Case Report

Central Toxic Keratopathy after Surface Laser Refractive Surgery: a Case Series and Brief Review

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Abstract

Purpose: To describe clinical presentation, management, and outcomes of central toxic keratopathy developing after surface laser refractive surgeries.

Patients and Methods: In this retrospective case series, the records of 10 eyes of 5 patients (1 male, 4 female) were reviewed. The laser refractive surgery consisted of photorefractive surgery (PRK; 2eyes) and laser-assisted subepithelial keratectomy (LASEK; 8 eyes). Mitomycin C, 0.02 % was applied intraoperatively in all eyes.

Results: The mean patient age was 30 ± 14.5 years, (22 to 56 years). Presenting symptom was decreased vision without pain or photophobia in all cases that began 3 to 9 days postoperatively. The slit-lamp examination revealed corneal opacities and corneal thinning in the central area of the cornea corresponding to the ablated zone. There were no corneal epithelial defects or corneal stromal infiltration. Upon presentation, the mean best-corrected distance visual acuity was 20/25 (LogMAR 0.83 ± 0.34). The opacification persisted for a minimum of two months to a maximum of 6 months before clearing. The patients were followed up for 12 months. Five eyes had a decrease of 1 to 2 lines in preoperative best-corrected distance visual acuity 6 months postoperatively. All eyes had hyperopic shift and astigmatism during the follow-up period. The mean spherical equivalent at final follow up was + 0.75 ± 1.15 diopter.

Conclusion: Central toxic keratopathy is a non-inflammatory central corneal opacification which is associated with significant hyperopic shift and stromal tissue loss. Visual prognosis is usually good but a decrease in best-corrected distance visual acuity may persist in some cases.

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Introduction

Central toxic keratopathy (CTK) is described as a rare, self-limited, non-inflammatory postsurgical condition that manifests with central corneal opacity and a significant hyperopic shift [1]. It resembles a number of other eye diseases like post-photorefractive keratectomy (PRK) haze, infectious keratitis, contact lens-induced keratitis, diffuse lamellar keratitis (DLK), and epithelial ingrowth [1].

CTK is very uncommon after surface laser refractive surgery. Central corneal opacification typically develops 3-9 days after refractive surgery, and stromal shrinkage results in significant hyperopic shift. Although striae are a characteristic feature of CTK, the condition can exist in the absence of striae. The findings in CTK typically resolve in 2 to 18 months.

Fraenkel et al., [2] reported the first case series of diffuse lamellar keratitis (DLK) consisting of four eyes with central focal interface opacities that developed within one week after laser in situ keratomileusis (LASIK). They observed a circular opacity located centrally within the LASIK interface, which was associated with stromal folds, variable thinning, and hyperopic shift [2]. Based on clinical response to topical steroids, they suggested that this complication is caused by an inflammatory response and concluded that treatment with steroids allowed stromal regeneration and resolution of the opacification [2]. This theory is not supported by other investigators. Sonmez et al., [3] who described CTK after surface laser ablation argued that this condition is a non-inflammatory opacification that is clinically distinct from DLK.

Here we describe clinical presentation, management, and outcomes of CTK developing after surface laser refractive surgeries.

Patients and Methods

This retrospective case series included 10 eyes from 5 patients (1 male, 4 female), aged between 22 and 56 years old. Ethics committee approval was obtained from the Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. The patients underwent PRK (2 eyes) or laser-assisted subepithelial keratectomy (LASEK) (8 eyes), performed by the same surgeon in three private eye clinics. Mitomycin C, 0.02 % was applied for 20 to 40 seconds in all cases. The duration of MMC application was selected based on the range of myopia.

Routine follow-up examinations were scheduled at days 1, 3, 7 and 9, and then every month for 3 months. Patients had free access to their surgeon in case any complications developed. Since infectious keratitis was the first differential diagnosis, the patients with CTK were examined daily for two weeks. Complete eye examinations including best-corrected distance visual acuity (BCDVA), manifest refraction and slit lamp biomicroscopy were performed at all follow up visits. Time to clearing of the opacification was also recorded.

