

Case Report

Late-Onset Haze and Severe Corneal Flattening after Combined Corneal Collagen Cross-Linking and Photorefractive Keratectomy (CXL Plus): A Case Report

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Keywords

Cross-linking · Photorefractive keratectomy · Cornea · Thinning · Flattening · Hyperopic shift · CXL Plus

Abstract

Introduction: Significant corneal flattening and haze are important complications that can occur after combined corneal collagen cross-linking (CXL) and photorefractive keratectomy (PRK) procedures (CXL Plus). **Case Presentation:** We present a 24-year-old man who underwent combined standard CXL and PRK. The patient experienced satisfactory vision for approximately 4 years after the surgery. However, after this period, he began to complain of visual blurring. Subsequent examination revealed significant corneal haze, excessive flattening in both eyes, and thinning (thinnest point 227 μm in the right eye, 244 μm in the left eye) 4 years postoperatively. Upon presentation, the corrected distance visual acuity (CDVA) was 20/200 in the right eye and 20/400 in the left eye. The presenting refraction was +2.50 sph, –3.50 cyl *114 in the right eye and +11.5 sph, –9.75 cyl *81 in the left eye. With rigid gas permeable contact lenses, the corrected visual acuity was 20/50 in both eyes. Before the CXL Plus surgery, initial refraction and CDVA were 20/50 in the right eye (–5.50 sph, –3.00 cyl *175) and 20/30 in the left eye (–5.50 sph, –2.75 cyl *175). The patient was treated by penetrating keratoplasty. The CDVA reached 20/30 at the final follow-up. **Conclusion:** Our report highlights significant corneal haze and

flattening that occurred 4 years after combined CXL and PRK treatment. These findings suggest that this procedure might not be safe in suspected patients of keratoconus. Further long-term follow-up research is necessary to evaluate the safety of combined CXL and PRK procedures.

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Introduction

Corneal collagen cross-linking (CXL) is one of the most accepted treatments to slow down or halt the progression of keratoconus (KCN). This procedure increases corneal rigidity and stabilizes the corneal collagen matrix in progressive KCN [1–3]. The method was first used by Wollensak et al. [4] for the treatment of progressive KCN in 2003. Clinical studies have shown that CXL is a relatively safe approach for stabilizing corneal ectasia, with low rates of complications [4–6].

CXL Plus is an off-label procedure that involves the simultaneous combination of CXL and a refractive procedure aimed at flattening the cornea to improve vision [4]. In the CXL PLUS procedure, the primary objective is to strengthen the cornea and halt the progression of the disease through CXL, while the quality of vision is enhanced through additional refractive surgeries such as photorefractive keratectomy (PRK) [4, 7].

The first reported case of performing PRK after CXL for the treatment of KCN was by Kanellopoulos and Binder [8]. Several limited studies have been published regarding the safety and efficacy of the CXL Plus [9–15]. It has been demonstrated that simultaneous PRK and CXL treatment is more effective compared to performing CXL followed by PRK after 6 months [12, 16].

While the early postoperative complications of CXL PLUS (CXL and PRK) are minimal, the long-term safety and efficacy results are still unknown [17]. In light of this, we present a patient who underwent combined CXL and PRK, and the procedure resulted in significant corneal flattening haze and thinning after 4 years. The case report has been written based on CARE guidelines, and the checklist has been uploaded as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000535987>).

Case Report

In January 2019, a 24-year-old Caucasian man was referred to our clinic for an evaluation of reduced vision that had been present for the past year. Both eyes experienced a decline in vision over time. The uncorrected distance visual acuity was 20/200 in the right eye and 20/400 in the left eye. Upon presentation, the refraction was +2.50 sph, –3.50 cyl *114 in the right eye and +11.5 sph, –9.75 cyl *81 in the left eye. With rigid gas permeable contact lenses, the corrected visual acuity was 20/50 in both eyes.

