

Posterior Linear Stromal Haze Formation after Simultaneous Photorefractive Keratectomy followed by Corneal Collagen Cross-linking

George D. Kymionis, Dimitra M. Portaliou, Vasilios F. Diakonis, Georgios A. Kontadakis, Maria S. Krasia, Anastasios G. Papadiamantis, Efehan Coskunseven, and Aristofanis I. Pallikaris

PURPOSE. To report the development of posterior linear stromal haze after simultaneous photorefractive keratectomy (PRK) followed by corneal collagen cross-linking (CXL).

METHODS. Combined simultaneous customized PRK followed by corneal collagen cross-linking was performed in 23 patients (28 eyes) with keratoconus. Corneas were examined biomicroscopically and by means of confocal microscopy before surgery and 1, 3, 6, 9, and 12 months after surgery.

RESULTS. Posterior linear stromal haze was observed clinically (slit lamp biomicroscopy) one month after surgery in 13 of 28 eyes (46.42%). No corneal edema or anterior haze formation was evident. Confocal microscopy revealed in those 13 eyes a hyperreflective area at the level of the posterior stroma 1 month after combined treatment. Both slit lamp examination and corneal confocal microscopy follow-up demonstrated a gradual anterior movement and a decrease in reflectance of this finding. At 12 months this posterior linear stromal haze, despite its anterior movement and decreased density, did not completely disappear at slit lamp and confocal microscopy analysis.

CONCLUSIONS. Posterior linear stromal haze formation may appear after simultaneous PRK followed by CXL in patients with keratoconus. This finding seems to gradually become less dense and slowly moves toward the anterior stroma. (*Invest Ophthalmol Vis Sci.* 2010;51:5030–5033) DOI:10.1167/iov.09-5105

Corneal cross-linking^{1,2} (CXL) is a new technique that induces collagen cross-links in the corneal stroma using the photosensitizer riboflavin (vitamin B2) and ultraviolet A irradiation. It has been demonstrated that the application of CXL is capable of stabilizing the cornea in keratoconus and in postrefractive surgery ectasia for up to 5 years after the procedure, but topography and visual outcomes of treated patients are minimally improved.³

The irregular astigmatism in ectatic disorders can be partially managed with the use of customized laser ablations. The goal of such an approach is to flatten the steep areas of the

anterior corneal surface. The application of customized topography-guided surface ablation has been reported in patients with stable or subclinical keratoconus with promising visual outcomes.^{4–6}

The effect of cross-linking can be detected by means of slit lamp biomicroscopy as a demarcation line⁷ between cross-linked and untreated cornea, visible at the end of the second postoperative week. This line ultimately implies either change in the refractive index or reflection properties of treated versus untreated cornea. No other signs indicating the CXL effect, visible by slit lamp examination, have been described in the literature.

In this case series we present 28 eyes of 23 patients with progressive corneal ectatic disorders that underwent combined simultaneously customized photorefractive keratectomy (PRK) and CXL. In 13 of 28 eyes, posterior linear stromal haze was evident throughout the follow-up period.

MATERIALS AND METHODS

Twenty-eight eyes of 23 keratoconus patients (mean age, 30 ± 9.35 years; range, 20–44 years) were included in the study. Preoperative topography mean K readings were 46.72 ± 2.87 D (range, 43.03–53.53 D), and mean central corneal thickness was 492.30 ± 51.48 μm (range, 452–576 μm). All eyes were treated by combined simultaneous customized PRK and corneal CXL with riboflavin and ultraviolet A irradiation. Inclusion criteria were identification of progressive keratectasia in corneal topographies, increase of maximal K-readings, and central thinning of the cornea over a period of 6 months, along with reported change in refraction.

Clinical Evaluation

Preoperative evaluation consisted of general and ocular health history assessment, autorefractometry and autokeratometry (RK-F1 Full Auto Autorefractor Keratometer; Canon Inc., Jamesburg, NJ), corrected distance visual acuity (CDVA), corneal topography (iTrace; Tracey Tech, Houston, TX), ultrasound pachymetry (Corneo Gage Plus; Sonogage Inc., Cleveland, OH) slit lamp examination of the anterior and posterior segments of the eyes, and in vivo corneal confocal microscopy (HRT II; Rostock Cornea Module; Heidelberg Engineering, Heidelberg, Germany).