Results

The patients reported pain and decreased vision 3 to 9 days after surface laser refractive surgery. At the time of presentation, the mean BCDVA was 20/25 (LogMAR 0.83 ± 0.34), ranging from 20/320 (counting finger) to 20/50. Manifest refraction exhibited an average hyperopic shift of + 4.15 ± 1.16 D ranging from + 2.50 D to + 6.50 D immediately after the development of CTK. Slit-lamp examination revealed central corneal opacities and corneal thinning. Topography showed corneal flattening (Figure 1). There was no conjunctival injection or anterior chamber

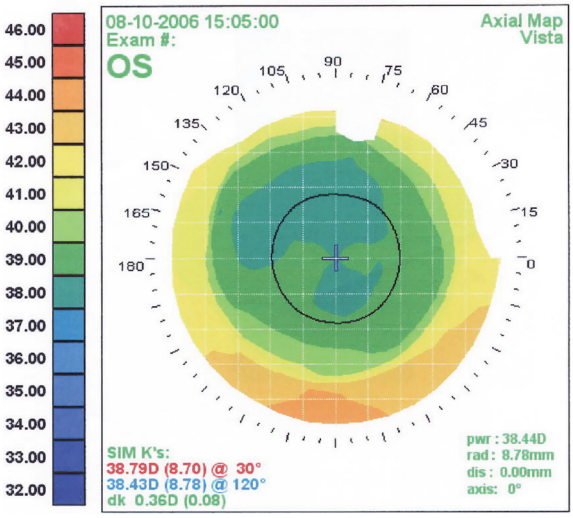

Figure 1: Corneal flattening in topography in a patient with CTK

reaction. The patients received frequent topical corticosteroid, tapered off over 2 months. Mean follow-up period was 14 ± 2 months (range12 to 16 months).

Table 1 presents the patients' data. As shown, the opacification persisted for a minimum of two months to a maximum of 6 months before complete clearing (average 4 months). The mean final BCDVA was 20/20 (LogMAR 0.0 ± 0.66). At 6 months postoperative, all eyes gained a BCDVA of 20/20 except two eyes that showed one and two lines of reduction in final BCDVA. Mean final spherical equivalent refraction and refractive astigmatism were + 0.15 and - 0.67, respectively. All eyes developed significant hyperopia and astigmatism during the follow-up period, which resolved totally in 4 eyes at the final follow up.

Discussion

CTK is described as a clinical syndrome of acute visual impairment after laser corneal refractive surgeries. It has not been reported after enhancement surgeries. It is characterized by non-inflammatory central corneal opacity, stromal shrinkage, and hyperopic shift. The condition generally occurs after laser surface ablation. CTK occurs 3 to 9 days postoperatively and some eyes show visible corneal thinning. There is a hyperopic shift that may be related to corneal thinning and flattening.

The etiology of this entity is unclear. Several hypotheses have been made [1, 2, 3]. Sonmez et al., [3] suggested that CTK is not solely an intrinsic patient response and some external inciting factors are necessary for its development. The fact that CTK always occurs in the area of laser ablation suggests that the ultraviolet laser energy plays some role. The condition may be related to substances that are photo activated by laser treatments [3,4].

These proposed substances include povidone-iodine solutions, meibomian gland secretions, hemoglobin, microkeratome oil, marking-pen materials, carboxymethylcellulose drops, and bacterial endotoxins [5-8]. The presence of unknown materials on bandage contact lenses, used after surgery, is also proposed as a possible etiology. Neira et al., [9] suggested that carefully rinsing the contact lens before fitting may decrease the incidence of CTK. In addition, epithelial defects occurring at the time of surgery can be a trigger [5-8]. The presence of CTK in eyes after PRK suggests it is unrelated to the flap or the microkeratome itself.

