Case Report

Topical Minoxidil Solution-Induced Central Toxic Keratopathy following Photorefractive Keratectomy: A Case Study

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Abstract

Purpose: To report the clinical findings of unilateral central toxic keratopathy (CTK) associated with inadvertent exposure to topical minoxidil 5% solution 1 day after bilateral photorefractive keratectomy (PRK).

Methods: Anterior segment slit-lamp photography, anterior segment optical coherence tomography (AS-OCT), pachymetry map, epithelial map, and manifest refractions were recorded.

Results: This is a case of a 27-year-old male who underwent bilateral PRK and presented 5 days after surgery with the complaint of acute decreased visual acuity in the left eye (LE). His LE was reportedly exposed to topical ethanol-based minoxidil 5% on postoperative day 1, which he was using as a posthair transplant treatment. Clinical examination showed hyperopic shift, poor visual acuity, central corneal opacity, epithelial irregularity, central corneal thinning, and flattening on AS-OCT. These findings were consistent with a diagnosis of CTK. The patient was monitored with conservative treatment and demonstrated full recovery after 6 months.

Conclusion: It is recommended to warn patients who have undergone refractive surgery concerning the use of ethanol-containing agents, such as minoxidil solution, because of the possible risk of CTK, a complication not formally recognized.

Keywords: Anterior segment optical coherence tomography, Central toxic keratopathy, Photorefractive keratectomy

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Introduction

Central toxic keratopathy (CTK) is an acute and painless focal corneal disorder.[1] CTK is typically defined as a noninflammatory corneal disease with clinical presentations of dense central or pericentral corneal opacity in the anterior to mid-stromal layer, remarkable corneal flattening, and late hyperopic shift.[2,3] CTK was initially described in a case series after mechanical microkeratome-assisted laser *in situ* keratomileusis (LASIK) in 1998.[4] The incidence of CTK is rare and estimated to be 0.016% after refractive surgeries.[1,3] Several case studies claimed that the incidence of CTK is not exclusive to the mechanical microkeratome-assisted LASIK surgeries and has also developed after femtosecond LASIK, photorefractive keratectomy (PRK), trans-PRK, and small incision lenticule extraction surgeries.[3,5-8] The incidence of CTK after procedures other than LASIK suggests that in contrast to previous clinical belief, the pathophysiology could not be related to the flap formation. The exact etiology of CTK remains uncertain; however, different inciting pathogeneses have been proposed, including intraoperative meibomian gland secretions and photoactivation of povidone-iodine by the excimer laser.[1,3] Furthermore, other studies report that toxic reactions due to nonsurgical elements such as contact lenses or idiopathic factors could result in stromal keratopathy mimicking CTK.[9-11] CTK usually occurs within 3–9 days after surgery.[1] The maximum hyperopic shift was observed approximately

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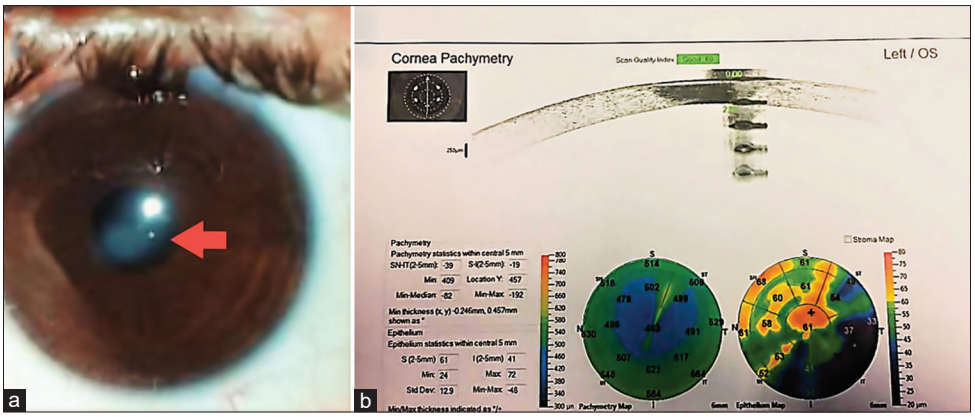

