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Letter to Editor

Central Toxic Keratopathy Following Corneal Collagen Cross-Linking

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Dear Editor,

Corneal collagen cross-linking (CXL) is a revolutionary procedure to halt keratoconus (KCN) progression, but it is not complication-free. Infectious keratitis, persistent epithelial defects, corneal edema, or severe melt have been reported after CXL (1). Most of the complications can be managed easily; some may lead to severe visual loss, such as central toxic keratopathy (CTK).

Herein, we present six eyes of four patients that underwent CXL for progressive KCN elsewhere and, then, were referred to Dokuz Eylül University, Department of Ophthalmology with findings consistent with CTK (Table 1). Patients underwent detailed ophthalmological examination including corrected distance visual acuity (CDVA) on Snellen chart, slit-lamp examination, Scheimpflug corneal tomography (Pentacam, Oculus®, Germany), and specular microscopy (CellCheck, Konan®, United States). The study adhered to the tenets of Declaration of Helsinki.

All patients complained of decreased vision after CXL with significant hyperopic shift. Slit-lamp examination revealed central corneal haze or scarring, vertical striae with indistinct margins, thinning and flattening, and clear peripheral cornea. No epithelial defect, epithelial laxity, staining patterns, stromal, or epithelial edema was detected. In Case 1, confocal microscopy showed acellular stroma, striations, and thick collagen bundles (Figs. 1a-c), and specular microscopy revealed endothelial cell count of 1602 cells/mm² OD, 2181 cells/mm² OS. In Case 2, significant inferior flattening at the tomography (Figs. 2a and b) was seen, whereas endothelial cell count was 2890 cells/mm² OS on specular microscopy. Confocal or specular microscopy could not be performed in Cases 3 and 4; however, central corneal haze and associated significant flattening in the tomographies were evident (Figs. 3a and b, 4a and b).

On consultation with their surgical-centers, patients' operative histories were clarified. All cases had pre-operative thinnest de-epithelialized pachymetry of >400 μ and underwent accelerated de-epithelialized CXL protocol which included saturation of the stroma by instillation of 0.1% riboflavin solution (Riboflavin, Ricrolin, Peschke Meditrade, Germany) for a total 20 min and 365 nm ultraviolet-A (UVA) light application for 10 min at an irradiance of 9 mW/cm², delivering a total dose of energy of 5.4 J/cm². None of the cases developed infectious keratitis or diffuse lamellar keratitis (DLK) in the early postoperative period, and corneal healing was uneventful.

Duration of the findings was at least 6 months in each case, with no resolution of the symptoms. Topical loteprednol bid, cyclosporine 0.05% bid, and carboxymethylcellulose qid treatments yielded no significant benefits in any of the cases. Topical cyclosporine 0.05% bid and peroral vitamin C 500 mg/day were commenced to provide anti-inflammatory effect and promote collagen re-synthesis and re-modeling in

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Table 1. Demographic characteristics and clinical findings of the cases at initial presentation

	Age	Gender	Laterality	Time from CXL	UDVA	CDVA	Sim K1 (D)	Sim K2 (D)	Thinnest corneal pachymetry (µm)	Refractive error
Case 1	30	Female	Right	9 years	20/400	20/50	31.3	34.5	424	+8.00−2.00 @ 60
	30	Female	Left	4 years	20/50	20/32	36.0	37.9	379	+2.00−2.50 @ 75
Case 2	35	Male	Left	6 months	20/125	20/125	31.6	35.1	87	+4.00+10.75 @ 168
Case 3	34	Male	Left	3 years	20/100	20/50	36.3	37.5	383	+1.75−1.00 @ 15
Case 4	24	Male	Right	5 years	20/100	20/63	41.1	42.2	362	+5.00−2.00 @ 150
			Left	5 years	20/200	20/50	43.9	47.4	339	−2.00 @ 180

CXL: Corneal collagen cross-linking; UDVA: Uncorrected distance visual acuity; CDVA: Corrected distance visual acuity; Sim K1: Simulated keratometry value 1, Sim K2: Simulated keratometry value 2, D: Diopters.

