



Very late-onset flap margin corneal ulcer following laser in situ keratomileusis

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Abstract

Purpose To report and characterize cases of very late onset (5 years or more after surgery) flap margin corneal ulcers after laser in situ keratomileusis (LASIK) procedure.

Methods A retrospective case series of consecutive patients who were diagnosed with very late flap margin corneal ulcers following LASIK, between January 2014 and July 2017. All patients were treated with topical antibiotics and were followed up until complete resolution.

Results A total of eight patients, with a mean age of 46.5 ± 11 years, (range 31–64 years), were included in this study. All patients underwent uneventful myopic LASIK 13.3 ± 3 (range 10–20) years before

presentation. Patients best corrected visual acuity (BCVA) at presentation was 0.20 ± 0.15 logMAR compared to a final BCVA of 0.10 ± 0.10 logMAR ($p = 0.28$). The ulcer was located in the bottom two clock hours of the flap margin (5–7 o'clock) in six (75%) patients and superior (11 o'clock) in the remaining two patients ($p = 0.048$). Seven patients (87.5%) suffered from blepharitis, and only one did not.

Conclusions LASIK may be associated with an increased risk of late-onset corneal ulcer occurring years after the procedure. Instability of the flap margin, blepharitis and dry eye are possible causes of epithelial disturbance and may account for this complication.

Keywords LASIK · Corneal ulcer · Late complication · Blepharitis · Dry eye

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Introduction

Laser in situ keratomileusis (LASIK) carries several advantages for refractive surgery correction including the ability to treat a wide range of refractive errors with minimal risk of regression and stromal scarring [1–4]. However, microbial keratitis following LASIK is a rare complication and is associated with several factors including prior corneal surgery [5], epithelial

barrier breaks [6], excessive surgical manipulation, delayed corneal epithelialization postoperatively, intraoperative contamination and use of topical steroids [7, 8]. The rate of infectious keratitis has been reported to be one in one to five thousand cases [9–14] following LASIK and is typically categorized into early onset (2 weeks or earlier) and late onset (2 weeks to 3 months following surgery) [13–15]. Very few cases have been published in the literature about very late-onset flap margin corneal ulcers over 5 years after surgery [16–19].

In this study, we report eight new cases of very late-onset flap margin-related corneal ulcers that developed a decade or more following LASIK.

Methods

The study was in compliance with the tenets of the Declaration of Helsinki. Approval was obtained from the Institutional Review Board (IRB) of the Tel Aviv Medical Center, Israel. This is a retrospective case series of consecutive patients who were diagnosed with very late onset (5 years or more) flap margin corneal ulcers following LASIK, in one tertiary referral center, between January 2014 and July 2017. All patients underwent a complete ophthalmological examination and were treated with topical antibiotics. Collected data included demographics, date of LASIK procedure, complete ocular examination findings, location and size of the corneal ulcer, laboratory workup, corneal scrapings stains and cultures outcomes, topical treatment used and follow-up findings. Dry eye disease workshop criteria that were assessed were tear break-up time < 5 s, central staining and Schirmer < 5 mm [20, 21].

Statistical analysis

Data were recorded in Microsoft Excel (2010)™ and analyzed using SPSS version 23 (SPSS Inc., Armonk, NY, USA). Binary variables were compared between subjects using Fisher's exact test. All tests were two-tailed, and statistical significance was defined as a *p* value of less than 0.05 in a two-sided test.

Results

History of prior LASIK

A total of eight patients (five females and three males) presented to our department with late onset flap margin-related corneal ulcer following LASIK, with a mean age of 46.5 ± 11 years, (range 31–64 years). All patients underwent uneventful myopic LASIK 13.3 ± 3 (range 10–20) years before presentation. All patients denied eye rubbing, contact lens usage or ocular trauma.

