Refractive Surgical Problem

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A 30-year-old woman was referred for a second opinion. She had chronic epitheliopathy of unknown origin in both eyes and decreased visual acuity. The patient had bilateral epithelial laser in situ keratomileusis (epi-LASIK) 3 months before the referral. A Moria epikeratome system was used in both eyes. The correction in the right eye was −5.11 +0.29 × 108 with an ablation depth of 74 μm. The correction in the left eye was −5.19 +0.50 × 53 with an ablation depth of 74 μm. According to the surgeon, the epithelial flaps were discarded in both eyes after excimer laser treatment; mitomycin-C (MMC) 0.2 mg/mL was used for 20 seconds after the treatment. Bandage contact lenses were placed at the end of the procedure and removed 5 days postoperatively after complete reepithelialization was achieved. The postoperative medication regimen consisted of topical antibiotics, prednisolone acetate, vitamin C, and cyclosporine ophthalmic emulsion (Restasis). The patient presented with no history of systemic illness.

The uncorrected distance visual acuity (UDVA) 3 weeks after surgery was reported to be 20/30 in both eyes. Her visual acuity started to decline (20/100 both eyes) 6 weeks postoperatively. At that time, examination showed epithelial microcystic changes and stromal haze of 9.0 mm in diameter in both eyes. Endothelial dysfunction with bullous keratopathy was seen; subsequent bouts occurred and included a reduction in the endothelial cell count (ECC) centrally. Several therapeutic measures were taken to try to alleviate the patient's symptoms, including therapeutic contact lenses, topical and subconjunctival steroids, cyclosporine ophthalmic emulsion twice a day, topical antibiotics, and hypertonic solution drops.

On presentation for the second opinion, the patient's UDVA was 20/150 in the right eye and 20/300

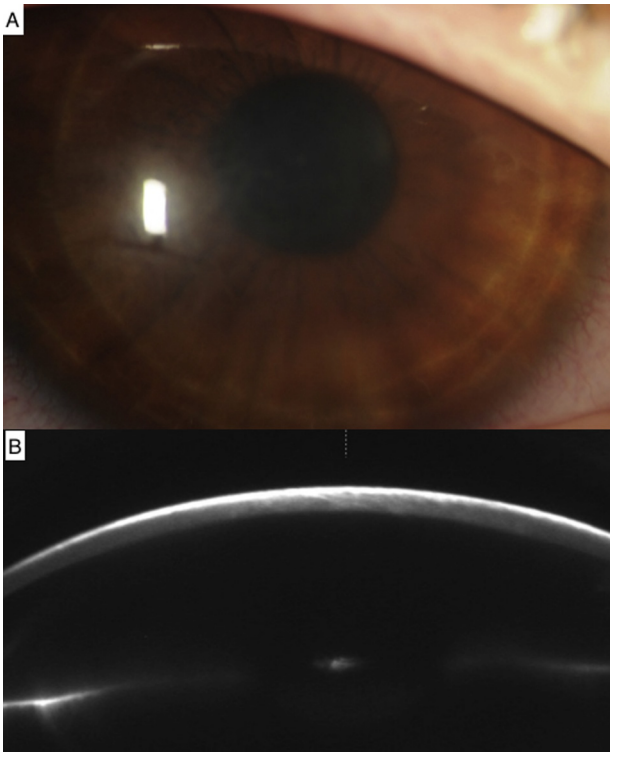

Figure 1. *A*: Postoperative slitlamp photograph showing corneal haze in the right eye. *B*: Scheimpflug tomographic image showing haze localized to the anterior one third of the cornea with a larger area of haze of approximately 8.0 to 9.0 mm.

