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CASE REPORT

Sterile keratitis after uneventful corneal collagen cross-linking in a patient with Axenfeld-Rieger syndrome

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Abstract

Purpose To report on a keratoconus (KC) patient with Axenfeld-Rieger syndrome (ARS) who developed sterile keratitis after accelerated corneal collagen cross-linking (CXL).

Methods An 18-year-old patient with ARS and KC who had previously undergone intrastromal ring segment implantation underwent accelerated CXL (9 mW/cm^2 UVA intensity for 10 min).

Results After uneventful surgery, the patient presented with severe photophobia, redness of the eye, and decreased vision 72 h following the procedure. Slit-lamp examination showed anterior multiple superficial stromal infiltrates in the central cornea with an overlying epithelium defect. Due to the lack of pain and absence of any pathogen from corneal samples, a diagnosis of sterile keratitis was considered. A combination of topical antibiotic and corticosteroid regimen was administered. Three months after CXL slit-lamp examination showed a mild stromal scar overlying the central cornea, which did not decrease visual acuity.

Conclusions The mechanism by which the sterile keratitis occurs following CXL remains unclear. For our case, the reason of post-CXL sterile keratitis could be considered as an immune response due to the staphylococcal antigens. Furthermore, the possible developmental disturbance of corneal stroma in ARS might have contributed to the development of post-CXL sterile keratitis.

Keywords Axenfeld-Rieger syndrome · Corneal collagen cross-linking · Keratoconus · Sterile keratitis

Introduction

Keratoconus (KC) is a progressive corneal ectasia characterized by deterioration in the structure of corneal collagen [1]. Corneal collagen cross-linking (CXL) is a safe and effective treatment protocol used to halt the progression of the disease [2].

Keratoconus is related to several genetic systemic disorders including Marfan syndrome, Turner syndrome, osteogenesis imperfecta, Ehlers–Danlos syndrome, Down syndrome, Crouzon's syndrome, and Axenfeld-Rieger syndrome (ARS) [3]. To date, only one study has reported on a patient with ARS and KC [4]. To our knowledge, there have been no reports regarding the results of CXL treatment for KC in a patient with ARS thus far. In this report, we presented a patient with ARS and KC who developed sterile keratitis after undergoing uneventful CXL treatment.

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Case presentation

An 18-year-old male KC patient presented with gradual loss of vision in both eyes. He did not use any medication or contact lenses. His right eye had undergone intrastromal ring segment implantation for KC (Fig. 1a). His uncorrected visual acuity (UCVA, Snellen) was 0.3 in both eyes which improved to 0.5 with − 2.0 − 2.5 @ 115° and − 1.75 @ 25° in the right and left eyes, respectively. Polycoria was presented in the left eye (Fig. 1b), and posterior embryotoxon in both eyes, which was visible only with gonioscopy. Intraocular pressure was 9 and 11 mmHg in the right and left eyes, respectively, and the fundus in both eyes was normal. In addition, the patient presented with midface abnormalities (telecanthus, prominent forehead, a flat and broad nasal bridge, and maxillary hypoplasia) and dental abnormalities (microdontia and hypodontia) (Fig. 1c), which are in concordance with ARS phenotype.

A Scheimpflug camera combined with a Placido disk corneal topographer (Sirius; CSO, Italy) showed a pattern consistent with Amsler–Krumeich stage IV KC for both eyes with maximum keratometry (K-max) of 51.50 D and thinnest corneal thickness (th-CT) of 385 μm in the right eye and K-max of 52.20 D and th-CT of 387 μm in the left eye. CXL treatment was planned for both eyes, and the patient underwent uneventful CXL in his right eye under topical anesthesia.