In July 2014, the patient visited another ophthalmology clinic seeking refractive surgery. He had been wearing glasses since his school years. According to the patient's records, his spectacle-corrected distance visual acuity (CDVA) before surgery was 20/50 in the right eye (–5.50 sph, –3.00 cyl *175) and 20/30 in the left eye (–5.50 sph, –2.75 cyl *175). With rigid gas permeable contact lenses, his corrected visual acuity was 20/25 in both eyes. Preoperative keratometric readings derived from the topography map were 44.59/47.21 diopters (D) in the right eye and 44.57/47.00 D in the left eye. The slit lamp examination, applanation tonometry, and funduscopy of both eyes were normal. The preoperative retinoscopy

revealed suspected scissoring of the red reflex in both eyes. The preoperative TMS4-topographer (Tomey Erlangen, Germany) showed a non-orthogonal asymmetrical bow tie with superior steepening. The preoperative minimum corneal thickness measured by the Pentacam-Scheimpflug imaging system (Oculus, Wetzlar, Germany) was 578 μm in the right eye and 560 μm in the left eye (K_{max} was 49.5, and mean K was 45.9 in the right eye, and 48.5 and 45.5 in the left eye, respectively). The preoperative Pentacam scan revealed superior steepening in the front axial curvature map of both eyes (Fig. 1a, b).

In September 2014, the patient underwent simultaneous combined CXL and non-topography-guided PRK (CXL Plus) at another surgical center. The decision to perform CXL Plus was probably due to the KCN suspect. The Allegretto Wave excimer laser (Alcon WaveLight, Erlangen, Germany) was used for PRK, while the Avedro KXL cross-linking system (Waltham, MA, USA) was used for CXL. In the first step, PRK was performed with the following settings: the optical zone was 6.5 mm with a 9 mm de-epithelialized corneal zone in both eyes. The ablation depth was 121.20 μm in the right eye and 117.90 μm in the left eye. Both eyes were treated with 0.02% mitomycin C for 1 min after surface ablation. The second step involved the standard epithelium-off CXL procedure, which was performed according to the standard Dresden protocol (3 mW/cm² for 30 min) using isotonic riboflavin [18]. The surgery and recovery were reported as uneventful. Two months after the surgery, the uncorrected distance visual acuity was 20/25 and remained stable for approximately 4 years.

During the slit lamp examination and anterior segment optical coherence tomography (Optovue, Inc., Fremont, CA, USA), central mid to deep stromal haziness (grade 2–3) was observed in both eyes (Figure 2a, b). Applanation tonometry and fundoscopic examination revealed normal findings. A systemic workup was conducted to evaluate any conditions that could affect corneal collagen, such as diabetes mellitus, metabolic disorders, and autoimmune diseases. All the workup results came back negative.

Corneal topography of both eyes revealed irregular flattening of the central cornea (Fig. 1b). The Pentacam scan of both eyes showed corneal flattening (38.00/40.60, K_{max} was 49.1, and mean K was 33.5 in the right eye; 30.10/37.70, K_{max} was 56.8, and mean K was 39.3 in the left eye) and thinning (thinnest point 227 μm in the right eye, 244 μm in the left eye) (Fig. 1c, d).

The patient was scheduled for deep anterior lamellar keratoplasty in the left eye using Anwar's technique. However, the big bubble was not formed, and during the second try for big bubble formation, the cornea was perforated, and the surgical plan was changed to penetrating keratoplasty. The postoperative period was uneventful. The CDVA reached 20/30 with spectacles at the final visit and 6 months after suture removal. The patient underwent deep anterior lamellar keratoplasty in the right eye after 1 year.

