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Severe long-term progressive corneal remodeling after bilateral simultaneous prophylactic crosslinking and topography-guided surface ablation with mitomycin

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ABSTRACT

To report a case of a 20-year-old woman who developed massive and progressive corneal remodeling in both eyes after bilateral PRK with mitomycin and CXL as an elective refractive procedure for mild keratoconus. The patient had 6 years of follow up, initially presenting with focal steepening of up to 20 diopters on both eyes one-and-a-half- years postoperatively that spontaneously reversed over the next five years while the high order aberrations worsened. At the present time, the patient depends on bilateral scleral contact lenses for her day-to-day activities. The use of combined elective PRK with mitomycin and prophylactic CXL could lead to progressive corneal deformation. Additional reports would help to establish the role of this combination procedure among the armamentarium to visually rehabilitate patients with keratoconus.

1. Introduction

Keratoconus (KC) is a corneal disease with stromal weakening, thinning and distortion. Disease management includes non-surgical interventions such as spectacles and contact lens, and surgical interventions such intracorneal ring segment implantation, lamellar keratoplasty, penetrating keratoplasty, among others. Additionally, the simultaneous use of surface ablation with mitomycin C (MMC) and corneal cross-linking (CXL) has been advocated to improve corneal contour in patients with keratoconus.[1,2] We present a case of bilateral simultaneous photorefractive keratectomy (PRK) with MMC and CXL in which corneal scarring and progressive corneal distortion that worsened over several years needing scleral contact lenses for visual rehabilitation.

2. Case report

2.1. Initial assessment

A 20-year-old woman patient had a preoperative uncorrected visual acuity (UCVA) of 0.3 LogMAR and 0.6 LogMAR in her right and left eyes. The refraction was +0.75–2.00 × 75 and + 0.75–2.00 × 105 with corrected distance visual acurity (CDVA) of 0.2 LogMAR OU. The Scheimpflug imaging technology (Pentacam, Oculus Gmbh, Wetzlar, Germany) showed an inferior crab-claw pattern in each eye, with a thinnest corneal point of 423 μm and 449 μm respectively (Figs. 1A and 2A). Her two-year old glasses formula was the same as the preoperative refraction but we were not sure if she was progressing since no sequential preoperative topographies/tomographies were available. She had a history of allergic conjunctivitis and volunteered to rub her eyes frequently. After informed consent was obtained, PRK with CXL and

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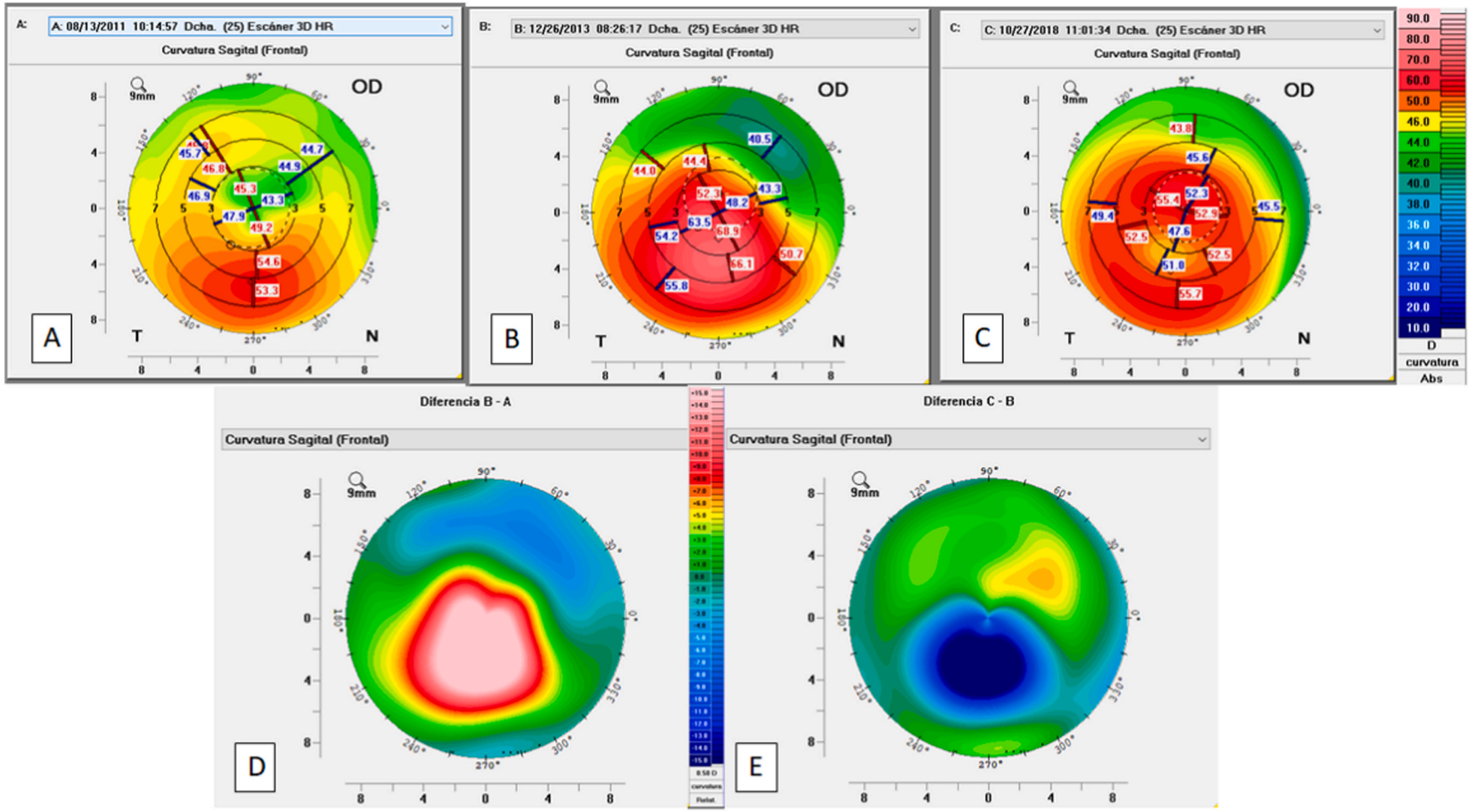