Patients were thoroughly informed about the experimental nature of the intervention, the possible outcomes, and the current clinical experience and gave their written consent in accordance with the Declaration of Helsinki and institutional guidelines.

Patient evaluations were repeated 1, 3, 6, 9, and 12 months postoperatively by means of slit lamp biomicroscopy and in vivo corneal confocal microscopy.

From the Institute of Vision and Optics, University of Crete Medical School, Crete, Greece.

Submitted for publication December 21, 2009; revised February 22, March 15, and March 29, 2010; accepted April 24, 2010.

Disclosure: **G.D. Kymionis**, None; **D.M. Portaliou**, None; **V.F. Diakonis**, None; **G.A. Kontadakis**, None; **M.S. Krasia**, None; **A.G. Papadiamantis**, None; **E. Coskunseven**, None; **A.I. Pallikaris**, None

Corresponding author: Dimitra M. Portaliou, Institute of Vision and Optics, University of Crete Medical School, 71003 Heraklion, Crete, Greece; mimi24279@gmail.com.

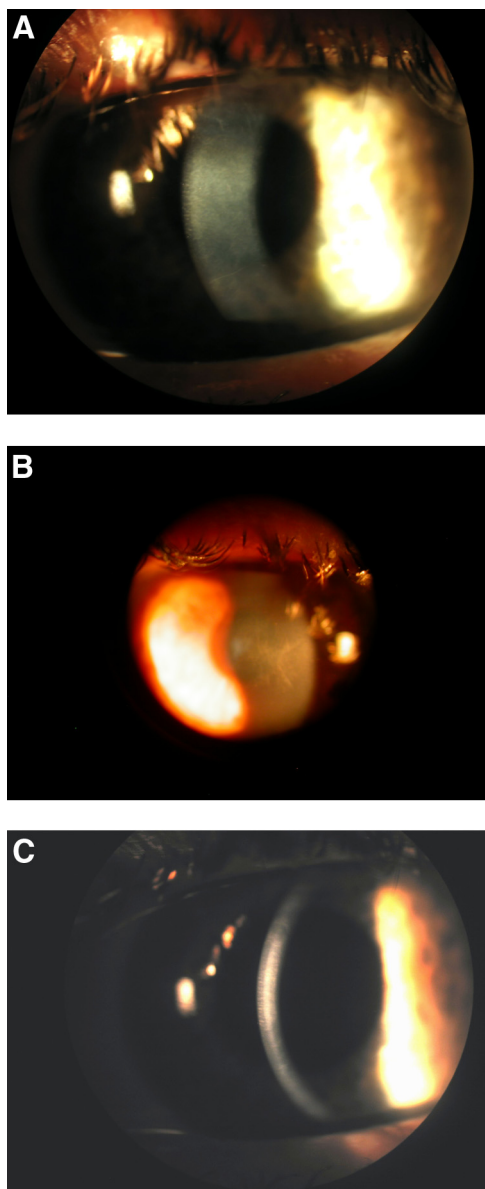


FIGURE 1. Slit lamp photograph of a patient treated with simultaneous PRK followed by CXL 1 month after surgery. The linear posterior haze was evident in the central treated area 1 (A), 6 (B), and 12 (C) months after surgery, showing significant improvement.

Surgical Procedure

The surgical procedure was conducted under sterile conditions. Patients' eyes were anesthetized with proparacaine hydrochloride 0.5% (Alcaine; Alcon, Fort Worth, TX). The epithelium was removed at the beginning of the procedure with a rotating brush. A solid-state laser with a wavelength of 213 nm (Pulzar Z1; CustomVis, Perth, WA) was used for the customized PRK procedure. System software allows use of a percentage of customization from 0% to 100%. Using 0% would be equivalent to a conventional laser treatment, and using 100% would be equivalent to full customized treatment. In cases of extreme irregular astigmatism, lowering this percentage could lower the maximum depth of tissue removed. In our patients we adjusted the customization and the spherocylindrical attempted correction to achieve a total ablation depth of $<50 \mu\text{m}$.