Discussion

The present study reports significant progressive corneal flattening, haze, and a hyperopic shift in both eyes of a patient 4 years after CXL Plus. The majority of eyes undergoing CXL experience less than 5.00 D of corneal flattening during the first year postoperatively [4, 19]. Herein, we reported a patient with late-onset corneal haze and flattening after CXL Plus treated by penetrating keratoplasty. Regarding the treatment options, corneal transplantation including lamellar or penetrating keratoplasty was the most acceptable option. Phototherapeutic keratectomy seemed ineffective due to the high amount of hyperopia and the depth of the scar.

The excessive corneal flattening in our patient could be attributed to both the CXL effect and the PRK. Correction of near 8.50 D refractive error generally leads to approximately 7 D of

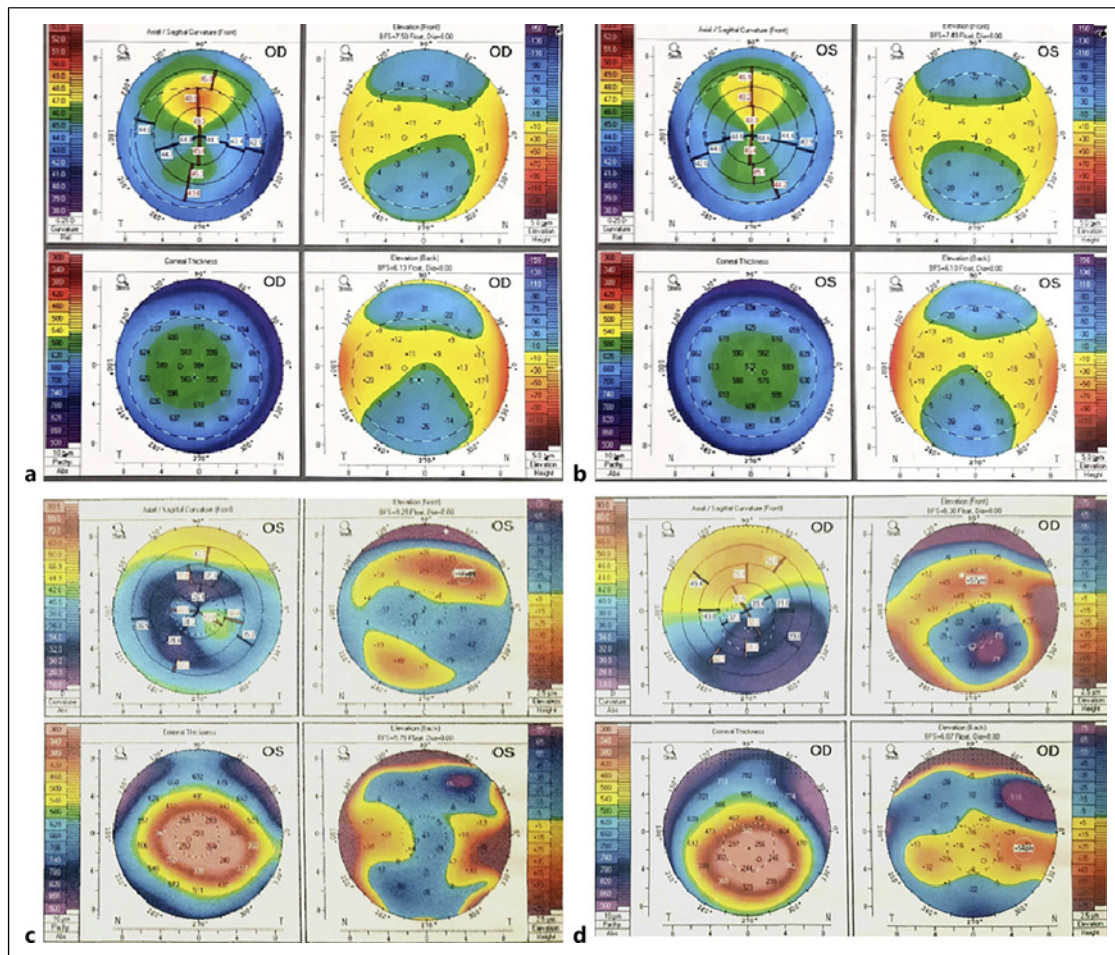


Fig. 1. Pentacam images demonstrating the preoperative (a, b) and postoperative (c, d) corneal tomography in the right and left eyes, respectively. Severe flattening is observed after combined CXL and PRK (CXL Plus).