Fig. 1. Serial Schleimpflug images of the right eye

A. Preoperative corneal topography showing a typical "crab claw" pattern. B. One-and-a-half-year postoperative corneal topography showing marked corneal steepening. C. Six-year postoperative corneal topography showing marked corneal deformation. D. Difference map B *minus* A showing close to 20 diopters of corneal steepening. E. Difference map C *minus* B showing spontaneous focal corneal flattening.

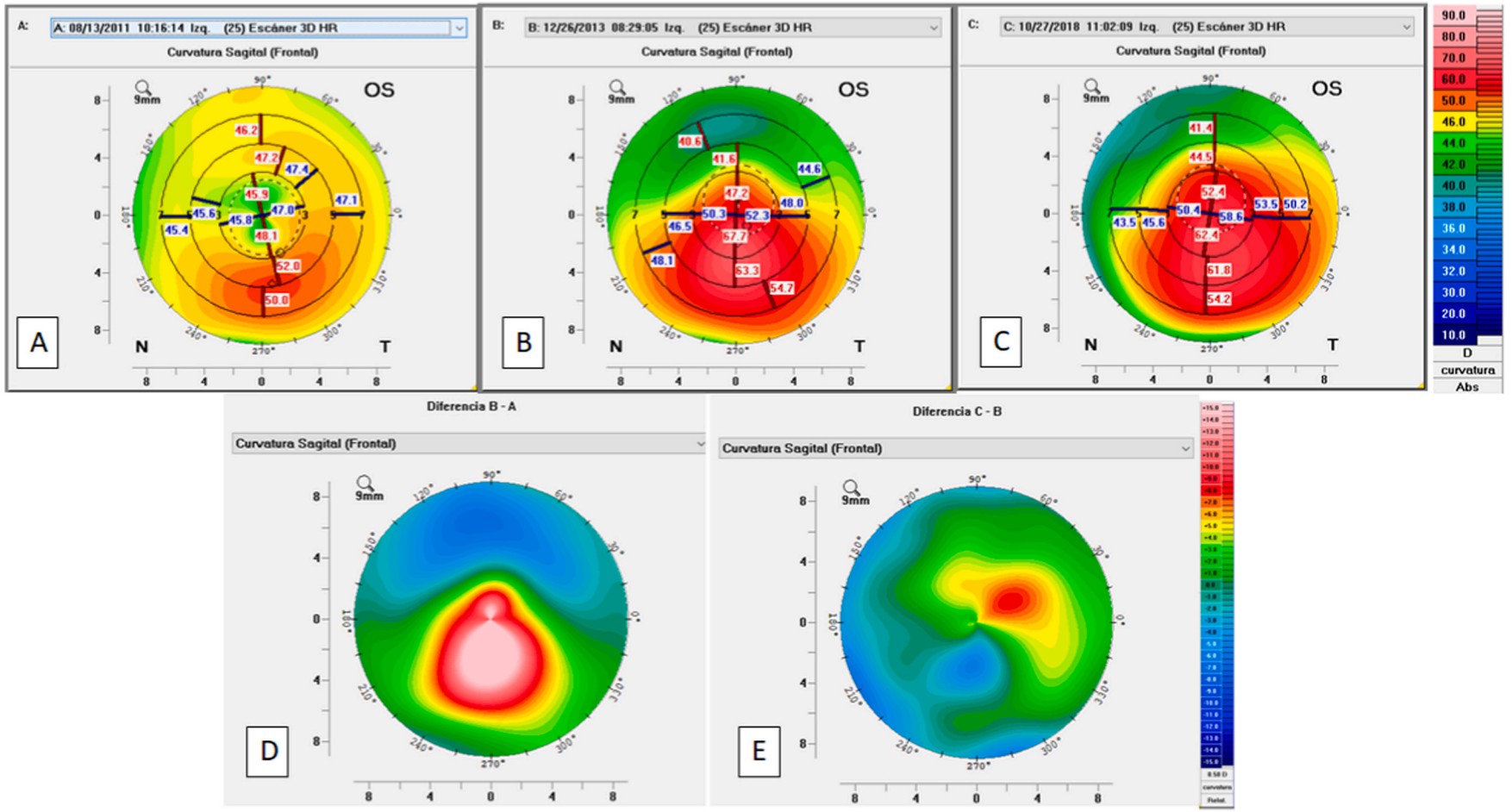

Fig. 2. Serial Schleimpflug images of the left eye

A. Preoperative corneal topography showing a typical "crab claw" pattern. B. One-and-a-half-year postoperative corneal topography showing marked corneal steepening. C. Six-year postoperative corneal topography showing marked corneal deformation. D. Difference map B *minus* A showing close to 20 diopters of corneal steepening. E. Difference map C *minus* B showing spontaneous focal corneal flattening.

MMC was performed in a modified Athens protocol to improve her refractive parameters in February 16 of 2012.

2.2. Surgical procedure

After topical anesthesia, the corneal epithelium was removed with 20% ethanol for 40 seconds using a 9.0-mm-diameter well. The Esiris excimer laser (Schwind eye-tech-solutions GmbH, Kleinostheim) was programmed to treat the higher-order aberrations (HOA) in both eyes using a corneal wavefront profile. The ablation profile was calculated based on measurements of the wavefront corneal topography (Keratron Scout, Optikon, Roma, Italy). The ablation was superior and inferior in an attempt to steepen the vertical meridian (a printout of the ablation pattern for the right eye was found in the surgical report but poor definition does not allow for publication here).