There is no consensus on the pathogenesis of CTK. Fraenkel et al., [2] and Parolini et al., [4] proposed that CTK is an inflammatory response and considered it as a form of DLK grade IV. Reporting a larger series of patients who developed CTK, however, Sonmez and Maloney [3] suggested that CTK

Table1: Demographic and clinical data of patients entering the present study who developed central toxic keratopathy after photorefractive keratectomy (PRK), or laser-assisted subepithelial keratectomy (LASEK)

Patient Number	Age	Gender	Eye	Preop RFN(D)	Preop VA	Procedure	Day of onset	Max Hyperopic equivalent	Time to Clear	6 months RFN	Final RFN	Final BSCVA	Final UCVA	Machine
1	22y	Male	OD	- 5.50	20/20	PRK	9	+ 3.0	6	Plano - 2.0 × 10	Plano-1.5 × 10	20/15	20/25	NIDEK
			OS	- 4.5 - 1.0 × 170	20/20	PRK	9	+ 4.0	6	Plano	Plano	20/20	20/20	NIDEK
2	25y	Female	OD	– 4.5 – 0.75 × 5	20/20	LASEK	3	+ 2.50	6	Plano	Plano	20/20	20/20	Allegretto
			OS	– 4.5 - 1.25 × 125	20/20	LASEK	3	+ 3.25	6	+ 1.0 - 0.75 × 15	+ 0.75 - 0.75 × 20	20/20	20/25	Allegretto
3	24y	Female	OD	– 7.0 – 1.0 × 180	20/20	LASEK	3	+ 4.0	5	Plano - 3.5 × 180	Plano - 2.25 × 180	20/25	20/25	Unknown
			OS	– 7.0 – 1.0 × 170	20/20	LASEK	3	+ 3.75	5	+ 2.75 - 2.0 × 165	+ 2.00 - 1.75 × 170	20/25	20/32	Unknown
4	56y	Female	OD	+ 2.5 - 1.0 × 90	20/20	LASEK	4	+ 4.50	4	Plano	Plano	20/20	20/20	Allegretto
			OS	+ 2.5 - 0.75 × 112	20/20	LASEK	4	+ 5.0	4	Plano	Plano	20/20	20/20	Allegretto
5	24y	Female	OD	- 4.50 D	20/20	LASEK	3	+ 6.50	6	+ 1.5 - 1.0 × 180	+ 1.25 - 0.50 × 180	20/20	20/25	Allegretto
			OS	- 6.0 - 1.25 × 180	20/20	LASEK	3	+ 5.0	6	+ 1.25	+ 1.0	20/15	20/20	Allegretto

is not an inflammatory reaction and can be differentiated from diffuse lamellar keratitis (DLK) clinically. The mechanism of corneal thinning and flattening is believed to be due to keratocyte apoptosis or enzymatic degradation. Keratocyte apoptosis can be triggered by abnormal hypersensitive response to substances such as mediators in the tear film. Mud crack appearance striae might appear as some clear refractile lines in the opacified background. Presence of striae suggests the stromal collapse in CTK [3]. Keratocyte apoptosis has also been suggested by confocal scan studies. Scott et al., [10] reported in vivo confocal microscopy in a post LASIK, CTK patient. They observed large areas of hyper reflectivity in the sub-epithelial and bowman layers without any keratocytes or inflammatory cells [10]. Based on these findings they agreed with the hypothesis of keratocytes apoptosis in the acute phase of CTK [10].

Several anterior OCT analyses in patients with CTK have revealed flattening of anterior corneal curvature and thinning of anterior stromal bed, that might induce the hyperopic shift seen in CTK [11]. Serial confocal microscopy has indicated reappearance and regeneration of keratocytes without the aggregation of inflammatory cells, which explains the lack of response to topical steroids [12].