Signs and symptoms and presentation

Patients best corrected visual acuity (BCVA) at presentation was 0.20 ± 0.15 logMAR (20/32 Snellen) compared to a final BCVA of 0.10 ± 0.10 logMAR (20/25 Snellen, *p* = 0.28). The left eye was involved in five patients (62.5%). There were no cases of bilateral corneal ulcers or multiple corneal ulcers. Patient complaints included foreign body sensation (*n* = 8), photophobia (*n* = 6) and decreased visual acuity (*n* = 2). The location of the corneal ulcer was in the bottom two clock hours of the flap margin (5–7 o'clock) in six (75%) patients and superior (11 o'clock) in the remaining two patients (*p* = 0.048). The mean area of the corneal ulcer was $0.50 \text{ mm}^2 \pm 0.24 \text{ mm}^2$ at presentation. Seven patients (87.5%) suffered from blepharitis and one did not (Fig. 1a, b). All patients had signs of dry eye disease grade 3 according to the dry eye disease workshop criteria.

Diagnosis and treatment

Scrapings for corneal micro-organism cultures were taken in four patients; three were positive and one negative. Positive cultures included *Staphylococcus epidermidis* (*n* = 2) and *Staphylococcus warneri* (*n* = 1). Four patients (50%) were treated with topical fortified cefazolin and gentamicin, and four were treated with topical moxifloxacin. The mean follow-up time was 8.3 ± 3.0 weeks (range 4–12 weeks) with a topical antibiotic treatment duration of 2.5 ± 0.5 weeks (range 2–3 weeks) and healing time of 1.5 ± 0.5 weeks (range 1–2 weeks). All patients demonstrated complete remission without any need to change or modify initial topical antibiotic treatment. None of the patients were treated with topical

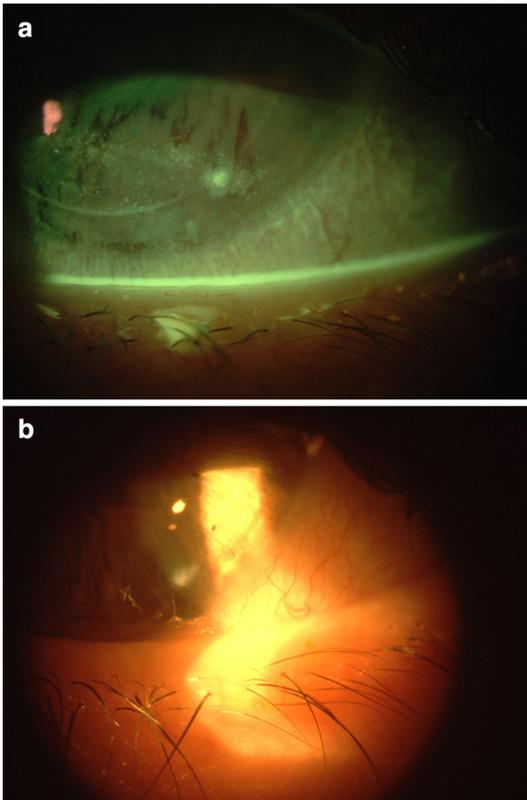


Fig. 1 a, b Patient No. 2—36-year-old woman, 12 years after LASIK procedure. Presented with blepharitis, PEE and corneal ulcer along the flap margins at 5 o'clock

corticosteroids. Table 1 summarizes data of all cases described above.

Discussion

In this study, eight new cases of very late onset flap margin-related corneal ulcers are described. There are a handful of case reports reporting very late-onset flap margin-related corneal ulcers post-LASIK. Varssano et al. [16] reported four patients who developed corneal ulcers more than 5 years after the procedure. Vieira et al. [18] reported two cases that developed 2 and 6 years following LASIK. Their first case presented with a central corneal ulcer 36 h following trauma, while the second case presented with inflammation of the flap interface following the use of contact lenses. Yeung et al. [17] reported a case of spontaneous flap margin-related corneal ulcer 11 years post-LASIK, and Ferrer et al. [19] described

a corneal ulcer at the interface 4 years following LASIK.

