CHAPTER 10

Complications With the Use of Collagen Cross-Linking

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Corneal collagen cross-linking (CXL) has become a new addition to the armamentarium for the treatment of keratectasias, in particular, keratoconus (KC) and post laser in situ keratomileusis (LASIK) ectasia.[1-15] CXL with the use of riboflavin (vitamin B^2) and ultraviolet A (UVA) irradiation cross-links the collagen fibers in the corneal stroma thereby strengthening and biomechanically stabilizing the cornea.[1] This is especially useful in KC where progressive corneal thinning and steepening leads to myopia and irregular astigmatism.[2] Promoting a new approach for the treatment of KC, CXL has become a viable option in addition to the established treatments available, including spectacle correction, rigid gas permeable contact lenses, intrastromal corneal ring segments,[3] and penetrating keratoplasty.[4]

Collagen Cross-Linking

We have employed collagen cross-linking over the last 10 years in the treatment of ectasia after refractive surgery, such as LASIK and photorefractive keratectomy (PRK), as well as the treatment of primary KC with relative success. In our center, we have now treated over 1000 cases of primary KC and/or ectasia following refractive surgery, and in over 800 cases, we combined the cross-linking treatment with the use of partial tgPRK procedure in order to facilitate visual rehabilitation. Complications have been quite seldom with our technique. We have experimented in the laboratory with the use of different riboflavin solution concentrations and different levels of energy and we have found that by doubling the concentration of riboflavin, one can enhance CXL by 10-fold and create opaque patches (Figure 10-1) in the cornea that will present significantly cross-linked tissue (Figure 10-2). We have not encountered this combination clinically even in our more recent studies in using high-fluence UV light at the level of 7 and 15 mW.

Infection

Another group of potential complication is infection. We have seen some complications that are very rare; in 750 cases that we have treated, we have encountered only one infection that was cured within a few days with the use of topical vancomycin solution and it was attributed to either contamination of the surgical field during the removal of epithelium and/or the contamination of riboflavin drops. Therefore, we have changed our technique of epithelium removal and utilize excimer laser episcrape thus having the advantage of the no-touch technique of the cornea epithelium and the reduction of the possibility of transferring pathogens up to the corneal surface and to the stroma with the CXL process. Obviously, single-use packaging of the riboflavin solution is essential in order to avoid contamination, from patient to patient, through the riboflavin solution. Many of these patients remain with a bandage lens for several days.

Agarwal A, Jacob S, ed.
Complications in Ocular Surgery (pp 115-120).

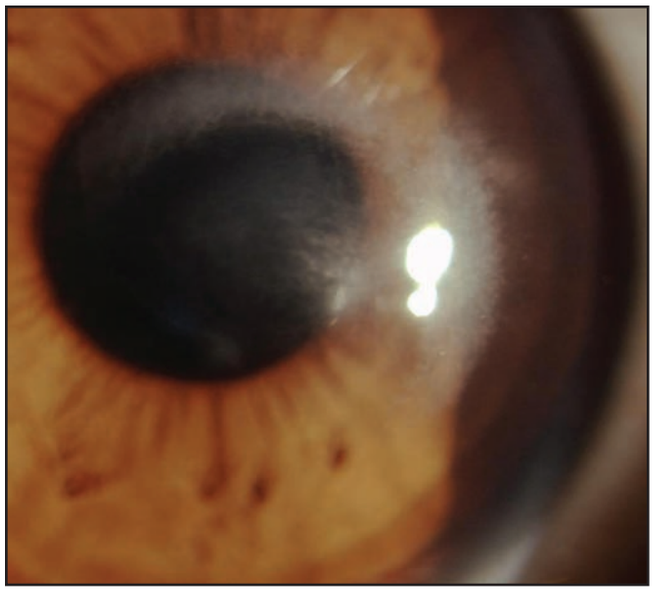

Figure 10-1. PRK-related haze on the pattern of the topo-guided PRK intervention.

Endothelial Toxicity

The third group of complications is potential endothelial toxicity from high levels of free oxygen radical information at the endothelial level, and this can potentially happen with high fluence of riboflavin, with high concentration of riboflavin at the endothelial level, higher fluence of UV light, and thinner cornea than expected. It has been recommended that if the cornea is thinner than 400 micrometers, thinnest/total cornea thickness to use hypotonic riboflavin solution in order to induce some cornea edema and avoid this potential complication.

