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Case Report

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Progressive Flattening after Corneal Collagen Crosslinking: A 10-Year Follow-Up

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Abstract

Purpose: *This study aimed to demonstrate the importance of long-term follow-up after corneal collagen crosslinking.*

Methods: *This case report showed an intense progressive flattening of keratometric parameters in a patient without risk factors such as high maximum keratometry, thin cornea, uncontrolled ocular allergy, collagen, or rheumatologic diseases. Even with significant haze formation and progressive flattening, the patient exhibited progression after a long follow-up period.*

Results: *The patient presented with grade 2 haze associated with progressive flattening of approximately 10 D in keratometric parameters (Kmax, K1, K2, and Kmean) during the first 5 years after surgery. Corneal opacity altered the minimum pachymetry reading on Pentacam to 265 microns. Anterior corneal follow-up optical coherence tomography revealed a thickness of 453 microns. The patient developed low visual acuity while wearing glasses. The scleral lens was fitted, allowing a visual acuity of 20/30, with satisfactory visual quality. Keratometric stability was observed between the fifth and tenth year. In the tenth year, the patient maintained haze, but there was a progression of 1.7 D in the Pentacam comparative map.*

Conclusions: *Long-term monitoring after corneal crosslinking should be performed. Eyes with haze and intense progressive flattening may fail after a long period.*

Keywords: Corneal crosslinking, Haze, Keratoconus

Introduction

Corneal collagen crosslinking (CXL) is an effective treatment for preventing the progression of keratoconus (KC). The application of riboflavin, together with exposure to UVA radiation, promotes a photochemical reaction that releases free radicals derived from oxygen. The first clinical use of CXL was in 2003 in the Dresden protocol [1].

The incidence of complications after CXL is low and is mainly related to the conventional technique of removal of the epithelium (epi-off). The main complication described in literature is haze, which is associated with keratocyte apoptosis. Generally, haze is transient and improves up to one year after the procedure [2]. However, some cases evolve with persistent haze, which decreases the visual quality of the patient. The risk factors related to a higher complication rate in CXL are high keratometry (greater than 58 D) and ocular allergies with chronic pruritus that are difficult to control [3].

Progressive flattening is an uncommon complication, with few studies in literature having a long follow-up period [4]. It is usually associated with haze, but its cause remains unknown.

Publications on progressive planing have a short follow-up time, and doubts remain regarding the long-term evolution of patients. This study aimed to show a case highlighting the progression of keratometric parameters after 10 years in a patient with progressive flattening and persistent haze.

Case Presentation

A 17-year-old woman was referred for evaluation at our hospital with a complaint of progressive low visual acuity for one year in both eyes, although it was worse in the right eye. She denied eye itching and did not use any eye drops. The patient had no personal or family history of ophthalmological alterations. She denied any rheumatological alterations or collagen disease.

Ophthalmological examination revealed the best-corrected visual acuity (BCVA) with 20/30 and 20/25 glasses. Biomicroscopy

revealed a Fleischer ring in each eye. Applanation tonometry revealed a pressure of 12 mmHg in both eyes (AO). Retinal mapping did not show AO changes. Skiascopy revealed an irregular AO band, and corneal topography confirmed the diagnosis of KC. After follow-up of the corneal sector, progression of maximum keratometry greater than 1 D in less than 12 months was documented, and CXL OD was indicated.

Preoperative examination of the right eye revealed the following: BCVA of 20/30p, specular microscopy showing 2977 cells/mm2, keratometry in the central 3 mm with K1 of 46.2 and K2 of 50.4, average keratometry (Km) of 48.3, maximum keratometry (Kmax) of 56.1, and finest point of 500 microns.

Conventional epi-off CXL was performed with 0.1% isotonic riboflavin in 20% dextran applied every 2 minutes for 30 minutes, and UVA irradiated at 3mW/cm2 for 30 minutes.

Corneal epithelialization occurred on the fifth day after the procedure with no signs of infection. In the postoperative period, the patient developed grade 2 haze and complained of low visual acuity, with a BCVA of 20/70 in the third postoperative month. One year after surgery, the patient maintained a complaint of low visual acuity, persistent grade 2 haze, and visual acuity with 20/60p glasses. The evolution of the keratometric measurements (K1, K2, Kmax, Km, and the thinnest point of the corneal thickness [CT]) are described in Table 1. We observed progressive flattening of around 10 D in the keratometric parameters during the first 5 years. From the sixth to tenth years, there was a tendency towards stability, and finally in the tenth year, the central keratometric measurements in the differential map showed an increase of 1.7 D and the Kmedium increased by 0.8 D. The evolution of pachymetry described in Table 1 shows significant thinning of the cornea, but these data are not reliable because they were obtained with a Scheimpflug system, which is not suitable for assessing corneal thickness in cases of corneal opacity. After 10 years of follow-up, anterior segment optical coherence tomography (AS-OCT) revealed a minimum pachymetry of 453 microns and diffuse opacity that reached the deep corneal stroma.