Figure 1: Central corneal opacity on slit-lamp imaging of the left eye (a), and anterior segment optical coherence tomography, pachymetry map, and epithelial map (b) 5 days after photorefractive keratectomy surgery

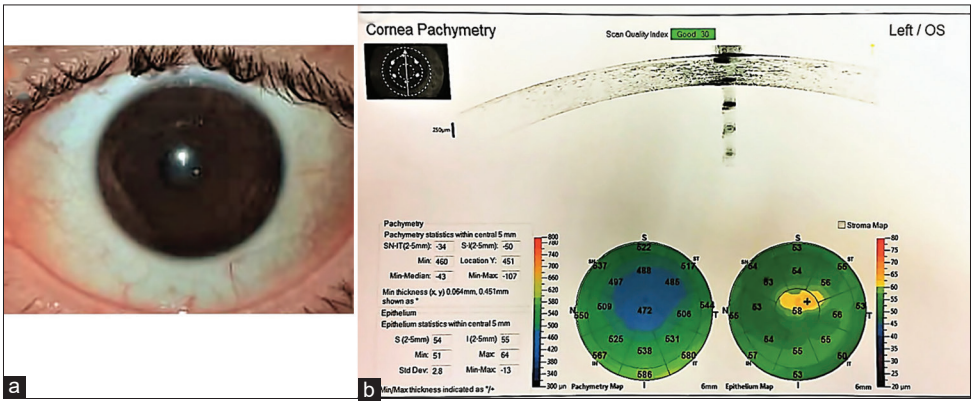

Figure 2: Slit-lamp imaging (a), and anterior segment optical coherence tomography, pachymetry map, and epithelial map (b) 6 months following photorefractive keratectomy surgery

1 month after refractive surgery and could be resolved gradually up to 2–18 months following the operation.[12] Because of the presumably self-limited and noninflammatory nature of CTK, Moshirfar *et al*. recommend an observational approach without therapeutic intervention.[1] Recent publication on CTK suggests that in some cases, irrigation of the stromal bed under the flap after femtosecond LASIK can enhance the recovery time of CTK but not the final visual outcome and prognosis.[7]

Minoxidil 5% is an over-the-counter topical solution for routine application to the scalp to stimulate hair growth in patients with androgenetic alopecia and as an adjunct therapy after hair transplant surgery. There are rare reports of ophthalmic side effects following routine use of topical minoxidil 5% solution.[13,14] In this case report, we present the clinical findings of unilateral CTK after bilateral PRK in a patient whose left cornea was inadvertently exposed to topical minoxidil 5% solution on the 1st postoperative day. To our knowledge, this is the first report of presumed minoxidil-induced unilateral CTK after PRK.

Case Report

A 27-year-old male who underwent PRK in June 2020 presented for removal of his bandage contact lenses 5 days after surgery. The patient reported exposure of his left eye (LE) to minoxidil solution (Pak Darou 5% Minoxidil solution) on the 1st postoperative day, with a significant burning sensation and irritation that resolved after several hours that day. He was on treatment for posthair transplant surgery with topical ethanol-based minoxidil 5% solution on the scalp once a day. According to the patient, the minoxidil solution inadvertently flowed into the LE. Informed consent for publication was obtained from this case.

On initial presentation, the uncorrected distance visual acuity of the right eye (RE) and LE was 20/25 and 20/200, respectively. The corrected distance visual acuity (CDVA) value was 20/25 for the RE and 20/50 for the LE. The patient attributed his vision reduction and increased irritation of the LE to the minoxidil exposure. Clinical examination revealed a compound hyperopic manifest refraction of +6.00/−5.00 × 45 in the LE and an insignificant refractive error in the RE. The preoperative manifest refraction of the LE was −3.00/−2.75 × 157 with the best CDVA of 20/20 and without any topographic signs of irregularity. On slit-lamp examination, the obvious finding was a central corneal opacity involving the stromal layer [Figure 1a]. Anterior segment optical coherence tomography (AS-OCT) (Optovue RTVue-100; Optovue Inc., Fremont, CA, USA), pachymetry map, and epithelial

map recordings of the LE within the central 5 mm of corneal profile 5 days after PRK procedure are shown in Figure 1b. Irregularities in the epithelial map, central corneal thinning in the pachymetry map, and central flattening in the AS-OCT image are illustrated in Figure 1b. Examination findings were consistent with a diagnosis of CTK. The corresponding findings of the RE were within normal limits.