Immediately after the PRK procedure, riboflavin 0.1% solution was instilled repeatedly for approximately 30 minutes. Penetration of the cornea and presence of riboflavin in the anterior chamber (riboflavin

shielding) was monitored by slit lamp examination. UVA irradiation was performed using an optical system (UV-X; Peschke Meditrade, GmbH, Huenenberg, Switzerland) with a light source consisting of an array of UV diodes (365 nm) in conjunction with a potentiometer to allow intensity regulation. Irradiance was performed for 30 minutes. During treatment, riboflavin solution was applied every 5 minutes to saturate the cornea with riboflavin. After the treatment, a silicon-hydrogel bandage contact lens (Lotrafalcon B; Air Optix; Ciba Vision, Atlanta, GA; 14.0-mm diameter, 8.6 base curvature, Dk = 140 barrers) was applied until reepithelialization occurred. Topical antibiotic-corticosteroid drops (tobramycin 0.3%, dexamethasone 0.1%; TobraDex; Alcon Laboratories, Inc., Fort Worth, TX) were used four times daily for 15 days.

All eyes were examined daily until the epithelium had completely healed. Contact lenses were removed at the fifth postoperative day, and no signs of edema or inflammation were noted by slit lamp biomicroscopy.

RESULTS

In 13 of 28 eyes (46.42%), posterior linear stromal haze corresponding to the central treated area of the cornea was detectable by slit lamp examination at the first postoperative month (Fig. 1A). This finding can be graded as mild haze (grade 1) according to the Fantes anterior stromal haze scale.⁸ It gradually became less dense and demonstrated an anterior movement over the 12-month postoperative period (Fig. 1B). At 12 months after surgery, posterior haze, despite its anterior movement and decreased density, did not completely disappear at the slit lamp (Fig. 1C). The rest of the examined eyes (15 eyes) showed no sign of posterior haze formation at slit lamp biomicroscopy.

The occurrence of posterior linear stromal haze was correlated with neither preoperative central corneal thickness ($P = 0.54$) nor amount of tissue (microns) ablated during customized treatment ($P = 0.23$).

Confocal microscopy was performed in all eyes, revealing a bright, reflective, spindle-shaped area and linear hyperreflective structures at the level of the posterior corneal stroma (at approximately $400\text{-}\mu\text{m}$ depth). This finding was evident 1 month after treatment between the acellular and the cellular corneal stroma (Fig. 2). Even though all eyes demonstrated this high reflectance, 13 of the 28 eyes with the posterior linear

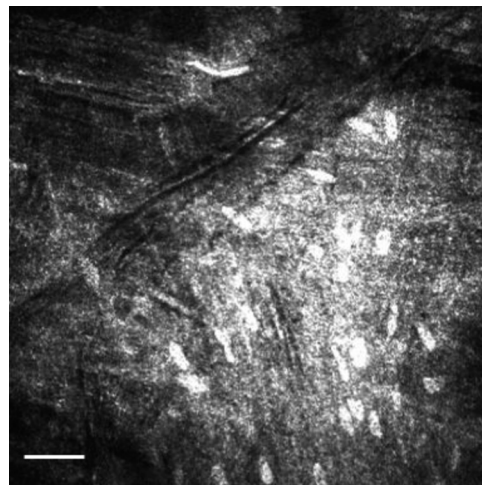


FIGURE 2. Corneal confocal microscopy image, 1 month after combined PRK-CXL treatment, showing a high reflective area adjacent to the endothelial layer ($35 \mu\text{m}$ anterior to the endothelium). Keratocyte-activated nuclei are evident along with linear hyperreflective structures. Scale bar, $52 \mu\text{m}$.

stromal haze had a more evident (higher reflectance, qualitatively evaluated) finding that in all cases was adjacent to the endothelial cell layer (20–30 μm anterior to the endothelium). During the follow-up period, these hyperreflective structures demonstrated a gradual relocation following a posterior-anterior pattern (Figs. 3, 4). At 12 months after surgery, confocal microscopy demonstrated a gradual anterior movement and a decrease in reflectance of this finding (Fig. 5). Full-thickness corneal stromal keratocyte repopulation was not demonstrated by means of confocal microscopy analysis in any of the studied eyes. This finding was more prominent in the eyes that demonstrated posterior haze than in the eyes that did not.

CDVA was not influenced by this finding. In particular, preoperative CDVA was 0.27 ± 0.21 (range, 0.70–0.00), whereas 1 year after surgery it was 0.18 ± 0.17 (range, 0.54–0.00) (logMAR). No eye lost lines of visual acuity.