The patient's refraction evolved with a hyperopic shift during the first five years. Until the third year after surgery, the patient maintained a complaint of low visual acuity with progressive worsening, but managed to maintain her daily activities without major difficulties. In the fifth postoperative year, the patient's vision with glasses was 20/70p, and the she was dissatisfied with the quality of vision. Thus, a scleral contact lens was fitted. Lens with lower and deeper sagittal height (SAG) were tested to make the corneal opacity more posterior. The patient was more satisfied with a greater SAG depth. The prescribed lens was Zenlens (Zenlens, Alden Optical), with base curve of 9.50, diameter of 16 mm, SAG of 4.75, and final degree of +8.00, and the patient had a good visual acuity of 20/30.

A comparison of the keratometric parameters in the last four years (Figure 1) shows the stability in the anterior sagittal map of the Pentacam HR (Oculus Optikgera¨te GmbH, Wetzlar, Germany). The differential map generated between the last two exams showed a central increase of 1.7 D and an increase of 0.8 D in the Kmean, despite the Kmax having shown a reduction of 0.5 D.

The BCVA remained stable at 20/30 in the last 4 years with scleral lens. The patient was satisfied and had good acceptance and tolerance of the lens, which was changed annually while retaining the same parameters and final grade.

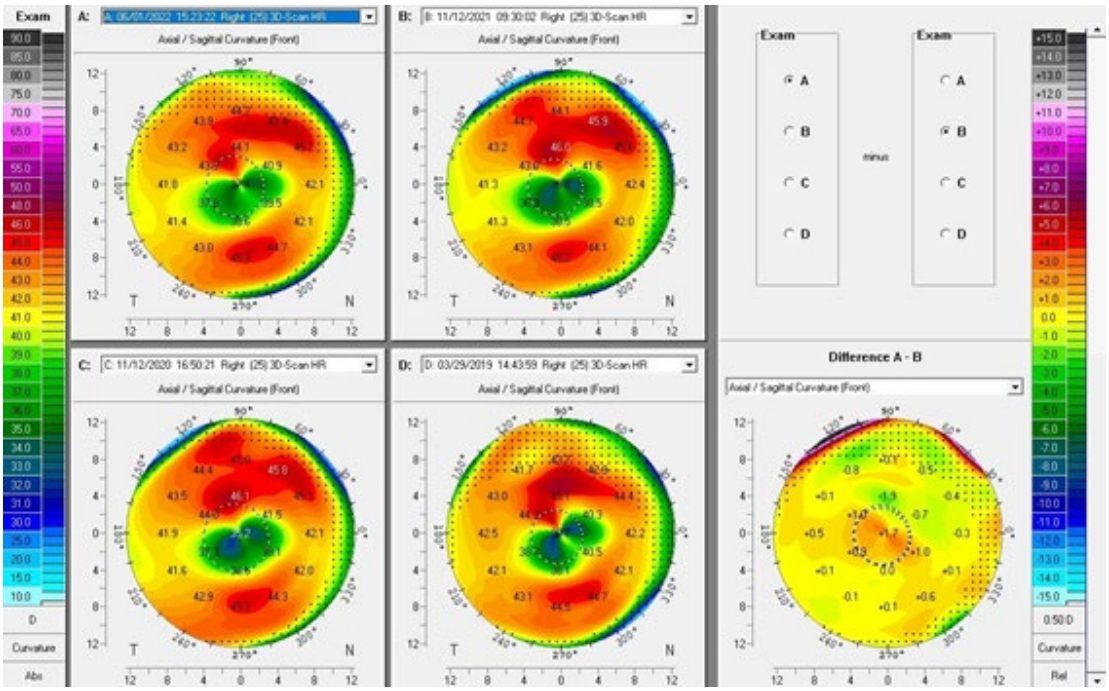

Figure 1: A comparison of the maps obtained in the last four years. The photo on the right shows the differential map (A-B) that compares the last two exams

In the last evaluation, the patient had BCVA in the right eye using a 20/30 scleral lens, tonometry result of 13 mmHg, specular microscopy finding of OD 2739 cells/mm2, and biomicroscopy finding of grade 2 haze, as shown in Figure 2. The patient was satisfied with the current vision, and she did not have to compromise her daily activities.

Table 1: Keratometric parameters. K1 and K2: minor and major keratometry from the central 3 mm, respectively. Km: average k. CT: thinnest pachymetry. Kmax: Maximum keratometry

	K1	K2	Km	CT	Kmax
PRE OP	46,2	50,4	48,3	500	56,1
1 year	42,6	47,0	44,8	287	55,2
2 years	40,8	44,7	42,75	309	49,9
3 years	39,2	43,2	41,2	279	48,5
4 years	39,1	43,2	41,15	313	48,0

5 years	38,4	42,4	40,4	316	47,0
6 years	36,0	42,2	39,1	276	46,8
7 years	36,0	41,6	38,6	273	46,6
8 years	36,3	40,6	38,45	270	46,7
9 years	36,3	40,9	38,6	264	46,8
10 years	37,1	41,7	39,4	265	46,3