corneal flattening. The extra flattening in our patient could be attributed to the combined CXL. Previous studies demonstrated that CXL leads to the loss of keratocytes in the corneal stroma and keratocyte repopulation is completed until month 6. These newly produced keratocytes may lead to stromal haze [20]. Additionally, excessive corneal flattening is associated with corneal thinning [21]. However, the exact mechanism or even diagnosis is not determined by our patient.

Corneal flattening greater than 10.00 diopters after CXL is a rare phenomenon. Santiago et al. [22] described early excessive corneal flattening (14 D and 7 D) in 2 patients 1 year after undergoing the standard CXL protocol. The author suggested that significant post-CXL corneal flattening may be associated with a central cone location and more advanced disease, resulting in a stronger CXL effect and more intense wound healing. In another study, progressive corneal flattening (11.10 D) was reported in one eye of a 23-year-old woman, along with associated corneal thinning of over 220 μm during a 5-year follow-up period [21].

There have been various reports in the literature regarding the outcomes of CXL Plus. First, Kanellopoulos and Binder [8] reported a case of KCN treated with sequential CXL and PRK in 2007. Subsequently, he found that the same-day procedure resulted in less stromal scarring compared to the sequential approach [16]. In 2014, he introduced the Athens

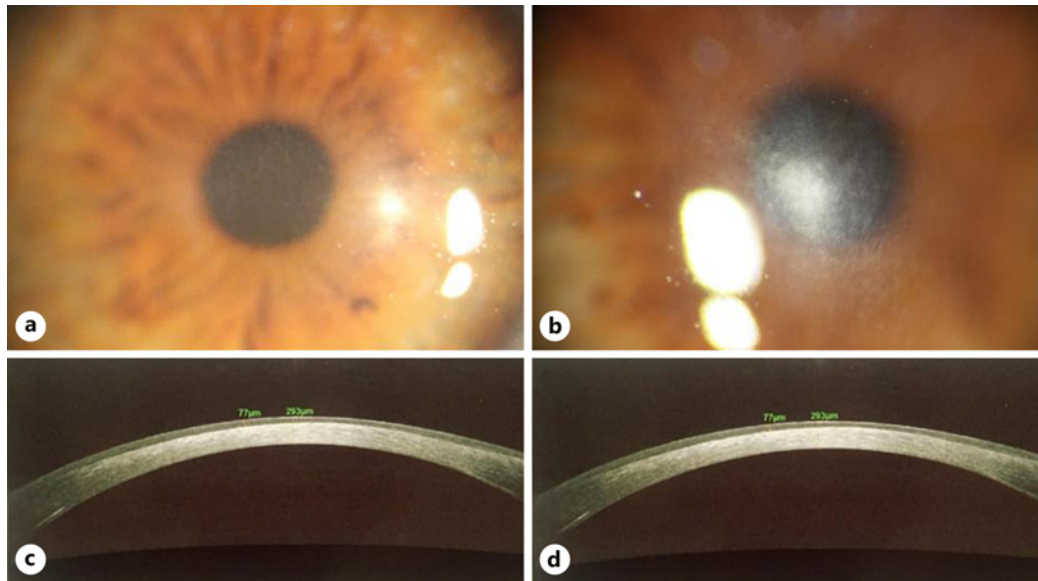


Fig. 2. Photo-slit images of the right eye (a) and the left eye (b) demonstrate corneal haziness in the central zone is more dominant in the left eye. Anterior segment optical coherence tomography of the right eye in the horizontal plane (c) and vertical plane (d) demonstrates full-thickness stromal haze in a thin cornea.

protocol for improving vision in advanced KCN, reporting no complications associated with this protocol [13]. However, there is still a debate regarding the advantage of simultaneous procedures over sequential approaches [12, 15].