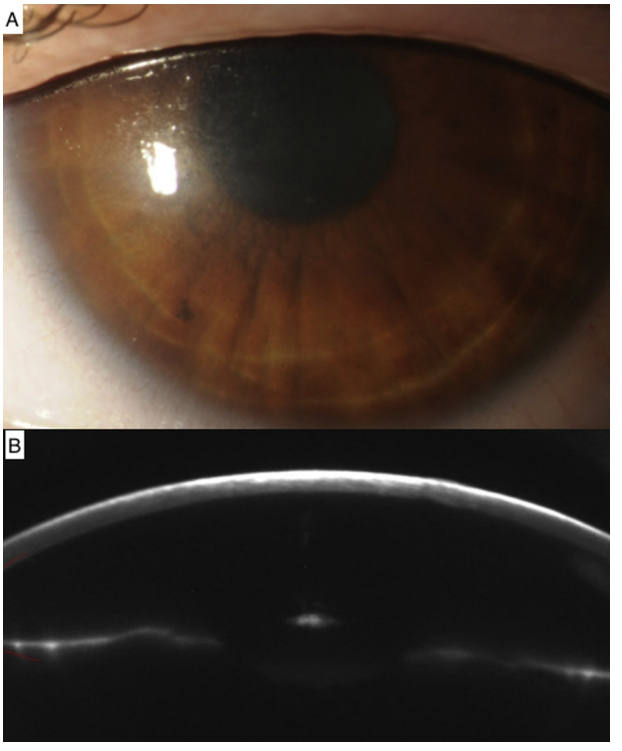

Figure 2. *A*: Postoperative slitlamp photograph showing corneal haze in the left eye. B: Scheimpflug tomographic image showing haze localized to the anterior one third of the cornea.

in the left eye. The intraocular pressure (IOP) was 16 mm Hg and 22 mm Hg, respectively. On slitlamp examination, microcystic edema, 1 to 2+ stromal haze (Figures 1 and 2), and trace Descemet folds were found in both eyes. The patient was very photophobic during the examination. Another patient who had surgery on the same day at the same clinic as the patient in this case developed a similar problem after epi-LASIK, with bilateral haze and a UDVA of 20/40 in both eyes.

What would explain the findings after epi-LASIK? What is the likely diagnosis? How would you rule out MMC toxicity versus the deeper keratome cut in terms of allowing the epithelial cytokines, especially transforming growth factor-β (TGF-β), to reach the stroma and generate myofibroblasts and subsequent haze? How would you approach this patient at the moment?

■ Several scenarios could have led to the unfortunate outcome in this case. Epikeratomes are designed to cut at a preselected depth to prevent stromal incorporation into the flap. However, the literature describes several cases of deep cuts that were identified after flap creation.[1–3] An enhanced inflammatory response was observed in 1 case that resulted in a focal area of subepithelial haze in the region of the deep cut only. In that case, deep cuts could have resulted in removal of the epithelium as well as a significant amount of stroma. The flap was then transected and discarded, leaving an open stromal bed.[4] Epikeratome trauma to the stroma in combination with a deep ablation might have led to a significant inflammatory response that was not quelled through the use of MMC and postoperative topical antiinflammatory medications.

A second theory involves MMC toxicity. Mitomycin-C is used primarily in eyes with deep ablations to prevent excessive haze formation. Endothelial dysfunction is a complication of MMC toxicity.[5] Improper dosing and prolonged exposure pose significant threats to the viability of the endothelium. The facility at which this procedure was performed receives its MMC from a compounding pharmacy at a concentration of 0.4 mg/mL. It is then diluted to a concentration of 0.2 mg/mL by select personnel experienced in the protocol. It is possible that improper dilution occurred at some step in the process. Prolonged exposure is unlikely considering the application time of 20 seconds. Decreased ECCs, microcystic edema, and bullous keratopathy support the theory of endothelial dysfunction.

Limbal stem cell dysfunction represents an additional mechanism in the outcome. As discussed, timely reepithelialization after ablation is vital in reducing stromal inflammatory mediators. Improper exposure of limbal stem cells to MMC can permanently damage the cornea's ability to produce epithelial cells.[6] This may lead to delayed, dysfunctional, or, in severe cases, nonexistent epithelial layer formation. Without a well-formed epithelial layer, stromal cytokine exposure causes significant subepithelial haze formation as a result of the uncontrolled production of myofibroblasts.