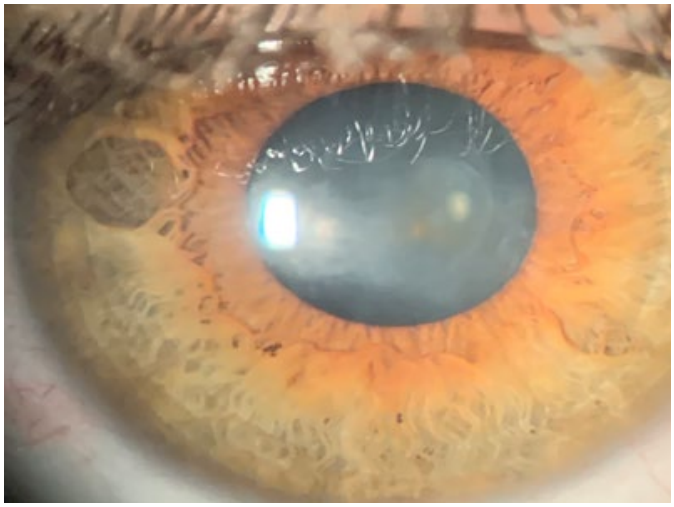

Figure 2: Biomicroscopy image depicting a grade 2 haze

Discussion

CXL is intended to stabilize keratoconus by keeping keratometric measurements stable, but a slight flattening from 1 to 2 D is an expected effect up to the first year. Progressive flattening is a rare but serious complication that causes a significant drop in the patient's acuity and visual quality.

The case above shows a patient who, in addition to haze, evolved with an intense flattening of 10 D during the first five years, followed by stability in the next four years, and progression in the tenth year.

The great challenge is to understand cases that have an unfavorable evolution, even with established safety criteria in the preoperative period. The patient in question did not have eye itching or collagen or rheumatologic diseases. She also had a maximum keratometry less than 58 D and thinnest point greater than 450 microns. Even so, she experienced progressive flattening of the cornea.

Devices using the Scheimpflug system are not suitable for assessing corneal thickness in cases of opacity, as they underestimate the measurement. AS-OCT is the best examination to follow pachymetry in cases of corneal opacity, in addition to properly assessing the depth of opacity.

Retreatment for CXL failure is a risk factor for excessive flattening and other CXL effects. Grentzelos, et al. demonstrated the stabilization of progressive flattening after the fifth year of CXL retreatment [5].

From the ninth to tenth year, a progression of 1.7 D was evident in the Pentacam differential map, indicating that the CXL effect may decrease over the years. Therefore, long-term follow-up of patients undergoing CXL is very important, especially in children and adolescents who have a greater tendency to evolve.

Several factors can influence the effects of CXL. Epi-off techniques show a higher risk of complications such as haze, but have a lower failure rate [6]. Accelerated CXL has a less intense effect and a higher risk of progression and failure than conventional CXL [7]. The type of light used can also influence the effect of CXL, since studies show that pulsed light in cycles with adequate in-

tervals promotes a photochemical reaction (type II) with a greater presence of O2, releasing free radicals derived from oxygen and generating a more effective reaction. On the other hand, in procedures with continuous light, there is an increased chance of reactions with less oxygen, consequently releasing hydrogen peroxide (type I reaction), which has a greater potential to cause anomalous healing [8]. The type of riboflavin solution can also influence the CXL results because solutions with hydroxypropyl methylcellulose have faster penetration than dextran. In procedures with riboflavin in dextran, corneal pachymetry decreases during soaking and UVA exposure because of the oncotic effect of the solution; therefore, it is more prone to complications [9]. Riboflavin and its isomers, with five monophosphates being the main ones, penetrate the cornea differently owing to the electronegative potential of keratan sulfate present in the extracellular matrix. Hafezi, et al. demonstrated that five monophosphates require less energy to be excited; therefore, it has a positive effect on CXL but is more difficult to penetrate the cornea because of its higher electronegative potential, being repulsed by keratan sulfate [10].

The aim of the future of KC is to better understand each step of surgery and to improve our knowledge of the biological response of each patient that can be influenced by genetic and enzymatic factors. Rabinowitz published a study on the genetics of keratoconus and identified some genes related to complications in CXL [11]. He also proposed to expand the screening of patients with KC with the inclusion of genetic scores to reduce adverse effects. Shetty, et al. highlighted the importance of lysyl oxidase (LOX) in the process and effectiveness of CXL, since patients with greater expression of LOX in the cornea have a greater effect of CXL [12].

The case above presents an intense progressive flattening associated with haze, but in the tenth year after the procedure, there was progression in the differential map and Km, which could be indicative of the recurrence of CXL; however, the progressive flattening and haze after the first procedure should be taken into account. Repeated CXL can lead to an even more pronounced response, compromising the patient's visual prognosis.

Progressive flattening remains a rare but challenging complication. Continuous long-term monitoring should be performed because of the risk of late failure, even in cases with intense flattening haze.

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