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Regeneration of Ectasia

Another complication is the potential of regeneration of ectasia following cross-linking. This has been reported in otherwise stable patients that had become pregnant, so pregnancy may cause a high risk for ectasia in the cornea even after collagen cross-linking. There have also been some anecdotal reports of ectasia resulting after a cornea has been stabilized with collagen cross-linking and then treated with a PRK procedure. This would make sense if the PRK procedure removed a significant amount of tissue and created a significant biomechanical change in the cornea, producing a more vulnerable situation for ectasia.

Athens Protocol

The goal of introducing tg photorefractive keratectomy (tgPRK) as a component to the CXL procedure is to normalize the corneal surface and to decrease the irregular astigmatism.[5] The synergistic effect of combined tgPRK and collagen cross-linking, the Athens Protocol, may provide further improvement in visual acuity than with CXL alone.[6] This prospective cohort study evaluated 412 keratoconic eyes in 412 patients who underwent consecutive combined tgPRK and CXL (the Athens Protocol). The inclusion criteria involved patients with a confirmed diagnosis of progressive KC by slit-lamp microscopic examination and by increasing corneal steepening of at least 1.00 D in keratometry associated with increasing myopia and/or astigmatism over a period of 3 or more months. Additional criteria included increasing inferior corneal steepening with thinning to a minimum of 350 µm in total corneal thickness. The exclusion criterion was corneal thickness less than 350 µm because of the potential risk of corneal destabilization with additional tissue removal.

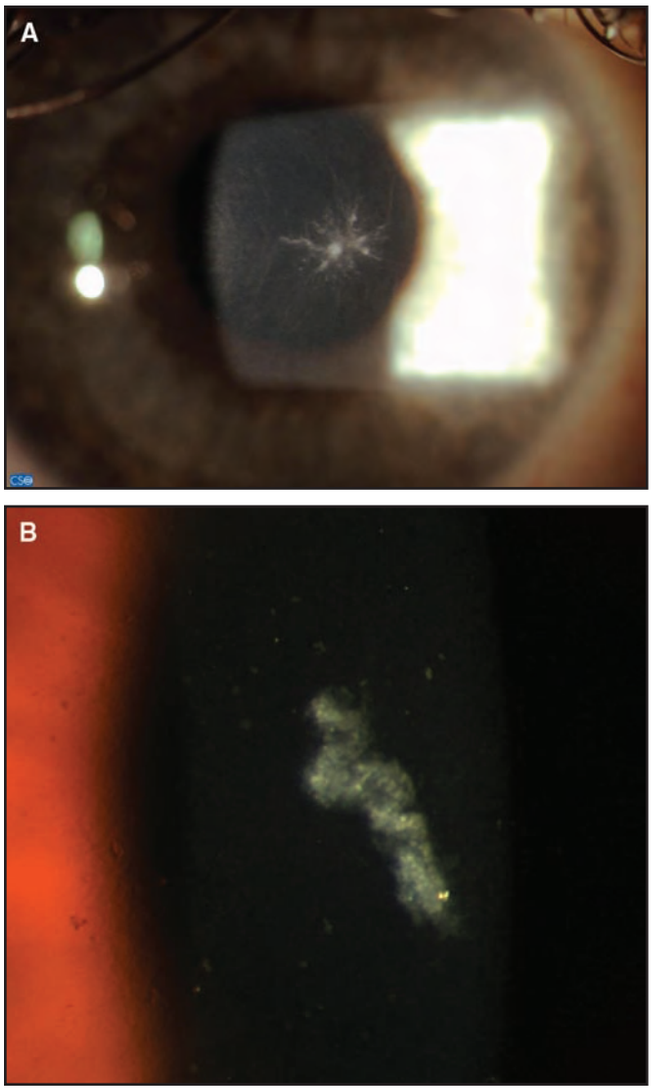

Figure 10-2. (A) Early re-epithelization scarring resolved with lubrication. (B) Early superficial epithelial scar resolved with lubrication and a few days of using bandage contact lens.

Clinical Evaluation

Preoperative clinical evaluation consisted of uncorrected visual acuity, corrected-distance visual acuity (CDVA), manifest refraction, cycloplegic refraction, keratometry (Topolyzer; WaveLight Laser Technologie AG, Erlangen, Germany), corneal topography (Oculyzer; Wavelight Laser Technologie AG, Erlangen, Germany), pachymetry (Orbscan II, Pentacam, and EchoScan U.S.-1800; NIDEK Co Ltd, Gamagori, Japan), and specular microscopy (Konan Medical, Boston, MA). A baseline slit-lamp microscopic examination was used as a reference to the follow-up assessments and evaluation of complications, which were conducted by one examiner (A.J.K). Patients were evaluated on postoperative days 1, 4, 30, 60, 90, and then every 3 months thereafter.