DISCUSSION

In this case series, patients underwent simultaneously customized photorefractive keratectomy and corneal cross-linking with riboflavin and ultraviolet A irradiation. The aim of custom-

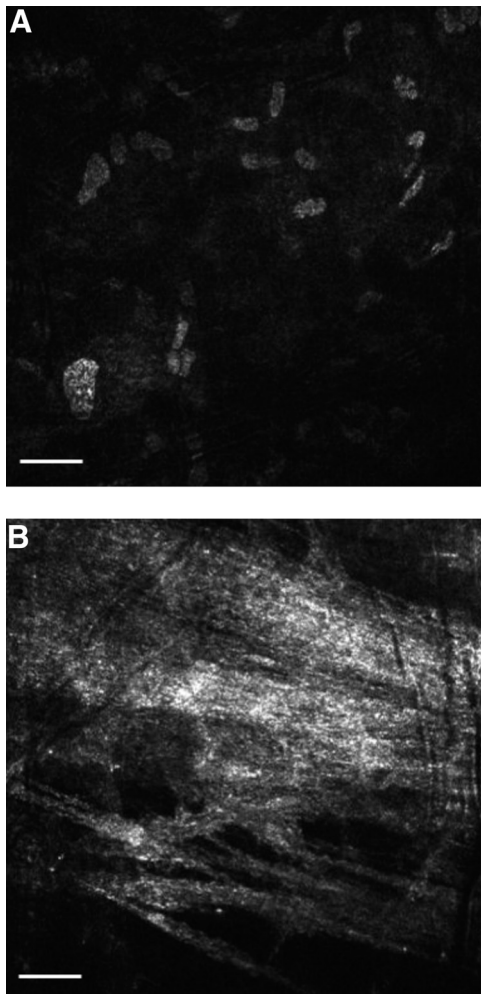


FIGURE 3. Corneal confocal microscopy image, 3 months after combined PRK-CXL treatment showing a high reflective area ($\sim 70 \mu\text{m}$ anterior to the endothelium) at 330- μm depth. Keratocyte-activated nuclei are evident (A), and linear hyperreflective structures appear anteriorly to the keratocytes (B). These hyperreflective structures consist of a barrier between the posterior acellular and anterior cellular corneal stroma. Scale bar, 52 μm .

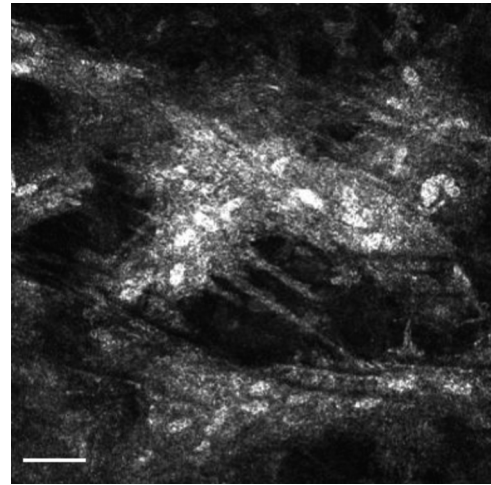


FIGURE 4. Corneal confocal microscopy image 6 months after combined PRK-CXL treatment showing a high reflective area ($\sim 90 \mu\text{m}$ anterior to the endothelium) at 300- μm depth. Linear hyperreflective structures are evident, and keratocyte-activated nuclei are seen in the background. Scale bar, 52 μm .

ized PRK was to remodel the irregular cornea to decrease the irregular astigmatism.⁹

Simultaneous customized PRK followed by CXL seems to be a promising treatment capable of offering patients functional vision and halting progression of the disorder. Previous studies^{9,10} have proven the safety and success of this combined procedure. The results demonstrate, up to 1 year after the procedure, no keratoconic progression in patients. Patients treated with simultaneous topography-guided PRK with CXL showed rapid and significant improvement in uncorrected and corrected distance visual acuity. Moreover, topographic evaluation of these patients showed marked improvement of corneal irregularity.