In a study evaluating the efficacy of CXL Plus in the treatment of grade 1 KCN over an 18-month follow-up period, positive outcomes were observed. However, complications like delayed epithelial healing, stromal opacities, primary herpes simplex keratitis, and progression of KCN were reported [14]. Our patient did not fill the criteria of KCN which highlights the possibility of long-term complications in combined procedure.

Currently, there is no standardized protocol for prophylactic CXL in refractive surgeries. Prophylactic CXL does not have a standard protocol, but researchers typically use a 0.1–0.5% riboflavin solution with an imbibition duration of 1–2 min. Moreover, less ablation depth is usually chosen like 50 microns. This protocol has fewer adverse side effects, such as long-term flattening and postoperative stromal haze or opacity. Patient selection criteria for prophylactic CXL are also not yet well defined. These criteria may include eyes with thin corneas, high ametropia, high astigmatism, and young patients with a positive family history of keratectasia. Prophylactic CXL should be limited to patients at a high risk of developing post-refractive keratectasia [23].

In the present study, the CXL procedure was performed according to the standard Dresden protocol. Therefore, it is plausible to attribute severe corneal flattening as one of the long-term effects of the simultaneous standard CXL protocol and PRK in this case. It is important to note that this patient did not meet the criteria for KCN based on KCN criteria. In such cases, it may be advisable to first perform PRK and monitor the patient's condition. If ectasia occurs, the CXL method can be employed. Another important point in these cases is that the prophylactic CXL protocol appears to be a safer approach for stabilizing corneas weakened by refractive surgery. When combining refractive surgery with CXL, it is preferable to consider the prophylactic CXL protocol with a shorter treatment time and less ablation depth. We acknowledge that the present study is limited by the lack of measurement of CCT by

anterior segment optical coherence tomography since the Scheimpflug imaging may not provide a reliable corneal thickness in the presence of corneal haze.

In conclusion, the present study reports significant corneal haze and flattening that occurred 4 years after combined CXL and PRK treatment. These findings suggest that this procedure might not be safe in suspected patients of KCN. Further long-term follow-up research is necessary to evaluate the safety of combined CXL and PRK procedures.

Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical data and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Mohammad-Mehdi Sadoughi had the idea and supervised the draft. Marjan Mazouchi wrote the first draft, performed the penetrating keratoplasty, and gathered the data. Kiana Hassanpour and Hamed Esfandiari edited the first draft and completed the data gathering.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

- 1 Colin J, Cochener B, Savary G, Malet F. Correcting keratoconus with intracorneal rings. *J Cataract Refract Surg*. 2000;26(8):1117–22.
- 2 Romero-Jimenez M, Santodomingo-Rubido J, Wolffsohn JS. Keratoconus: a review. *Cont Lens Anterior Eye*. 2010;33(4):157–66; quiz 205.
- 3 Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. *J Cataract Refract Surg*. 2008;34(5):796–801.
- 4 Wollensak G, Spoerl E, Seiler T. Stress-strain measurements of human and porcine corneas after riboflavin-ultraviolet-a-induced cross-linking. *J Cataract Refract Surg*. 2003;29(9):1780–5.
- 5 Belin MW, Lim L, Rajpal RK, Hafezi F, Gomes JAP, Cochener B. Corneal cross-linking: current USA status report from the cornea society. *Cornea*. 2018;37(10):1218–25.
- 6 Evangelista CB, Hatch KM. Corneal collagen cross-linking complications. *Semin Ophthalmol Early Online*. 2017;1–7.