Differential diagnosis of CTK include: diffuse lamellar keratitis (DLK), sub epithelial haziness after PRK and acute infectious keratitis (Table 2). CTK is most often confused with corneal ulcer. Corneal ulcer, however, can be readily differentiated from CTK via recognition of clinical features as well as through careful observation and attention to

onset of clinical findings. Another differential diagnosis is haze formation after PRK. The typical haze after PRK is sub-epithelial and occurs three months postoperatively (Figure 2), whereas in CTK, the opacification lies in the anterior and mid stroma and occurs during the first postoperative week [3,11,13,14] (Figure 3). Also, it is important to distinguish CTK from the sub-epithelial infiltrates syndrome occurring after PRK. Teal et al., [15] first described this syndrome, as sub-epithelial inflammations after PRK in patients using topical non-steroidal anti-inflammatory drugs (NSAID) postoperatively. The opacities are multiple and more peripheral than CTK opacity. None of our patients received topical NSAIDS postoperatively.

CTK is self limited and many authors have described its resolution without any treatment. In the majority of our cases, the opacification resolved over a period of 2 to 6 months and most patients obtained BCDVA of 20/20. Our findings show that corneal curvature and thickness are restored after healing, resulting in the resolution of induced hyperopia. None of our patients required further surgery. The

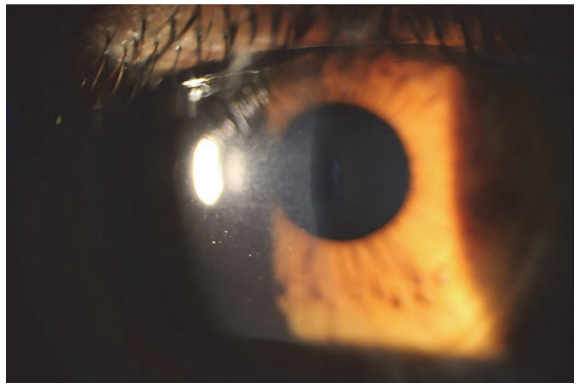

Figure 2: Typical subepithelial haze after PRK

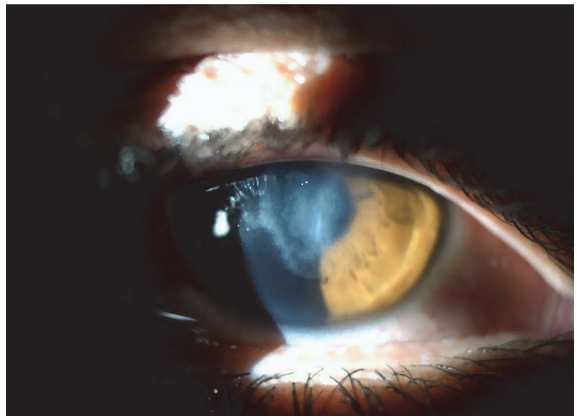

Figure 3: Central toxic keratopathy opacification

Tabel 2: Differential diagnosis of central toxic keratopathy

Finding	CTK	DLK	Post PRK haziness	Acute infectious keratitis
Time of onset	3 to 9	First day	After one month	Within 3 days of surgery
Inflammation	Noninflammatory	Mild to severe	Noninflammatory	Inflammation + AC reaction
Location	Central, may extend to endothelium	Peripheral or cenral	Cental and subepithelial	Peripheral or cenral
Hyperopic shift	Yes	No	No	No
Procedure	LASIK, PRK	LASIK	PRK	LASIK, PRK
Time to resolution	2 to 18 months	One week	Months to years	Weeks

CTK: Central toxic keratopathy; DLK: Diffuse lamellar keratitis; LASIK: Laser-assisted in situ keratomileusis; AC: Anterior chamber

use of steroids in these patients might not improve the clinical outcome [16,17]. However; it can aggravate corneal thinning caused by CTK.

This study had some limitations. We could not report the confocal scan or OCT findings as we had no access to these imaging techniques at the time of the study. In addition, alterations in corneal curvature over time could not be assessed in this study due to lack of access to corneal tomographies including Orbscan and Pentacam.

Conclusion

Central toxic keratopathy is a non-inflammatory central corneal opacification which is associated with significant hyperopic shift and stromal tissue loss. Visual prognosis is usually good, but a decrease in best-corrected distance visual acuity may persist in some cases.

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Footnotes and Financial Disclosures

Conflict of Interest:

The authors have no financial or propriety interest in any of the materials used in this manuscript.