CASE REPORT

Macular phototoxicity after corneal crosslinking

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Introduction: Keratoconus is a progressive degenerative corneal disease of variable severity. Its management includes medical and surgical treatment. Corneal crosslinking (CXL) is being increasingly used to stabilize the condition. Macular phototoxicity is a well-known side effect of light exposure; however, its incidence after treatment with riboflavin and UV light is unknown. This study reported the clinical features of a patient with macular phototoxicity after UV-A exposure and described the structural and angiographic retinal changes observed in the patient.

Patient, Clinical Findings, and Diagnosis: A 37-year-old man with keratoconus underwent corneal refractive surgery (topography-guided custom ablation with accelerated and high-fluence CXL). Postoperatively, he had decreased vision in the operated eye. Ophthalmoscopy, spectral-domain optical coherence tomography, and fluorescein angiography revealed retinal pigment epithelial changes, ellipsoid zone disruption, and window defects, respectively. The patient was diagnosed with macular phototoxicity. The corrected distance visual acuity stabilized at 20/100 after 6 months.

Conclusions: Macular phototoxicity may occur after UV-A exposure during CXL. The use of accelerated and high-fluence protocols might have contributed to its occurrence in this patient.

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Keratoconus is a bilateral, progressive, ectatic corneal disorder characterized by corneal thinning and protrusion. Its clinical features widely vary depending on the disease stage, ranging from no symptoms and normal slitlamp biomicroscopy findings to profound visual loss and readily detectable clinical signs.1

Corneal crosslinking (CXL) is a procedure that includes the combined administration of riboflavin and UV-A to strengthen the cornea and halt disease progression by altering the biomechanical properties of the cornea.2,3 CXL to treat keratoconus in humans was first performed in 2003 by Wollensak et al.4 Subsequently, several studies have shown that CXL is effective for halting disease progression, and the popularity of this procedure has increased in the past decade.5,6 The administration of riboflavin results in the irradiated UV-A being confined to the anterior 300 μm of the cornea. Hence, a minimum corneal thickness of at least 400 μm must be maintained after epithelial removal to avoid phototoxic damage to the corneal endothelium.7 Although CXL is generally considered to be safe, ocular side effects can occur.8,9 Macular phototoxicity is unlikely to occur as most of the UV-A is absorbed by the anterior segment; therefore, this side effect has not been frequently investigated. In this study, we describe the clinical features of a patient who experienced this side effect and the structural and angiographic retinal changes induced by UV-A exposure during CXL.

Patient Consent Statement
The patient provided written informed consent for the publication of this report.

CASE REPORT

A 37-year-old man with keratoconus sought medical advice to improve his vision. His medical, surgical, and drug histories were unremarkable. On examination, his corrected distance visual acuity (CDVA) with rigid gas-permeable contact lenses was 20/25 in both eyes. Anterior segment examination revealed clear corneas and clear crystalline lenses bilaterally. The intraocular pressure was within the normal range. No abnormal findings were noted on posterior segment examination. Preoperatively, the minimum corneal thickness in the right eye was 464 μm.

The patient underwent topography-guided custom ablation and CXL of the right eye using the Avedro KXL System. First, 9 mm of epithelium was removed using...
alcohol 20%, following which riboflavin 0.1% (VibeX Rapid, Avedro, Inc.) was applied to the cornea every 2 minutes for 10 minutes. The accelerated pulsed (15 mW/cm² for 16 minutes) and high-fluence (7.2 J/cm²) protocols were followed, and the procedure was uneventful. Subsequently, a bandage contact lens was applied. The patient received a topical antibiotic for 1 week and a topical steroid for 8 weeks.

At the 1-week postoperative visit, the patient complained of decreased vision in the operated eye. Slitlamp biomicroscopy revealed a deep stromal/pre-Descemet membrane haze. Fundus examination was normal. Although the haze improved with time, the vision continued to deteriorate (Figure 1).