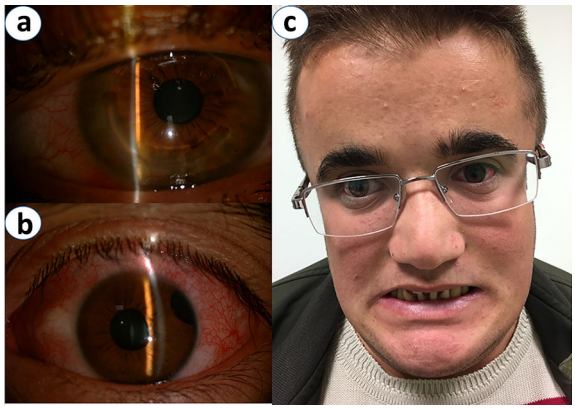

Fig. 1 Images of the patient with Axenfeld-Rieger syndrome. **a** Right eye with an intrastromal corneal ring segment. **b** Left eye with polycoria. **c** Facial photograph showing midface abnormalities (telecanthus, prominent forehead, a flat and broad nasal bridge, and maxillary hypoplasia) and dental abnormalities (microdontia and hypodontia)

During the CXL procedure, the corneal epithelium was removed mechanically by using a crescent knife at an intended 8.5-mm zone after loosening the cornea epithelium with 20% alcohol solution. After epithelial removal, the residual corneal thickness was measured with an ultrasonic pachymeter (PalmScan AP-2000-Ultima, Micro Medical Devices, USA). The th-CT was measured below 400 μm after epithelial removal, and a single-use hypotonic riboflavin eye solution (0.1% riboflavin without dextran, Meran Medicine, BNM Inc., Istanbul, Turkey) was applied at the center of the cornea every 2 min for 30 min. After riboflavin saturation of corneal stroma, the th-CT was measured above 400 μm. Ultraviolet A (UVA) irradiation was accomplished using a commercially available UVA system (Apollon system; Meran Medicine, BNM Inc., Istanbul, Turkey). Before treatment, the intended 9 mW/cm2 surface irradiance (5.4 J/cm^2 surface dosage after 10 min) was calibrated using a UVA meter (UVA-365, Lutron Electronic). Along the UVA irradiation, riboflavin solution was applied every 2 min to ensure saturation and to moisten the cornea. A silicone hydrogel bandage contact lens (Acuvue Oasys, Johnson&Johnson, Vision Care) was applied at the end of the surgery. Postoperative treatment included ofloxacin eye drops (Exocin, Allergan Inc.) q.i.d. for 1 week, fluorometholone acetate 5% eye drops (Flarex, Alcon Inc.) q.i.d. on a tapering schedule for 1 month, and artificial tears q.i.d. for 1 month. The patient was instructed to come back every day until the epithelium healing was completed.

On the third postoperative day, the patient presented with severe photophobia, redness of the eye, and decreased vision in the right eye. On examination, his UCVA was 0.05 and slit-lamp examination revealed conjunctival hyperemia, anterior multiple superficial stromal infiltrates, and mild stromal edema in the central cornea with an overlying epithelium defect approximately 4.00 mm × 6.00 mm in size (Fig. 2). The bandage contact lens was removed and sent for microbiologic evaluation, and also corneal scrapes were performed for microscopy, along with cultures for bacteria and fungi. Subsequently, topical corticosteroid drops were discontinued, and topical moxifloxacin (Vigamox; Alcon Inc) was administered hourly along with tetracycline eye ointment (2 times daily) and preservative-free lubricant (Eyestil; Teka Inc). No microorganism was identified in the smear examination of corneal scraping. Nevertheless, the

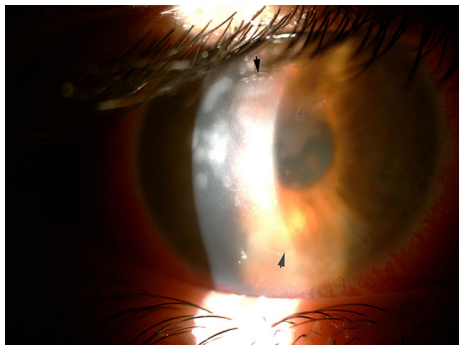

Fig. 2 Slit-lamp photograph of the right eye at day 3 following CXL. Note hyperemic conjunctiva and anterior multiple superficial stromal infiltrates and mild stromal edema in the central cornea, with an epithelium defect approximately 4.00 mm × 6.00 mm in size. Arrows indicate the upper and lower borders of the epithelial defect