Surgical Procedure

Topographic data from the proprietary WaveLight-customized platform (Topolyzer) served as the basis for the Placido disc partial tgPRK. The resulting topographic data were drawn from an average of 8 topographies with the following parameters: zero postoperative asphericity, no tilt correction, and a 5.5-mm optical zone. The WaveLight platform allowed the use of a Placido disc image or a Pentacam-derived image. The goal was to treat up to 70% of cylinder and the remaining amount of sphere up to a maximum of 70%, so as not to exceed 50 µm in stromal removal from the thinnest cornea, which resulted in the practically attempted correction of maximal 3 D of cylinder and 1 to 2 D of myopic sphere.

The surgical procedure was performed in the institution mentioned above by the same surgeon (AJK) under sterile conditions. Following placement of an aspirating lid speculum (Rumex, St Petersburg, FL), the epithelium was removed by phototherapeutic keratectomy (PTK) with the excimer laser (WaveLight Eye-Q 400Hz and later the WaveLight EX500). Parameters of the PTK ablation included a 6.5-mm optical zone and a depth of 50 µm for all cases. This method of epithelium removal was preferred over the use of alcohol-assisted mechanical removal. The alcohol-assisted mechanical removal strips the entire epithelium and produces a steeper surface especially over the cone in KC that may not correspond with the diagnostic topography. After the PTK epithelial ablation, the tgPRK treatment was then applied. Mitomycin C (MMC) 0.02% solution in a soaked cellulose sponge was placed on the ablated tissue for 30 sec followed by irrigation with 10 mL of chilled, balanced salt solution.

Next, riboflavin sodium phosphate ophthalmic 0.1% solution (slightly hypotonic to cornea: 340 mOsm) (Leiter's Pharmacy, San Jose, CA) was applied topically every 2 min for 10 min. In the cases performed with the EX500 excimer laser, the build in online optical pachymetry was used to evaluate residual stromal thickness up until the UV light exposure. Four diodes emitting UVA light of approximately 370 nm wavelength (365 to 375 nm) and 6 mW/cm^2 radiance at 2.5 cm was projected onto the corneal surface for 15 min. During this time, riboflavin solution was applied topically every 2 min. Following the completion of this procedure, a bandage contact lens (BCL) was placed. The postoperative regimen consisted of topical ofloxacin (Allergan Inc, Irvine, CA) 4 times a day for 10 days, prednisolone acetate 1% (Pred Forte, Allergan) 4 times a day for 60 days, and oral vitamin C 1000 mg daily for 60 days. Sunglasses were highly recommended to protect from all natural light. The BCL was removed at approximately day 4 following complete re-epithelialization.

Results

Postoperative CDVA ranged from 20/100 to 20/50. Mean follow-up was 35 months (range 14 to 72 months). The minor complications encountered were postoperative pain the first day, delayed epithelial healing from day 4 to day 20, transient epithelial and subepithelial scarring, transient stromal haze, and further ectatic progression in a few cases. No significant pain on postoperative day 1 was reported in 45% of the cases, moderate pain in 25%, and severe pain in 30%. Delayed epithelial healing occurred in 75% of cases by day 6 and 10% by day 10. Transient Salzmann-like epithelial scarring, seen in 25% of the cases, persisted for an average of 1 month. The epithelial scar resolved with lubrication (30%), lubrication and BCL (25%), autologous serum administration in addition to lubrication and BCL (25%), or surgical removal at the slit-lamp (20%).

At 6 months postprocedure, only 12 of the 412 cases had persistent subepithelial corneal scarring (Figures 10-3 and 10-4), but none that was bothersome to the patient's visual function and necessitated penetrating keratoplasty. Transient stromal haze was noted in 15% of the cases, which resolved by month 6 in 95% of these cases. However, 8 of 412 cases demonstrated persistent stromal haze beyond month 6 and one case late stromal haze 1 year after the procedure after intense sunlight exposure that resolved with 6-month topical treatment with Lotemax.

Only 7 of 412 cases showed signs of ectatic progression, for which 4 required repeated CXL. One case with ectatic progression had undergone pregnancy out of 7 total pregnancies recorded of the 412 cases without ectasia recurrence.