The most likely explanation is deep epikeratome cuts with or without potential MMC toxicity of the endothelium and limbal stem cells. Twenty seconds is a relatively short application time. The concentration would have to have been excessively high to have had a significant effect on the endothelium. In addition, this scenario does not explain the formation of subepithelial haze. A high dose of MMC should prevent this examination finding from occurring. A randomized trial comparing epi-LASIK patients with and without MMC[7] identified lower levels of corneal haze and tear-film TGF-β1 in eyes receiving MMC. Limbal stem cell deficiency is also unlikely. Although it has been reported, significant deficiency is rare when MMC is used with surface ablation.

When approaching a case like this, it is important to address the inflammatory etiology and the condition of the ocular surface. Topical steroids every 2 hours for the first 5 days followed by 4 times a day and a tapering dose of oral methylprednisolone should be initiated to reduce haze. The ocular surface can be addressed with a bandage contact lens and fish oil supplementation. Topical antihypertensives can help reduce edema in a partially compromised endothelium. When identified before flap lifting, deep cuts might be more appropriately managed by observation until stromal inflammation has resolved; this would be followed by photorefractive keratectomy (PRK).[3]

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■ Keratocyte differentiation to myofibroblast due to TGF-β1 produced by regenerating epithelium has been shown to be responsible for corneal haze after surface ablation procedures. Epi-LASIK, a surface ablation technique in which a flap consisting of epithelium and basement membrane is created, theoretically decreases cytokine production by maintaining a healthy epithelium. However, the epithelial flaps were discarded in this case; therefore, the procedure was converted to PRK, increasing the risk for haze.[1,2] Other factors, such as depth of ablation, ultraviolet radiation, delayed epithelial healing, pregnancy, and oral contraceptives could contribute to the development of haze.

Mitomycin-C is useful in modulating the corneal wound-healing response.[2] Nevertheless, toxicity has been reported as endothelial cell damage after the use of prophylactic MMC in vitro, in animal models, and in a few clinical studies.[1,3,4] Cytotoxicity can present as corneal opacity, delayed reepithelialization, corneal edema, and endothelial cell loss[2] and is usually associated with higher concentrations and prolonged exposure.

With the clinical findings in this case, the most likely diagnosis is endothelial toxicity secondary to MMC. However, the differential diagnoses of corneal opacity after surface ablation procedures include corneal haze and central toxic keratopathy. Other less likely diagnoses are corneal dystrophy, corneal degeneration, infectious keratitis, and drug toxicity/deposits. Pressure-induced interlamellar stromal keratitis and diffuse lamellar keratitis presented after LASIK only (ie, flap needed). To rule out a deeper epikeratome cut, histopathologic studies would have been useful to properly analyze the epithelial flap. (Unfortunately, the flaps were discarded.)

Although the MMC concentration and exposure time were within the normal range for prophylactic treatment, corneal toxicity can still occur.[3,4] Other factors that can cause endothelial cell loss are insufficient irrigation with a balanced salt solution after the use of MMC, an error in the dilution by untrained or new personnel, and a previously unhealthy endothelium. Mitomycin-C toxicity may begin in the first week, or even 6 months after, surface ablation.[3]

Additional data, such as a preoperative ECC to determine the percentage of cell loss and a postoperative refraction, are required for therapeutic decisions. Close follow-up with endothelial microscopy, optical coherence tomography, or ultrasound pachymetry are highly recommended. Mitomycin-C has a prolonged and cumulative toxic effect; this response could have been the result of an increase in free radicals, even 6 months after the procedure.[3,4] The IOP values are not reliable because of the corneal edema; the most likely causes of the elevated IOP are the subconjunctival and topical steroids. Hypertonic solutions, topical antihypertensive drugs, and bandage contact lenses can be used to alleviate the patient's symptoms. Other alternative treatments for endothelial decompensation in eyes with good visual potential are anterior stromal puncture, PTK, amniotic membrane transplantation, and collagen crosslinking.[5] If no improvement in the corneal edema and visual acuity occurs by 6 to 8 months, a lamellar or penetrating keratoplasty can be pondered.

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■ We believe that knowing the preoperative and postoperative corneal thickness as well as obtaining sequential postoperative ECC and morphology assessments are essential to determine whether endothelial toxicity is playing a major role in this case. The hypothetical advantages of laser-assisted subepithelial keratectomy and epi-LASIK over PRK are the

preservation of the epithelial basement membrane, or at least some components of the epithelial basement membrane, at the cleavage plane, which prevents cytokines and cell–cell interactions between epithelial cells and the underlying stromal keratocytes and bone marrow–derived stromal cells. Wound healing would be very abnormal if there were concurrent epithelial, stromal, and endothelial cell activation. We do not know of any study that evaluated wound healing after surface ablation in the presence of corneal endothelial dysfunction.