antibiotic regimen was continued. There was no growth in cultures at the end of 48 h. The lesion was diagnosed as sterile keratitis. On the postoperative day 5, there was a significant decrease in the epithelium defect. Subsequently, low potency topical steroid (5% fluorometholone) drops was added to the treatment regimen 4 times daily. There was no further progression of the infiltrates. On the postoperative day 10, slit-lamp examination showed the eye to be relatively quiet eye along with completely healed corneal epithelium over grade 2 stromal haze. At this stage, topical antibiotics were discontinued, and frequency of topical steroids was increased to 8 times daily. At the 1-month postoperative follow-up, slit-lamp examination revealed completely quiet eye with a mild central anterior stromal scarring with a best-corrected visual acuity (BCVA) of 0.5. After progressive recovery of corneal infiltrates, the topical steroids were tapered and discontinued at 8 weeks. At the 3-month postoperative follow-up, only a mild stromal scar that did not decrease visual acuity was seen overlying the central cornea. The patient's UCVA was improved to 0.4 from 0.3, and BCVA was 0.5 with correction of + 1.25 − 2.5 @ 110° 3 months after CXL. The corneal cone became flatter 3 months after CXL procedure shown in the anterior cornea tangential differential map (Fig. 3). His left eye has not undergone CXL yet.

Discussion

Axenfeld-Rieger syndrome is a genetic disorder commonly characterized by anterior segment dysgenesis with systemic developmental abnormalities [5]. Posterior embryotoxon and iris abnormalities with variable presentations are the most common ocular findings [6]. Systemic findings include mild midface abnormalities (e.g., maxillary hypoplasia, prominent forehead, a broad and flat nasal bridge, hypertelorism, and telecanthus), dental (e.g., microdontia, hypodontia, and oligodontia) and cardiovascular abnormalities, and redundant umbilical skin [6].

Reported cases of ARS have variable phenotypic features. In our case, posterior embryotoxon could be seen only with gonioscopy as previously noted [7]. Shields stated that approximately 25% of patients with ARS had posterior embryotoxon visible only with gonioscopy [7]. Polycoria was also noted in the left eye in this patient. In terms of systemic abnormalities, the patient had craniofacial dysmorphism and dental abnormalities. Due to the ophthalmic findings and typical phenotype of our patient, he was diagnosed as ARS. In addition, the diagnosis of KC was also considered according to the clinical evaluation and corneal topography analysis. Deteriorated neural crest cell migration and differentiation during embryonic development are considered important in the pathogenesis of ARS. The corneal stroma, which is mainly affected in KC, also has its origin in these neural crest cells [8]. However, only one study has reported on a patient with ARS and KC [4], and possible genetic defects or etiologic factors have not been identified yet.

To our knowledge, this is the first case of ARS with KC where the patient underwent CXL treatment and developed post-CXL sterile keratitis. Although CXL is a safe treatment option in KC, several complications of CXL including corneal haze, melting, and infectious and sterile keratitis have been reported [9–11]. In the present case, the lack of pain and absence of any pathogen on smear examination and culture, as well as the rapid improvement in the epithelial defect and the infiltrates were presumed to be of sterile origin. The exact mechanism of the occurrence of the sterile keratitis after CXL is still unclear. Sterile corneal infiltrates are associated with extended contact lens wear, nonsteroidal antiinflammatory drug use, systemic autoimmune disease, or enhanced cell-mediated