In the right eye, a 54 μm ablation of HOA was performed. The ablation diameter was 5.0 mm (deeper superiorly than inferiorly) with an additional 0.4 mm transition zone. No refractive correction was input into the laser due to thickness considerations. We were cognizant that the HOA stromal ablation could be different than the corneal-epithelial-surface-topography-measured wavefront but that was the software available to us. Mitomycin C 0.02% for 120 seconds was applied after the excimer laser application. The cornea was soaked with 0.1% riboflavin with 20% dextran (no hypotonic riboflavin was available in the country at the time), one drop every 3 minutes for 30 minutes and one drop of riboflavin was applied every 5 minutes while irradiating. The thinnest of 10 central and paracentral ultrasound pachymetry readings (Sonogage Inc, Cleveland, OH, USA) was 404 μm before irradiation. Ultraviolet A (UVA) of 365 nm (3 mW/cm^2) was used (IROC, Peschke, Switzerland). Given the borderline pachymetry, the UVA application time was empirically reduced to 20 minutes (3.6 J/cm2)A bandage contact lens was placed at the end.

A similar procedure was done in the left eye. The thinnest pre-UVA application ultrasonic pachymetry was 405 μm. Forty-three μm of HOA were treated (in a similar ablation profile as described above) along with half of the refractive error according to the laser nomogram for mixed astigmatism (Plano – 0.60 × 105°) for a total of 56 μm total ablation. The rest of the procedure was done similarly to the right eye.