We suspect MMC toxicity to the endothelial cells is a factor and that the MMC could have been mixed to a higher concentration than planned. Although there is no way to know this for certain, that a second patient had a similar adverse event the same day suggests a surgery-suite issue rather than patient issue.

The epikeratome may have cut deeper than intended, resulting in invasion of Bowman layer. This would not only predispose the cornea to haze formation but would also increase the possibility that MMC penetrated closer to the endothelial cells. Comparing preoperative and postoperative pachymetry measurements would be again helpful. We can be confident the laser ablated the planned amount of tissue. If the intraoperative residual stromal bed (RSB) or postoperative pachymetry was significantly less than expected (recognizing the cornea has both haze and edema), a thicker-than-expected flap can be inferred. However, it is unlikely the epikeratome would create significantly thicker-than-planned flaps in more than 1 eye, let alone in more than 1 patient. Still, this must be considered.

It is not clear to what extent the patient's current visual acuity is affected by corneal edema or by the density of the stromal haze. Our approach for now would be clinical observation with serial corneal thickness measurements. A mild steroid used once a day might prevent more haze formation. No subconjunctival steroids or other medications would be indicated. If endothelial toxicity were present and severe enough to be irreversible, no improvement in vision would be expected and further visual deterioration would follow. Fortunately, DMEK can be attempted in phakic patients if endothelial cell dysfunction progresses. We must keep in mind that early endothelial transplantation carries better visual outcomes. Postoperative visual acuity inversely correlates with the development of subepithelial haze in corneas with longstanding edema.

There is also a chance that the current visual acuity is now mainly secondary to corneal haze and that the initially observed corneal edema has resolved. If endothelial dysfunction has reversed, observation of the corneal haze for a few months is recommended before a further surface procedure is performed. In this case, prudence is recommended before any surgical approach is attempted.

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■ This is an atypical case of bilateral post epi-LASIK endotheliopathy with corneal dysfunction associated with high IOP and haze, leading to a decrease in visual acuity, photophobia, and pain.

Several factors might be involved in the pathogenesis of this unusual case. In the visits reported, there is no reference to anterior chamber reaction and there is a lack of information on the topical steroid treatment protocol and the RSB. In laser procedures, the blood–aqueous barrier seems to be altered, probably in correlation to the depth of photoablation and the total corneal thickness.[1] In addition, the use of topical steroids can mask ongoing inflammation, including uveitis of unknown cause or caused by herpes simplex virus. Uveitis, no matter the cause, would explain the ECC decrease and high IOP, which contribute to the microcystic epithelial changes and symptoms such as photophobia, pain, and decreased visual acuity. Steroid withdrawal with a rebound effect of inflammation would explain the worsening of the case 6 weeks after surgery.

Because a similar case happened on the same day with the same technique, toxicity from an inadvertently higher MMC concentration must be ruled out. There is evidence that the aqueous concentration of MMC increases in a dose-dependent manner with increasing exposure time and application concentration,[2] potentially damaging the endothelium. However, the toxicity effect is expected to be immediate and the fast epithelial healing and visual acuity recovery in the first 3 weeks postoperatively contradict this hypothesis. Yet, although unlikely, early topical steroid discontinuation may have played a role in a rebound effect of the toxic response.

Individual stromal wound-healing response to epi-LASIK should also be considered. It is well known that after surface ablation the controlled cascade of cytokines is critical for normal healing absent scarring. Interleukin-1 and TGF-β, among other disrupted epithelium-derived cytokines, are known to provoke keratocyte apoptosis and myofibroblast activation, respectively. Myofibroblasts scatter light more intensely than quiescent keratocytes and produce large amounts of disorganized extracellular matrix, playing an important role in corneal haze. There is evidence in an animal model[3] that surface irregularity and an associated defect in the regenerated basement membrane are related to haze development after