Discussion

Like any surgical procedure, combined tgPRK and CXL (the Athens Protocol) has its own set of

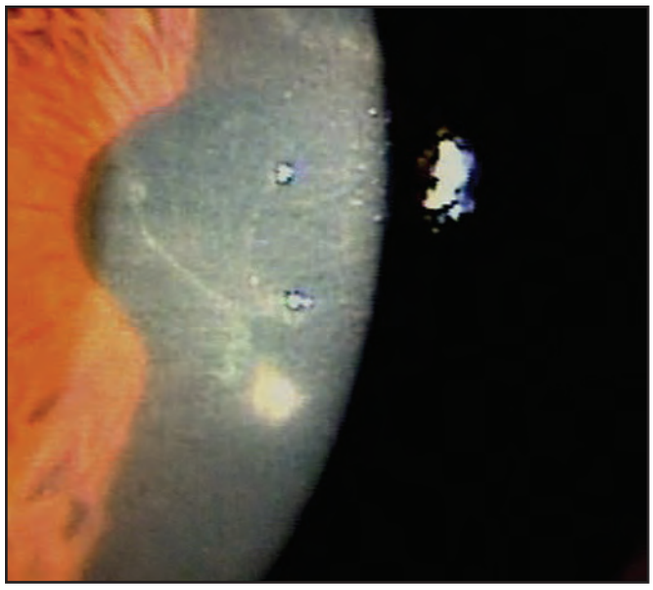

Figure 10-3. White scar in anterior stroma possible over CXL.

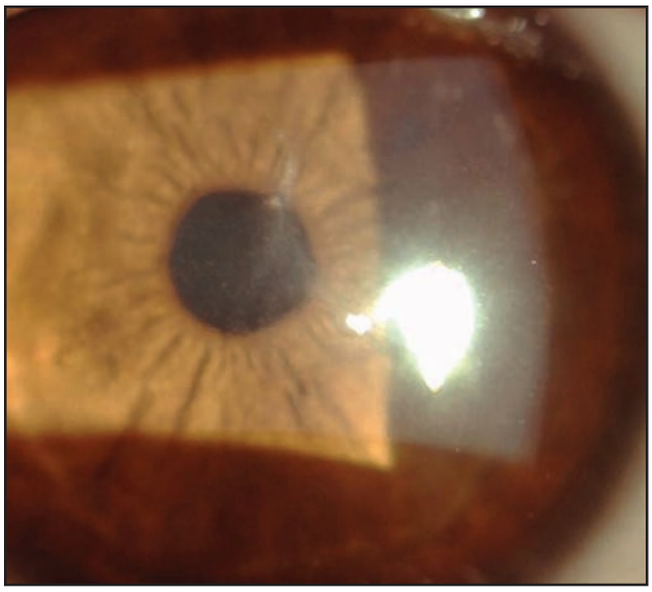

Figure 10-5. Salzmann-like hyaline subepithelial scar, resolved with lubrication.

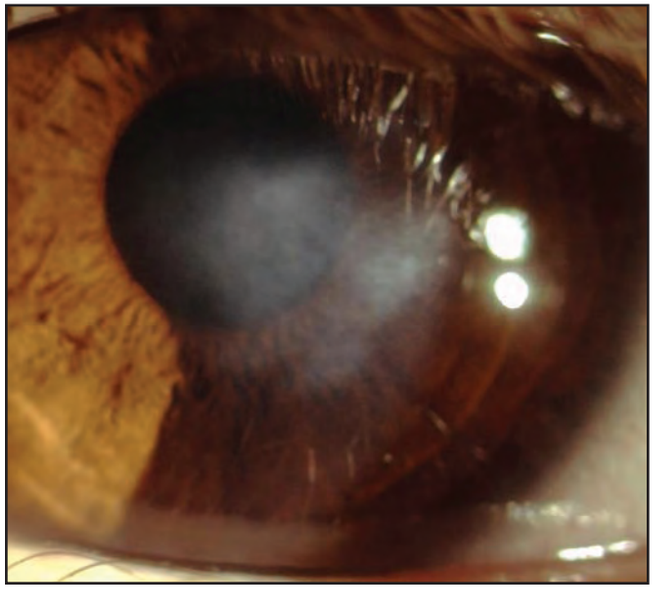

Figure 10-4. Late anterior stromal haze developing after excessive sunlight exposure in a 16-year-old male.