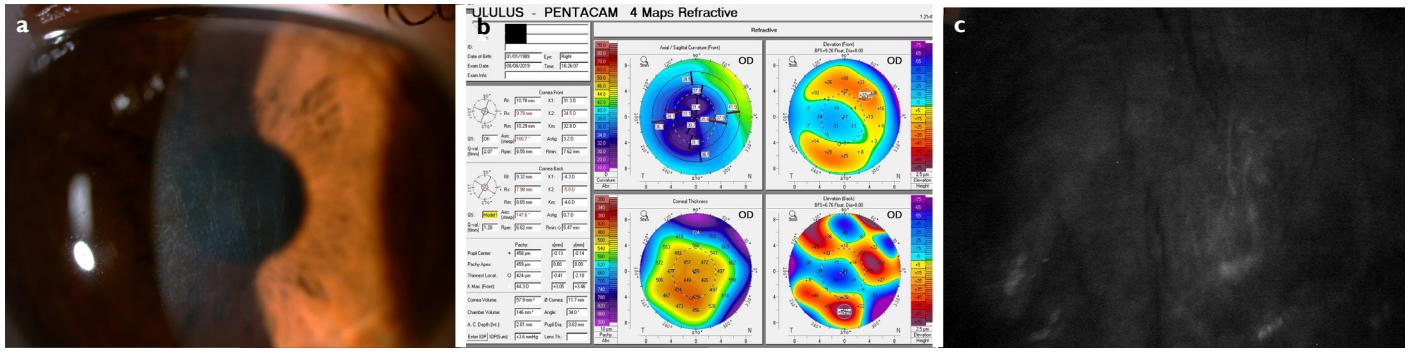

Figure 1. Right eye central corneal scarring and vertical striae **(a)**, severe central corneal flattening in Scheimpflug tomography **(b)**, and acellular stroma, striations, and thick collagen bundles at the confocal microscopy **(c)** of case 1.

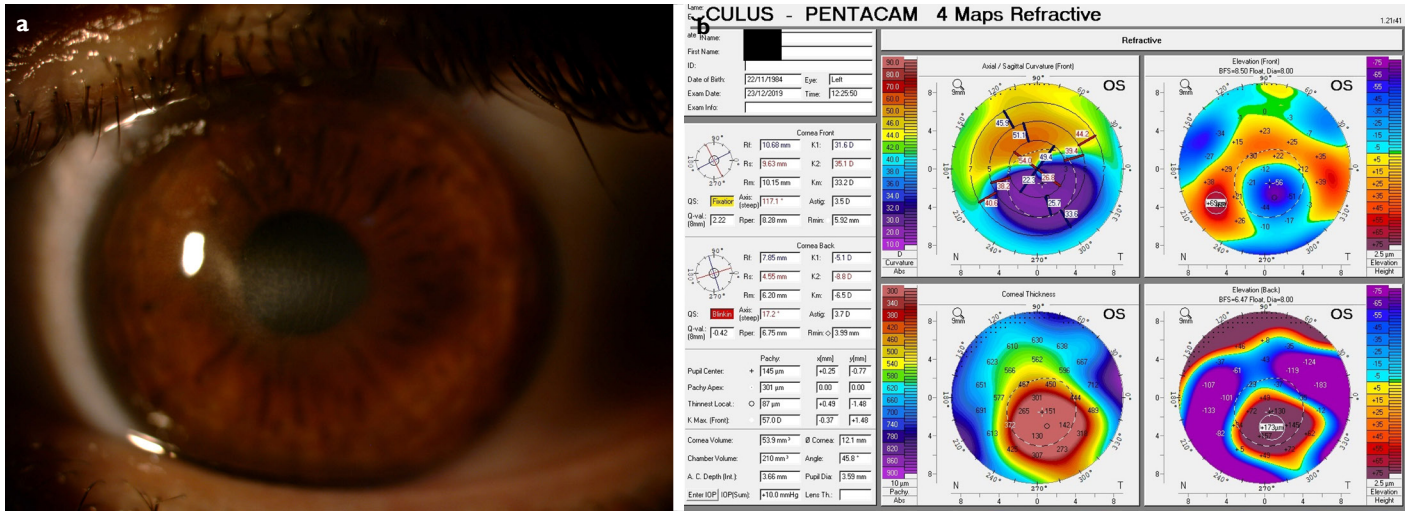

Figure 2. Left eye central corneal scar with clear peripheral cornea **(a)** and severe central corneal flattening in Scheimpflug tomography **(b)** of case 2.

