follow-ups are needed to investigate the risk of rare complications.

Keywords: Corneal Collagen Cross-linking; Peripheral Stromal Keratitis; Keratoconus

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INTRODUCTION

Keratoconus (KC) is the most common ectatic corneal disorder, and is usually bilateral, asymmetric, and progressive in nature. Corneal collagen cross-linking (CXL) has become the standard initial intervention in eyes with progressive KC in which

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keratoplasty is not indicated. It is the only method that can halt the progression of corneal ectasia by inducing cross-links between stromal collagen fibers, which is achieved through the interaction between UVA light and riboflavin as a photosensitizer.[1] The standard (epithelium-off) procedure includes a stromal riboflavin saturation phase in which the de-epithelialized cornea is exposed for about 30 minutes followed by UVA light irradiation which could be performed with different intensities and durations.[2] The prolonged exposure of the de-epithelialized cornea predisposes it to adverse complications such as microbial keratitis and melting.[3] Herein, we report for the first time, a case of bilateral peripheral stromal keratitis after an uneventful CXL.

CASE REPORT

An otherwise healthy 29-year-old woman came to the clinic complaining of bilateral ocular redness and discomfort in the past 4 months and her condition gradually deteriorated. The patient had undergone bilateral CXL using the standard Dresden protocol to treat progressive KC in another center 10 months ago. She had no history of other ocular and systemic diseases and did not use any topical or systemic medications. Systemic examinations focusing on the head and neck lymph nodes, thyroid, skin, and joints revealed no pathologic findings.

At the presentation exam, the uncorrected visual acuity (UCVA) was 20/200 in both eyes using the Snellen chart. The best spectacle corrected visual acuity (BSCVA) was 20/60 in the right eye and 20/80 in the left eye with −4.50-5.00 * 90 and −4.00-4.25 * 90, respectively.

On the slit-lamp examination, both eyes showed moderate conjunctival hyperemia and dilation and engorgement of the perilimbal episcleral vessels. There was peripheral corneal stromal infiltration, extending 360 degrees from superior to inferior, with a lucid interval from the limbus as well as an area of overlying epithelial defect in the right eye [Figure 1]. The left eye was similarly affected but to a lesser extent. The anterior chamber was deep and had trace cell in the right eye. Intraocular pressure measured by a Goldmann applanation tonometer was 18 mmHg and 14 mmHg in the right and left eye, respectively, and posterior segment examination of both eyes was unremarkable.All laboratory tests including a complete blood count, erythrocyte sedimentation rate, and thyroid function tests were normal, and the levels of serum C-reactive protein, rheumatoid factor, anti-nuclear antibody, and angiotensin converting enzyme were within normal limits. The corneal smear and culture obtained during the symptomatic phase of the disease revealed no bacterial growth, indicating the presence of sterile ulcerative keratitis.

The patient was treated with frequent application of lubricating eye drops and ointments and 0.1% betamethasone in the form of eye drops every 3 hours for 2 weeks which was then tapered off. At the short interval follow-up, after achieving an improvement from the first episode, she experienced multiple similar recurrences which were treated like the first episode. Each episode lasted for about 2 weeks and disease-free intervals were about 3 to 4 months. No specific trigger was noted by the patient. In two years, at her last follow-up, she showed significant improvement in both subjective symptoms and corneal signs. Her BSCVA was 20/30 with −3.00-5.50 * 90 in the right eye and 20/40 with −4.00, −4.50 * 90 in the left eye. Figure 2 shows her last photo-slit: a 360 degrees scar in the peripheral zone of the cornea of the right eye. The thinned area, obvious in scarred regions, had no significant influence on her visual acuity. Based on Galilei tomography, the maximum keratometry (Kmax) and corneal astigmatism were nearly stable during the course of follow-up.

DISCUSSION

Both infectious and non-infectious complications have been reported after CXL. Infectious complications,

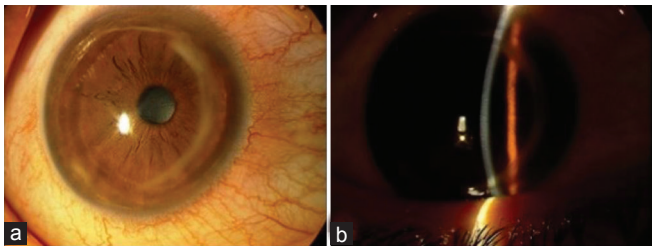

Figure 1. Photo-slit of cornea at aggravation (a) Right eye shows moderate conjunctival hyperemia and dilation; perilimbal episcleral vessel engorgement; peripheral corneal thinning; stromal infiltration; and lucid interval from the limbus. (b) Narrowed beam of slit-biomicroscopy shows thinning adjacent to stromal infiltrations.