Postoperative regimen consisted of a plano bandage contact lens (Soflens 66®, Bausch & Lomb), gatifloxacin (Zymaran®, Allergan, Irvine, CA) and fluorometholone (FML®, Allergan, Irvine, CA) four times a day for one week.

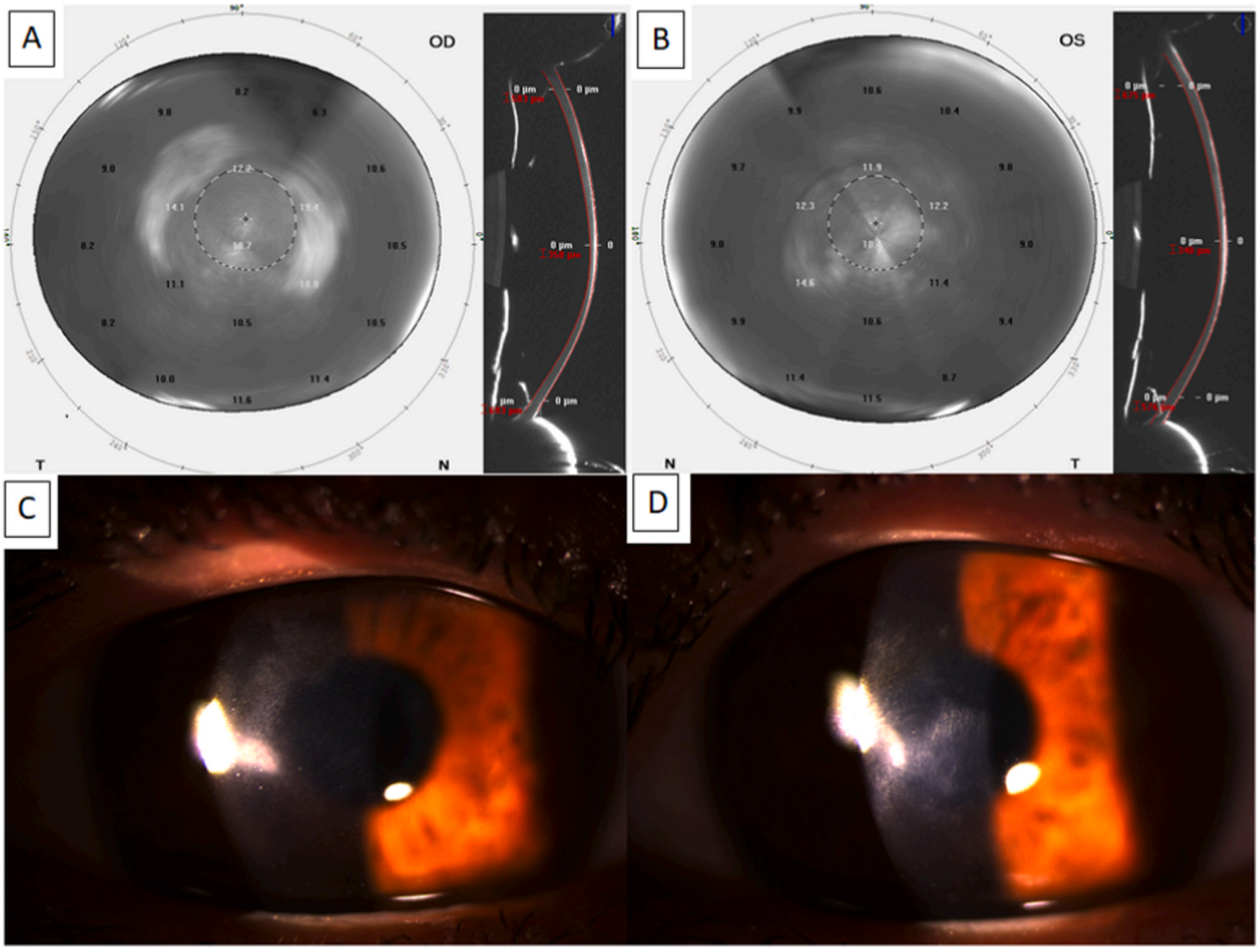

Fig. 3. Postoperative Scheimpflug corneal densitometry
A. Right eye. Note the full-thickness corneal sÊrring shown in the en-face image as the red line is moved all the way to the endothelium (354 μm) in the tangential insert. B. Left eye. Note the full-thickness corneal scarring shown in the en-face image as the red line is moved all the way to the endothelium in the tangential black and white insert. C. Corresponding slit-lamp microphotograph of the right eye showing patchy stromal haze. D. Corresponding slit-lamp microphotograph of the left eye with similar but more central findings. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2.3. Clinical follow-up