The patient was instructed to discontinue the future application of topical minoxidil. Furthermore, as topical steroids in such cases are controversial, the preprescribed dosage of fluorometholone eye drops was tapered in the LE. To prevent corneal apoptosis, lubricant eye drops, Vitamin C, and doxycycline were prescribed. Six months later, CDVA and refraction of the LE were 20/20 and +0.50 diopter, respectively, and the cornea was clear. Figure 2a illustrates the elimination of central corneal opacity 6 months after the presentation. Figure 2b shows the AS-OCT, pachymetry map, and epithelial map recordings of the LE 6 months after observation. The most remarkable changes of AS-OCT and topographic maps between 5-day and 6-month examinations are presented in Table 1.

Discussion

To the best of our knowledge, we present the first documented report of a patient who developed unilateral CTK due to corneal exposure to ethanol-containing minoxidil 5% hair solution following an uneventful bilateral PRK surgery. The case initially presented with classic manifestations of CTK, including noninflammatory central stromal opacification, corneal flattening, and hyperopic refractive shift with spontaneous resolution over time.[3] The diagnosis of CTK was established according to the findings on manifest refraction, slit-lamp examination, and AS-OCT. It is noteworthy that we initially suspected exposure keratopathy according to the patient's self-report of exposure to an ethanol-containing solution. However, as exposure keratopathy is mainly associated with more intensive symptoms of ocular discomfort, corneal abrasion, and no hyperopic shift, we reasonably made the diagnosis of CTK.[15] We also ruled out other forms of corneal opacities following refractive surgeries according to the disorder characteristics as listed in Table 2.[1]

Minoxidil solution (Pak Darou 5% Minoxidil) contains 5% minoxidil and 47.2% ethanol (ethyl alcohol). Early studies on the postoperative effect of topical minoxidil as a medication for improving refractive outcomes after radial keratotomy and decreasing corneal haze after PRK advocated the enhancing effects of this agent by inhibiting keratocyte proliferation activity in the injured cornea.[16,17] Ethanol is an agent that has been commonly used in ophthalmic surgeries such as alcohol-assisted PRK and pterygium excision for many years.[18,19] The basic application of ethanol in ophthalmic surgeries is producing epithelial debridement that relates to its potential ability for epithelial cells to weaken. The most frequent dosage of ethanol in anterior segment surgeries is in the form of 20% diluted ethanol.[20] Previous studies reported that ethanol exposure at concentrations <20% over ocular surface for no more than 60 s seems to be risk-free.[18,21] However, high-concentration ethanol-containing minoxidil products may impose an instant toxic effect on corneal epithelial cells due to the higher dosage of ethanol.[22] Despite therapeutic applications of ethanol in ophthalmic surgeries, few studies have investigated the toxic effects of ethanol on the corneal surface. As the minoxidil solution that has been administered by the patient contains high-dose ethanol (47.2%), it may impose apoptosis on the epithelial cells of the cornea.[20] In a study conducted by Oh *et al*.,[20] corneal epithelial cells in the culture were exposed to the different dosages of ethanol for 30 s. Following that, they analyzed the cytotoxicity reactions and the presence of inflammatory cytokines in the epithelial cells for the next 3 days. They found a decrease in the viability of whole epithelial cells that was due to apoptosis, and the induced response was dependent on the ethanol concentration. In addition, they found a remarkable increase in the appearance of proinflammatory cytokines and chemokines in epithelial and stromal cells of the exposed corneas. They concluded that short-time exposure to ethanol could exert prolonged effects on corneal surface due to disorganizing epithelial cells and concurrent inflammatory responses which both events could make ocular surface susceptible to many diseases. It has been previously postulated that toxic or immune reactions could be a risk factor in developing CTK after refractive surgeries.[1,3,12] Likewise, our case was unintentionally exposed to the ethanol-containing minoxidil solution as a cytotoxic factor that finally resulted in developing CTK.