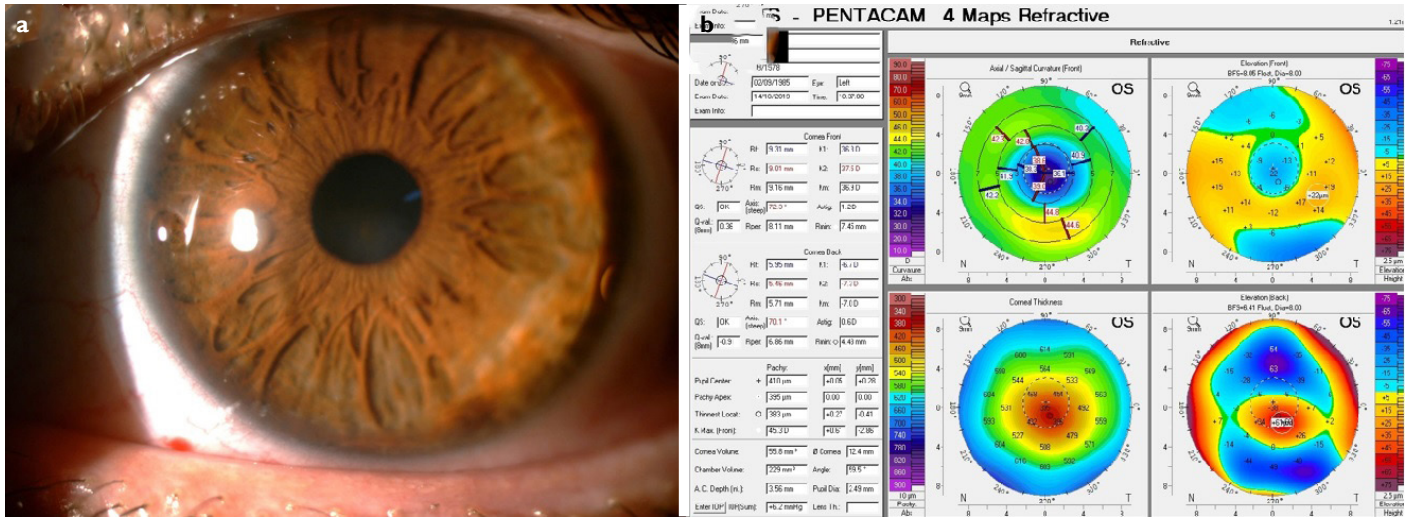

Figure 3. Left eye stromal haze in the center of the cornea **(a)** and severe central corneal flattening in Scheimpflug tomography **(b)** of case 3.

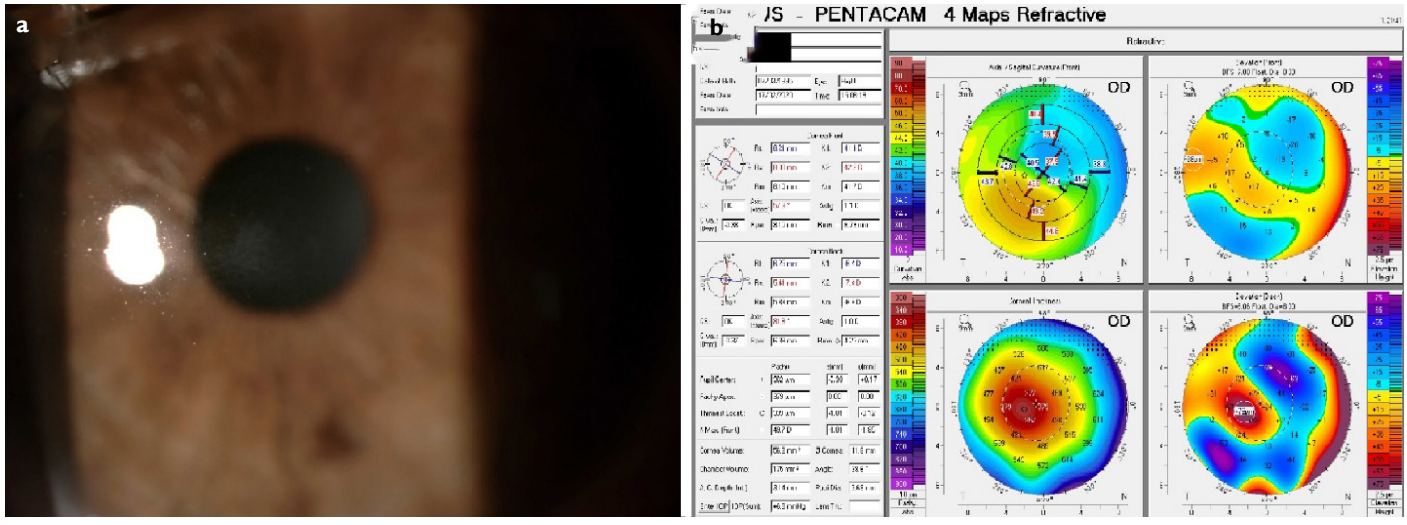

Figure 4. Right eye central corneal scarring **(a)** and mild central corneal flattening in Scheimpflug tomography **(b)** of case 4.

Case 2, as he was still in the early post-operative period.