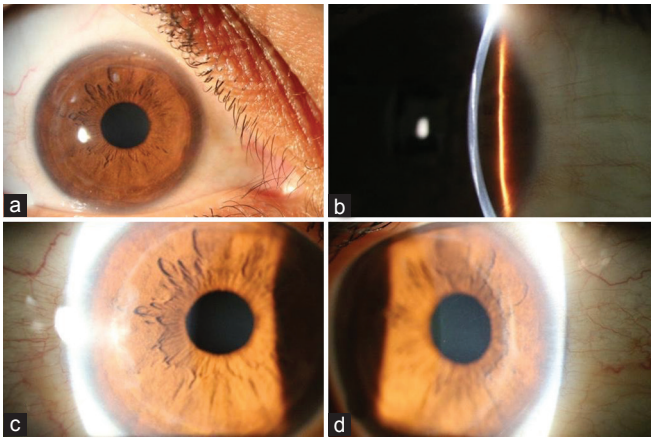

Figure 2. Photo-slit of cornea at last follow-up (a) Right cornea shows 360 degrees scar in corneal peripheral zones. (b) Slit beam shows thinning and stromal scar. (c and d) Focal beam of slit-lamp biomicroscopy shows scarred areas more clearly without infiltration.

including fungal, herpetic, *Acanthamoeba*, or bacterial keratitis, might be associated with epithelial defects, corticosteroid use, and infectious contamination of the cornea or the instruments used during the procedure.[4-7] However, non-infectious events, reported by many authors, occur mainly due to the stimulation of immunologic responses. Sterile infiltrates are a relatively common complication after CXL that may lead to corneal transplantation in most severe cases.[8] Corneal melting without a responsible infectious pathogen has been reported with or without the use of topical NSAIDs.[9,10]

The most likely diagnosis for this case is non-vasculitic peripheral ulcerative keratitis. Peripheral corneal thinning with stromal infiltration and an overlying epithelial defect as well as an adjacent episcleritis, negative culture results, moderate discomfort, and responding to steroid therapy are in favor of her diagnosis. Considering other differential diagnoses, Mooren ulcer, which was absent in our patient, typically presents with more severe pain. Since our patient was closely followed up and she had no history or symptoms of longstanding staphylococcal blepharitis documented in her records, blepharokeratoconjunctivitis is a less probable diagnosis.

Matrix metalloproteinase 1 (MMP-1), also known as collagenase 1, is believed to be a causative agent of peripheral ulcerative keratitis (PUK) in patients with rheumatoid arthritis (RA). Several sources have been proposed to induce expression of MMP-1, including conjunctival epithelial cells, limbal inflammatory cells, stromal keratocytes, infiltrating macrophages, and stimulated corneal fibrocytes.[11-13] It can be hypothesized that CXL activates macrophages, transformed myofibroblasts, or corneal keratocytes, which in turn stimulate MMP-1 production, triggering a pathway in PUK similar to the one in RA. Furthermore, there is growing evidence supporting the role of inflammatory factors, especially MMPs and MMP inhibitors, in the pathogenesis of KC.[14] The exact role and mechanisms of these proteases in KC still remain unknown, but it can be assumed that a similar cascade to that observed in RA, and potentially PUK, causes peripheral keratitis following CXL.

Akpek and colleagues reported a case of PUK after an uneventful cataract extraction with a small clear corneal incision in an 80-year-old healthy woman in whom early active RA was discovered after a systemic evaluation.[15] Despite our patient's negative laboratory results, it is possible that she has an underlying rheumatologic disease which would have been discovered during a long interval follow-up. The other way stromal keratitis is caused, in this case, may be through the alterations in antigenicity that occur in corneal native proteins after CXL, which results in the immune system recognizing these proteins as non-self.[16] Similar to the immune reactions after keratoplasty, recognition of these modified antigens by antigen-presenting cells and activation of the ocular immune system may last for a few months, which explains the long time interval between the CXL and the recurring stromal keratitis in our case.

In conclusion, we reported a case of bilateral recurrent stromal keratitis after standard CXL for progressive KC. Stromal keratitis was treated with frequent applications of topical corticosteroids. To our knowledge, this is the first case of stromal keratitis recurrence. Although CXL is considered to be a safe method, studies with longer follow-ups are needed to investigate the risk of such rare complications.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understand that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of Interest

There are no conflicts of interest.

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