- 7 Kymionis GD, Grentzelos MA, Portaliou DM, Kankariya VP, Randleman JB. Corneal collagen cross-linking (CXL) combined with refractive procedures for the treatment of corneal ectatic disorders: CXL Plus. *J Refract Surg*. 2014;30(8):566–76.
- 8 Kanellopoulos AJ, Binder PS. Collagen cross-linking (CCL) with sequential topography-guided PRK: a temporizing alternative for keratoconus to penetrating keratoplasty. *Cornea*. 2007;26(7):891–5.
- 9 Kanellopoulos AJ, Asimellis G. Keratoconus management: long-term stability of topography-guided normalization combined with high fluence CXL stabilization (the Athens Protocol). *J Refract Surg*. 2014;30(2):88–93.
- 10 Sachdev GS, Ramamurthy S, Dandapani R. Comparative analysis of safety and efficacy of photorefractive keratectomy versus photorefractive keratectomy combined with cross-linking. *Clin Ophthalmol*. 2018;12:783–90.
- 11 Iqbal M, Elmassry A, Tawfik A, Elgharieb ME, El Deen Al Nahrawy OM, Soliman AH, et al. Evaluation of the effectiveness of cross-linking combined with photorefractive keratectomy for treatment of keratoconus. *Cornea*. 2018;37(9):1143–50.
- 12 Kontadakis GA, Kankariya VP, Tsoulnaras K, Pallikaris AI, Plaka A, Kymionis GD. Long-term comparison of simultaneous topography-guided photorefractive keratectomy followed by corneal cross-linking versus corneal cross-linking alone. *Ophthalmology*. 2016;123(5):974–83.
- 13 Lin DT, Holland S, Tan JC, Moloney G. Clinical results of topography-based customized ablations in highly aberrated eyes and keratoconus/ectasia with cross-linking. *J Refract Surg*. 2012;28(11 Suppl):S841–8.
- 14 Malta JBNS, Soong HK, Moscovici BK, Campos M. Two-year follow-up of corneal cross-linking and refractive surface ablation in patients with asymmetric corneal topography. *Br J Ophthalmol*. 2019;103(1):137–42.
- 15 Abou Samra WA, El Emam DS, Farag RK, Abouelkheir HY. Simultaneous versus sequential accelerated corneal collagen cross-linking and wave front guided PRK for treatment of keratoconus: objective and subjective evaluation. *J Ophthalmol*. 2016;2016:2927546.
- 16 Kanellopoulos AJ. Comparison of sequential vs same-day simultaneous collagen cross-linking and topography-guided PRK for treatment of keratoconus. *J Refract Surg*. 2009;25(9):S812–8.
- 17 Greenstein SA, Shah VP, Fry KL, Hersh PS. Corneal thickness changes after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg*. 2011;37(4):691–700.
- 18 Koller T, Pajic B, Vinciguerra P, Seiler T. Flattening of the cornea after collagen cross-linking for keratoconus. *J Cataract Refract Surg*. 2011;37(8):1488–92.
- 19 Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-a light in keratoconus: long-term results. *J Cataract Refract Surg*. 2008;34(5):796–801.
- 20 Dhawan S, Rao K, Natrajan S. Complications of corneal collagen cross-linking. *J Ophthalmol*. 2011;2011:869015.
- 21 Kymionis GD, Tsoulnaras KI, Liakopoulos DA, Paraskevopoulos TA, Kouroupaki AI, Tsilimbaris MK. Excessive corneal flattening and thinning after corneal cross-linking: single-case report with 5-year follow-up. *Cornea*. 2015;34(6):704–6.
- 22 Santhiago MR, Giacomini NT, Medeiros CS, Smadja D, Bechara SJ. Intense early flattening after corneal collagen cross-linking. *J Refract Surg*. 2015;31(6):419–22.
- 23 Chan TCY, Ng ALK, Chan KKW, Cheng GPM, Wong IYH, Jhanji V. Combined application of prophylactic corneal cross-linking and laser in-situ keratomileusis: a review of literature. *Acta Ophthalmol*. 2017;95(7):660–4.