Four days after the procedure there was a 1 mm epithelial defect and trace superficial haze in the right eye, and a deep central dense haze in the left eye. The epithelium in both eyes closed one week after surgery and the contact lenses were removed. One month after the procedure the UDVA was 0.2 and 0.4 and CDVA was 0.2 LogMAR in both eyes with a refraction of +1.50–1.75 × 130 and + 1.75–2.50 × 20. At this time, the right eye presented with mild haze and left eye a dense deep-stromal haze and blurred vision. She was compliant with the postoperative steroid regimen, protected herself from UV light for three months as instructed and did not use ascorbic acid as she was not instructed to do so.

One year after, the UDVA was 0.5 and 0.4, CDVA was 0.30 LogMAR in right eye (−0.25 - 7.00 × 78) and non-refractable OS. There was a deep central stromal haze in both eyes. Eighteen months postop the differential Scheimpflug axial corneal maps showed bilateral corneal steepening close to 20 diopters in both eyes (Fig. 1 ABD and 2 ABD), despite bilateral full-thickness stromal scarring evident on the en-face Scheimpflug images. (Fig. 3A and B). Similar findings were seen on the differential Scout (Keratron Scout, Optikon, Roma, Italy) corneal topography (Fig. 4A and B.) Despite the corneal ectasia, because the presence of 100% corneal haze we decided to observe the patient.

Six years after surgery, the mid-stromal haze persisted in both eyes and UDVA was 0.70 and 1.3 LogMAR, with DCVA of 0.4 (−4.25 - 2.50 × 53) and 0.5 LogMAR (−11.25 - 3.25 × 93) respectively. At this point, she had been using bilateral scleral contact lenses to provide an appropriate visual function as a dentist, giving a DCVA of 0.2 and 0.3. There was progressive corneal flattening from year one to year six (Fig. 1 BCE and 2 BCE). Regarding HOA there was an increase in vertical coma (z51 6.0) in the right eye and in spherical aberration (z4.0) in the left eye from year 1 ½ to year six.

3. Discussion

Satisfactory short- and long-term results from a single-center have been reported with the Athens protocol as a therapeutic procedure for treating patients with keratoconus.1,2 Likewise, short-term data that have been reported using simultaneous CXL and PRK with maximal ablation of 50-µm,3 and 80-µm.4

This case shows full-thickness corneal haze with initial steepening followed by spontaneous flattening, increase in HOA and loss of lines of vision even after scleral contact lens rehabilitation.

Despite having obtained an intraoperative ultrasonic pachymetry >400 µm on each eye, a conservative UVA application of 20 minutes (66% of the total irradiance) was used since the calculated corneal thickness based on preoperative pachymetry minus the total estimated ablation was 389 µm and 393 µm respectively. While greater UVA total energy could potentially have prevented the initial progression seen here, a greater energy might also have been associated with an even more pronounced corneal haze and distortion than what was encountered. Recently, Kling and Hafezi proposed an algorithm that considers several variables (including riboflavin kinetics, oxygen diffusion and UVA absorption) and by predicting the biomechanical CXL stiffening effect allows the treatment of thin corneas by reducing the irradiance time.5,6 Although this study was published a posteriori, the rationale used in our patient is in line with this proposed individualized model.

Given the prominent corneal steepening observed on the Pentacam at 18 months after the combined surgery, one could argue that a second CXL would have been of utmost importance. The presence of bilateral full-thickness scarring as per corneal densitometry (Fig. 3A and B) lead us to hold off on any additional potential scar-inducing procedure. The fact that eventually most of the steepening regressed spontaneously (Fig. 1 BCE and Fig. 2 BCE) points in the direction of CXL-induced corneal remodeling instead of PRK-induced corneal ectasia.