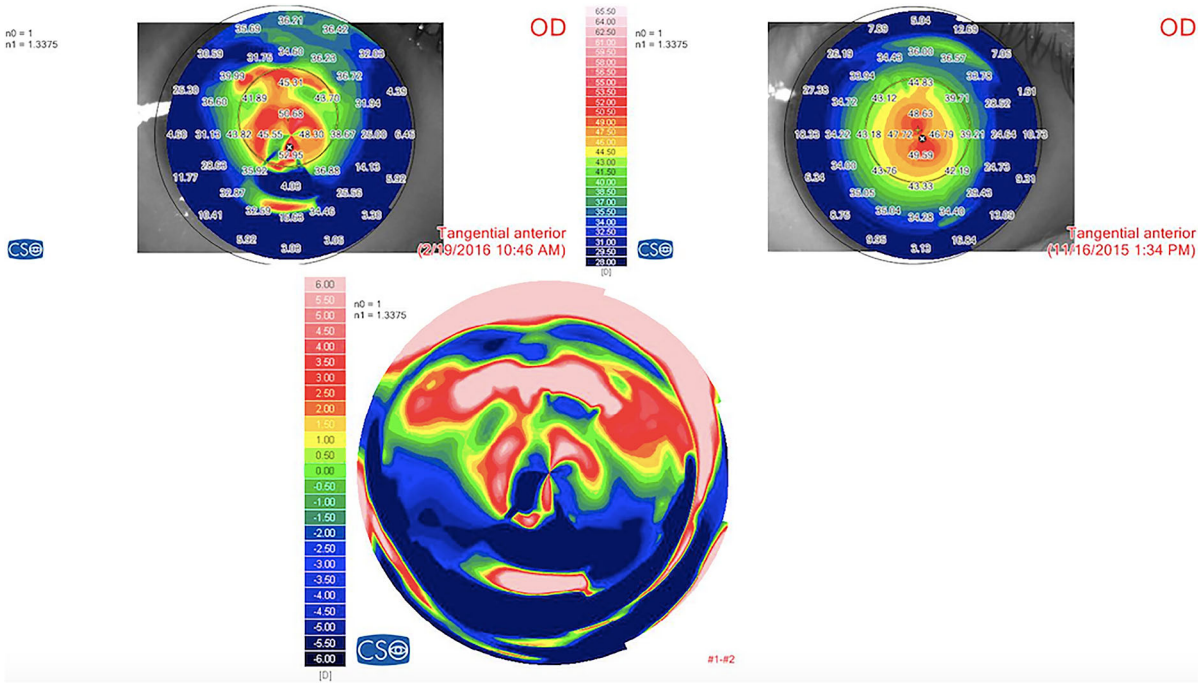

Fig. 3 Corneal topography images of the right eye before CXL and 3 months after CXL. The anterior cornea tangential differential map indicates the flattening of the corneal cone

immunity to staphylococcal antigens [12–14]. In our case, an immune response should be considered because of the absence of the clinical signs of the infectious keratitis, the pattern of the infiltrates, and the rapid response to steroids. The central nummular sterile infiltrates were seem to be associated with staphylococcal antigens deposited at high concentrations in areas of static tear pooling under the contact lens, and the epithelial defect was most likely the staphylococcal antigens entrance door [15, 16]. Moreover, the developmental impairment in corneal stroma in ARS, which might have enhanced immunologic response to staphylococcal antigens, also could be considered as a risk factor for post-CXL sterile keratitis. Further studies are required to clarify this point.

In a large series of keratoconic eyes undergoing CXL, Koller et al. [9] reported sterile infiltrates in 7.6% of eyes, and recovery was observed after 4 weeks with no significant reduction in BCVA. This result was in concordance with our case, where the patient experienced an improvement in UCVA. This may be partly explained by the flattening of the corneal cone due to the mild corneal scarring in the visual axis.

To the best of our knowledge, this is the first case of ARS with KC where the patient underwent CXL treatment and developed post-CXL sterile keratitis leaving stromal scarring. For our case, the reason of post-CXL sterile keratitis should be considered as an immune response due to the staphylococcal antigens. Furthermore, the possible developmental disturbance of corneal stroma in ARS might have contributed to the development of post-CXL sterile keratitis. Further studies investigating the relationship between post-CXL sterile infiltrates and underlying etiologic factors in patients diagnosed with ARS are necessary.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study involving human participant were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Human and animals rights This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from the participant included in this study. Additional informed consent was obtained from the participant for whom identifying information is included in this article. The participant gave written informed consent for publication which was added to the supplementary material section.

Patient consent The patient has consented to the submission of the case report for submission to the journal.

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