After 6 months, there was still subjective deterioration in vision. A thorough examination was performed, which revealed changes in retinal pigment epithelium (RPE) in the foveal region (Figure 2, A); however, the crystalline lens was clear. An examination of the left eye revealed normal findings. Spectral-domain optical coherence tomography (SD-OCT), which was performed to evaluate the retinal structure, revealed disruption of the ellipsoid zone and outer retinal atrophy in the fovea of the right eye (Figure 3). Fluorescein angiography (FA) revealed window defects and staining in the foveal region, which were consistent with the SD-OCT findings, respectively. There was no fluorescein leakage or evidence of choroidal neovascular membrane formation (Figure 2, B–D). The patient was diagnosed with macular phototoxicity. An examination with a potential acuity meter and laser interferometry revealed no improvement in visual acuity. The minimum corneal thickness was still more than 400 μm (416 μm) (Figure 4). The results of ancillary tests of the left eye were unremarkable. The patient's CDVA with rigid gas-permeable contact lenses stabilized at 20/100 in the subsequent visits until the last follow-up (30 months).

DISCUSSION
CXL is now considered a therapeutic option for progressive keratoconus. Several studies have proven its efficacy in halting disease progression, decreasing maximum keratometry readings, and improving CDVA. Studies have emphasized the
importance of ensuring that the minimum corneal thickness is at least 400 μm before treatment to avoid damage to internal ocular structures, especially the lens and retina. Several recent in vivo and in vitro studies have revealed that UV-A exposure can cause damage to the corneal endothelium. Light can damage the retina through 3 mechanisms, namely, the photothermal, photomechanical, and photochemical effects. As in the case of UV light exposure, the photochemical effect is believed to be the most common mechanism by which retinal damage occurs after exposure to free radicals. Therefore, other ocular structures, such as the retina, might be susceptible to phototoxic damage caused by UV-A exposure during CXL.

Based on our patient’s age and sex, a diagnosis of central serous choroidopathy was considered. However, it was ruled out as there was no clinical or angiographic evidence to support this diagnosis (Figure 3).

Certain medications, such as chloroquine, lomefloxacin, hematoporphyrin, hypericin, and phenothiazine, are known to cause ocular phototoxicity, particularly in the retina, when they are administered with UV-A. However, our patient had used none of these medications. The lack of improvement seen on examination with a potential acuity meter and laser interferometry indicates a nonrefractive source of visual loss. Very few studies have examined the structural, angiographic, and electrophysiological changes in the retina after
CXL using SD-OCT, FA, and multifocal electroretinography. In a pilot study, it was observed that in 17 patients who experienced a slight reduction in CDVA and an increase in corneal thickness at 7 days after treatment, both CDVA and corneal thickness returned to the baseline values 30 days later. Similarly, another study showed that a transient increase in macular thickness and microstructural alterations in the macular structure that were observed on SD-OCT returned to normal after 6 months. It was hypothesized by the authors that the changes in the former study were due to the occurrence of a self-limiting inflammation after UV-A exposure, whereas the structural alterations in the latter study were due to changes in the corneal characteristics and amount of astigmatism after CXL. In this case, we observed significant disruption of the inner segment/outer segment junction layer (ellipsoid zone) on SD-OCT, which is a typical sign of phototoxicity. Moreover, changes in RPE were evident on ophthalmoscopy. These findings are consistent with the fact that the outer retina and RPE are likely to sustain phototoxic damage. Although there exists reports of phototoxic damage to the inner segment/outer segment junction layer (ellipsoid zone) on SD-OCT, which is a typical sign of phototoxicity. Moreover, changes in RPE were evident on ophthalmoscopy. These findings are consistent with the fact that the outer retina and RPE are likely to sustain phototoxic damage

WHAT WAS KNOWN
- Corneal crosslinking (CXL) is commonly used to treat progressive corneal ectasia.
- UV-A therapy can lead to ocular damage.
- Patients undergoing CXL using the Dresden protocol should have a minimum corneal thickness of at least 400 µm to ensure safety of the internal ocular structures.

WHAT THIS PAPER ADDS
- To our knowledge, this is the first report of macular phototoxicity and significant nonrefractive visual loss after corneal CXL.
- When using accelerated or high-fluence protocols, practitioners should carefully select patients to avoid this rare but possibly serious side effect.

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Disclosures: None reported.

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