Severe long-term progressive bilateral corneal distortion was the

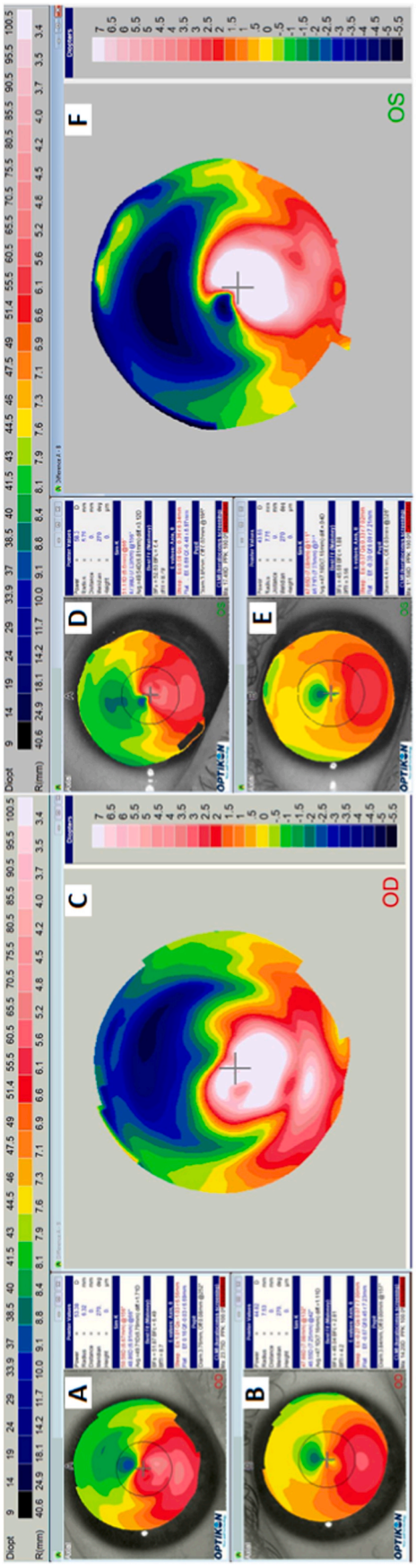

Fig. 4. Six-month difference map taken with a placido-based topographer
A. Preoperative corneal topography map OD. B. Six-month topography OD. C. Difference map showing the marked steepening in the inferor part of the cornea. D. Preoperative corneal topography map OS. E. Six-month topography OS F. Difference map showing the marked steepening inferorly.

result of the combination of PRK and CXL in addition to MMC. The use of 0.02% MMC for 2 minutes in a primary combined refractive surgery procedure or as re-treatment for corneal haze control, has been reported as safe and effective.7 On the other hand, recent research have shown that mitomycin C application following cross-linking significantly increases corneal haze.8 This study hypothesizes that the haze mechanism differs between PRK and CXL, and suggests that the apoptosis caused by MMC acts synergistically with CXL, resulting in greater cell loss in the treated area and consequently larger amount of cytokine release. Tsatsos et al.9 report a case of high myopia were a combination of PRK, MMC and CXL lead to severe corneal scarring, persistent epithelial defects, thinning and distortion that required rigid contact lenses for proper function, in a way similar to ours. In the event that our patient did not tolerate contact lenses, the next step in visual rehabilitation would have been corneal transplantation in any of its modalities. The fact that the preoperative UCVA was 0.30 and 0.60 LogMAR and that CDVA was 0.18 with a minor glasses' prescription should not be forgotten.

When doing CXL, unpredictable short-term10 or long-term11 progressive corneal flattening with significant hyperopia have been reported, which adds a factor of uncertainty to the simultaneous use of PRK and CXL. A recent meta-analysis of LASIKextra, SMILEextra and PRKextra that concludes that they might enhance the procedures, however complications such as corneal ectasia, diffuse lamellar keratitis and central toxic keratopathy are also mentioned.12 Other alternatives to regularize the cornea in cases of keratoconus using the excimer laser mostly to remove the epithelium with sectorial removal of thin slivers of stroma (less that 10 μm) with simultaneous CXL but no MMC have been reported such as the Cretan13,14 or the Tel-Aviv15 protocols.

We are cognisant that this case could be an isolated event of a severe bilateral complication after a combination of PRK, MMC and CXL. We encourage surgeons to use available therapeutic tools judiciously to improve vision or stop documented progression in cases of keratoconus but to limit the use of purely refractive surgery alternatives.16 Further reporting of cases combining PRK and CXL in keratoconus would yield a better understanding of the role of this form of therapy in our ever growing surgical armamentarium.

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Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

IRB approval was obtained (required for studies and series of 3 or more cases).

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All listed authors meet the ICMJE criteria.
We attest that all authors contributed significantly to the creation of this manuscript, each having fulfilled criteria as established by the ICMJE.

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Declaration of competing interest

Potential conflict of interest exists:

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