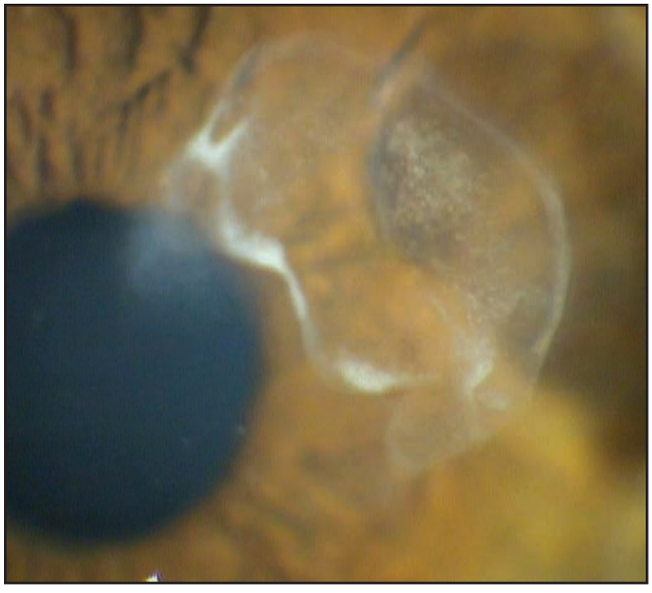

Figure 10-6. Anterior stromal thinning in midperiphery.

complications. The main early transient complications noted were postoperative pain, delayed epithelial healing, and Salzmann-like epithelial scarring (Figure 10-5). These findings require (in our opinion) careful, close monitoring by the clinician and close external disease care in order to avoid more severe and permanent scarring or stromal melt.

A significant percentage of patients experienced moderate to severe pain on postoperative day 1 after the Athens Protocol. This is most likely due to removal of the epithelium, much like the individual procedures PRK and CXL.[7] Topical nonsteroidal anti-inflammatory drugs (NSAIDs) have been successful with pain management in traditional surface ablation procedures. Due to the nature of the keratoconic corneas and increased risk of delayed epithelial healing and perforation, topical NSAIDs were avoided[8] (Figure 10-6).

Delayed epithelial healing was reported if the epithelium did not heal completely after 5 days postprocedure. After CXL alone, the mean epithelial healing time was found to be 3.25 days, ranging from 1 to 8 days.[9] Our study found 10% of cases that did not heal completely by day 10. The combination of the 2 procedures, PRK and CXL, and possibly the use of MMC, may contribute to the delay (Figure 10-7).

The strengths of this study are the large number of patients and the long-term follow-up for a relatively

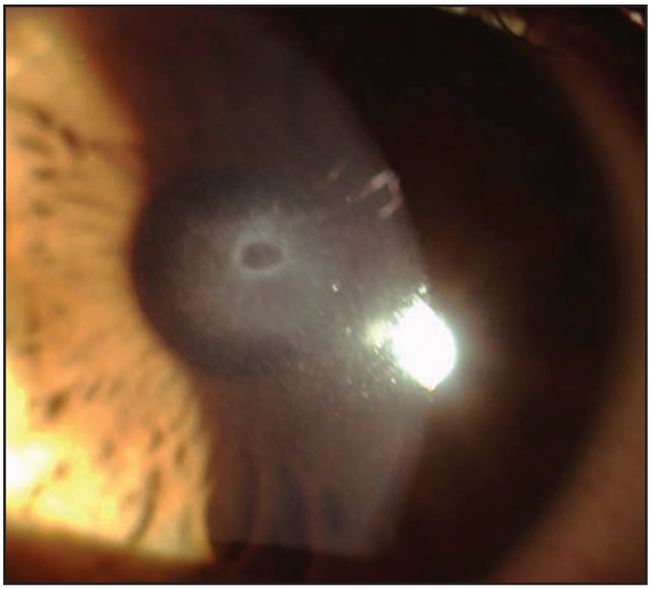

Figure 10-7. Ring-like difficulty in re-epitheliazation 2 weeks after the Athens Protocol. Resolved after mechanical removal with a 30-gauge needle and allowing epithelium to freely cover the defect.

novel procedure. This enabled us to present some seldom late complications associated with this procedure. The main limitation is the observational study design, which does not include a control group. Generalizability is also limited since the study took place at a single clinical site. The effect of the Athens Protocol in advanced KC with corneal thickness less than 350 µm was not monitored in this study.

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