Most of the previously reported CTK cases have occurred following LASIK.[2,3] However, there are some reports of CTK development after other refractive surgery procedures,[3,5,6,8] contact lens use,[9,10] and idiopathic causes.[11] The current belief is that the exact cause of CTK remains a matter of debate.[2] Sonmez and Maloney postulated that toxic corneal response to external particles might be a risk factor in developing CTK.[3] Our case supports this hypothesis, as we observed that the corneal opacity resolved spontaneously after the patient's use of routine post-PRK medications. Early clinical signs of corneal inflammation or infection are conjunctival injection, stromal edema, and corneal infiltrations. In the next phase, the stromal layer may lose its tissue. In contrast, as shown in our case, CTK corneas are prone to stromal and epithelial thinning and anterior corneal flattening during the 1st days after the procedure without any concurrent inflammatory events.[1-3,12] Previous reports of *in vivo* confocal microscopy proved the

Table 1: Changes in different corneal thickness values between 5 days and 6 months examinations

Corneal parameter (μm)	Day 5	Month 6
Central corneal thickness	452	472
Minimum pachymetry	409	460
Minimum epithelial thickness	24	51

Table 2: Differential diagnosis of postrefractive surgery corneal opacities

Disorder	Features	Localization	Resolution time after the incidence
CTK	Noninflammatory and toxic Onset within 3-9 days after different types of laser refractive surgeries Remarkable visual acuity reduction Hyperopic shift No pain	Central and well defined	Between 2 and 18 months
Diffuse lamellar keratitis	Mild-to-severe inflammation Onset on the 1st day after LASIK Minimal effect on visual acuity No hyperopic shift Foreign body sensation	Central or paracentral and diffused	During the 1st week
Postsurgical haze	Noninflammatory Onset within the 1st month after advanced surface ablation procedures or corneal cross-linking Mild-to-moderate effect on visual acuity No hyperopic shift	Central and diffused	Over several months to several years
Epithelial ingrowth	Epithelial cells in the flap interface Onset within the first 2 months after LASIK Minimal effect on visual acuity No hyperopic shift No pain	Focal at the flap edge	During the 1st year
Infectious keratitis	Infectious Onset within 3-21 days after different types of laser refractive surgeries Variable effects on visual acuity No hyperopic shift Moderate-to-severe pain	Central or paracentral and dense	Several weeks

CTK: Central toxic keratopathy, LASIK: Laser *in situ* keratomileusis

noninflammatory nature of CTK.[23,24] These reports proposed that a cytokine apoptosis process without any inflammatory cells and necrotic debris could contribute to CTK onset.[23,24] In general, the primary management strategies in CTK patients are using lubricants for relieving corneal irritation, metalloprotease inhibitors such as doxycycline, and medications that accelerate corneal wound healing such as ascorbic acid.[10]

Despite the uncertain etiology, CTK corneas generally have a fair-to-good prognosis for visual rehabilitation. As stated before, our patient achieved normal visual acuity at the final examination. We also observed that the stroma and epithelium continued thickening until 6 months after CTK. We believe that this is the first case report of a patient whose cornea was inadvertently exposed to ethanol-containing minoxidil that may have precipitated the development of CTK after PRK. Identification of the unique hallmarks of AS-OCT in this disease, including stromal opacification, epithelial thinning, and corneal flattening, could help the practitioner to make a proper diagnosis and outline the best-laid treatment plan. We conclude that the etiology of CTK is not limited to intraoperative problems or postoperative contact lens-related factors, and ethanol should be considered a possible risk factor for developing CTK after refractive surgeries. The use of ethanol-free agents may minimize the risk of corneal problems after refractive surgeries. It is recommended to warn patients who have undergone refractive surgeries to avoid high-dose ethanol-containing agents or be cautious in administering such agents because of the possibility of CTK, a complication not formally recognized. Further *in vivo* studies are needed to unveil the relationship between toxic environmental factors and CTK development.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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