For visual rehabilitation, contact lens trials were performed. In Case 1, silicone hydrogel soft contact lenses for KCN (Toris-K, SwissLens) and inverse geometry rigid gas permeable lenses (Rose K2 Post Graft, Menicon Co. Ltd) improved CDVA for three lines; however, she could not tolerate the lenses. In Case 3, fitting with the Toris-K12 soft KCN lens (diameter: 14.0, base curve: 8.40, power: +0.50) could increase his CDVA up to 20/25. New spectacles were prescribed for Case 2 and Case 4, who did not accept contact lens fitting.

Central toxic keratopathy was first defined in 1998 and had alternative names such as central lamellar keratitis, central flap necrosis, and keratinocyte-induced corneal microedema (2,3). The condition includes central/paracentral non-inflammatory corneal amorphous opacities accompanied by striae, loss of stroma with corneal thinning and flattening of the corneal curvature, and associated hyperopic shift (2,4). Central toxic keratopathy was reported after corneal surgeries such as CXL, photorefractive keratectomy (PRK), laser-assisted in situ keratomileusis (LASIK), with contact lens use, topical anesthetics use, or as idiopathic occurrence (5,6). Hainline et al.(3) reported nine eyes and Cotino et al.(7) reported four eyes with CTK, in 17,100 (0.05%) and 522 (0.77%) eyes underwent LASIK. Moshirfar et al.(8) reported 12 eyes with CTK out of 20,622 femtosecond laser-assisted LASIK procedures (0.06%) in 5 years. However, there have been no studies to assess the epidemiologic data for CTK after CXL.

The exact cause of CTK is unknown. One hypothesis claims a reaction against substances such as surgical glove components, meibomian gland secretions, marker pen ink, or povidone-iodine (4,5). Stromal loss in CTK is considered as a result of keratocyte apoptosis, enzymatic destruction of the extracellular matrix, and disorganization of collagen lamellae, as observed in confocal microscopy (9). Here, Case 1 re-

vealed acellular stroma, striations, and thick collagen bundles. Another theory blames keratinocyte damage and cytokine release for the changes in interstitial fluid pressure and corneal microedema. In addition, appearance of stromal immune complexes in some patients suggested immunological processes to play a role in the etiopathogenesis (10). Removal of epithelium with excessive forces, excessive application of riboflavin solutions and UVA irradiation during CXL can cause CTK postoperatively. Development of CTK in one eye may pose a risk to the second eye, as in Case 1. In CTK cases after PRK, pathology was almost always seen in zones where laser ablation was performed (11). Excessive UVA application during CXL might be a causative factor for CTK.

In patients that underwent surgery with excimer laser or UVA and have complaints of photophobia, foreign body sensation, and blurred vision; CTK should be considered in the differential diagnosis. Anterior segment optical coherence tomography may reveal an inverted dome-shaped appearance showing posterior opening in the central cornea;(4-6) confocal microscopy with lack of keratocytes and disorganized collagen matrix proves the diagnosis. CTK can be differentiated from infectious keratitis with absence of an infiltrate, conjunctival hyperemia, ciliary injection, and purulent secretion (4). Differential diagnosis from DLK can be made with the absence of inflammation, lesion location (i.e., CTK is not limited to the interface, can expand toward residual stromal bed), and treatment response (i.e., CTK may worsen with steroids) (4,11).

No agent is effective for treatment of CTK. Due to non-inflammatory nature, the patients do not benefit from steroids. Regeneration of the stromal extracellular matrix is provided by keratinocytes, and metalloproteinases inhibit this process. Doxycycline, which acts as a metalloproteinase inhibitor; and ascorbic acid, which is a cofactor of the enzymes in collagen synthesis may have a positive effect in stromal regeneration (12). We used peroral vitamin C in Case 2 to benefit from these mechanisms, with no clear benefit. Corneal opacities heal without invasive intervention in some cases. Patients can be followed closely without surgical intervention (4). However, Tu and Aslanides(13) reported that flap lift and irrigation in the early CTK resulted in an arrest of the development of the opacity in one out of three patients. In post-LASIK CTK, corneal opacity usually regresses within 2–18 months, but this process can be prolonged or remain permanent (7).

In conclusion, the exact etiology of CTK is still unknown. A specific treatment method has not been defined yet. Central opacity may regress a little, stromal thickness may increase over time, but the targeted visual acuity may not be achieved due to permanent hyperopic shift and residual striae. Considering flattening of the cornea, soft KCN contact lenses and inverse-geometry lenses can be alternatives for visual rehabilitation in selected cases. Since CTK may develop in patients whose visual acuity has already decreased due to KCN; it seems rational not to plan bilateral simultaneous CXL, which is a device and technology-dependent procedure. Further studies are required to have a better knowledge about CTK after CXL.

Disclosures

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