After surgery, 13 of 28 eyes (46.42%) had linear haze in the posterior stroma of the cornea detectable by slit lamp examination. In these eyes, using corneal confocal microscopy, we detected an area with high reflectance at the level of the posterior stroma characterized by spindle-shaped and linear

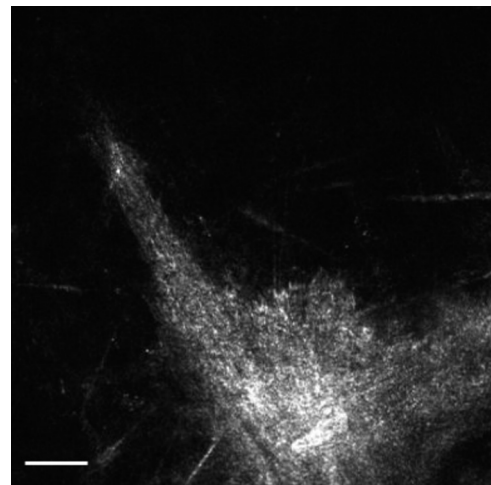


FIGURE 5. Corneal confocal microscopy image 12 months after combined PRK-CXL treatment showing a high reflective area ($\sim 190 \mu\text{m}$ anterior to the endothelium) at 200- μm depth. Linear hyperreflective structures are evident, and keratocyte-activated nuclei are seen in the background. Scale bar, 52 μm .

hyperreflective structures. The reflectance was located adjacent to the endothelial cell layer at the first postoperative month. The high-reflective, spindle-shaped structures have been linked with migration and activation of keratocytes that become transformed during locomotion, assuming a spindle- or needle-shaped morphology.¹¹ Furthermore, the linear hyperreflective structures could be associated with increased collagen deposition, collagen disorganization, and excessive production of extracellular material from the activated keratocytes.

To our knowledge, there are no similar reports of stromal haze after the standard CXL treatment. As demonstrated in previous studies of corneal confocal microscopy after CXL,^{12,13} the anterior 300 to 350 μm of the corneal stroma are acellular (absence of keratocyte nuclei), whereas the posterior stroma demonstrates a high keratocyte density. Nevertheless, the incidence of posterior haze development was not reported. In our case series, the treated eyes underwent photoablation. As demonstrated by in vivo confocal studies,¹⁴ after refractive surgery, significant keratocyte nuclei activation (high-reflectance nuclei) occurs. This may explain the high reflectance revealed in our case series because our patients underwent photoablation in combination with CXL, and, therefore, photoablation might have induced keratocyte activation, causing the formation of posterior linear stromal hyperreflectance (haze).

Moreover, an interesting finding is the proximity of the stromal changes to the endothelium, which might be a manifestation of the deeper effect of the CXL procedure. This could be attributed to better penetration of riboflavin after the ablation procedure, but this is only a speculation.

From the first month to 1 year after CXL, this finding of high reflectance relocated anteriorly following the described keratocyte repopulation after CXL treatment, which occurred in a posterior-anterior fashion. This finding seemed to gradually become less dense and slowly moved toward the anterior stroma without complete disappearance at slit lamp examination and confocal microscopy. At 12 months, the full-thickness corneal stromal keratocyte repopulation was not demonstrated by means of confocal microscopy analysis in any of the studied eyes, in contrast to the 1-year follow-up after standard CXL, during which the full-thickness keratocyte repopulation was reported.^{11,12} This finding was more prominent in the eyes that demonstrated posterior haze than in the eyes that did not. Posterior linear stromal haze did not interfere with patients' CDVA.

Posterior linear stromal haze formation was correlated with neither patients' preoperative central corneal thickness nor ablation depth. An important issue worth mentioning is that only 46% of the eyes (and not all them) developed posterior haze. We can only presume that there were no specific predisposing factors leading to posterior haze formation other than patient individuality as a response to the combined treatment.

One of the main limitations of our study was the lack of precision mapping of the cornea with the use of a Scheimpflug analyzer that could provide more accurate information regarding corneal thickness. Determination of the thinnest point in patients who will undergo CXL is essential; therefore, the Scheimpflug analyzer could have been a useful tool. In our patient series, both central corneal thickness (CCT) and corneal thickness at the apex of the cone were evaluated by ultrasonic pachymetry (Corneo Gage Plus; Sonogage Inc.,

Cleveland, OH). Patient evaluation was conducted in accordance with the standard CXL protocol; therefore, patients with pachymetry $<450 \mu\text{m}$ in the apex of the cone were not included in the study to maintain a minimum thickness of 400 μm after epithelial removal and ablation. The patient with the thinnest CCT (452 μm) had a centrally located keratoconus. CCT was easier to define and measure by ultrasound pachymetry, which is why that was our instrument of choice.

This is the first case series reporting the postoperative appearance of posterior linear stromal haze after combined PRK and CXL treatment for the management of ectatic disorders. Larger patient samples and longer follow-up are necessary to give an adequate explanation and the possible clinical impact of this finding.

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