In this series of cases, all patients presented with mild visual deterioration and maintained stable vision at their final follow-up. It is possible that this is due to the peripheral location of the corneal ulcers (flap margin) and the relatively small size (mean 0.5 mm^2 , range $0.2\text{--}2.4 \text{ mm}^2$) of the ulcers. In addition, all patients demonstrated excellent response to topical antibiotics without any need to change the type of initial antibiotics during treatment. Unfortunately, corneal scrapings for microorganisms cultures were taken in only four patients and the sample size is too small to make significant statistical conclusions. Short-term post-LASIK keratitis could conceivably be explained by entrance and penetration of pathogens facilitated by the lamellar flap created during LASIK. These pathogens can conceivably cause infection even after the epithelium has healed possibly explaining keratitis occurring within the first few months following surgery. [13–15] However, this theory does not explain very late onset keratitis.

The cohesive tensile strength of the stromal LASIK scar has been reported to be only 2.4% of normal controls (0.7 g/mm compared to 30.1 g/mm) and appears to change only minimally over time [22]. Additionally, the new collagen fibrils in the stromal scar reconnect abnormally with old cut fibrils ends. [23] We speculate that small epithelial breaks at the flap interface may allow for entry of pathogens. Indeed, supporting this theory is the fact that in all of our cases, and most of those previously reported in the literature, the ulcer was located at the flap margin [24–26]. These findings support the theory that instability of the corneal epithelium following LASIK could provide a point of entry for pathogens [18].

The Beaver Dam Eye Study established that 13.3% of individuals developed symptomatic dry eye disease over 5 years and 21.6% over 10 years [27]. Patients with dry eye are likely to have an increased risk for infection owing to several mechanisms such as changes to the composition and quantity of the tear film, possibly decreasing protective tear proteins and causing disruption of the corneal epithelium, thus creating a possible opening for microbial invasion [27–29]. Microbial keratitis incidence ranges between 5 per 100,000 persons in the USA to 799 per 100,000 persons in Nepal with 5–10% attributed to dry eye disease [30–34]. Most of the patients in this study

Table 1 Summary of eight cases of very late-onset LASIK flap margin corneal ulcers

#	Age (years)	Sex	Corneal ulcer onset (years)	Size of ulcer (area) mm	Eye involved	Clock hour location	Blepharitis	Initial BCVA (logMAR)	Final BCVA (logMAR)	Cultured micro-organism	Topical Treatment	FBS	Follow-up duration (weeks)	Treatment duration (weeks)	Recovery time (weeks)
1	57	F	11	0.5 × 0.5 (0.25)	Right	11	+	0.20	0.15	Staph. epidermidis	Fortified	+	12	3	1
2	36	F	12	0.8 × 0.2 (0.16)	Left	5	+	0	0	NA	Moxifloxacin	+	8	3	2
3	64	M	20	0.4 × 0.7 (0.28)	Right	6	+	0.15	0.1	No growth	Fortified	+	8	3	2
4	47	F	14	0.2 × 0.2 (0.04)	Left	11	-	0.1	0.05	NA	Moxifloxacin	+	4	2	1
5	31	M	10	0.3 × 0.6 (0.18)	Left	5	+	0	0	NA	Moxifloxacin	+	4	2	1
6	53	F	14	1.2 × 2.4 (2.88)	Left	7	+	0.3	0.1	Staph. epidermidis	Fortified	+	12	2	2
7	47	M	12	0.2 × 0.5 (0.1)	Left	6	+	0.2	0.2	NA	Moxifloxacin	+	8	2	1
8	37	F	14	0.5 × 0.5 (0.25)	Right	7	+	0.3	0.2	Staph. warneri	Fortified	+	10	3	2

M male, *F* female, *mm* millimeter, *BCVA* best corrected visual acuity, *logMAR* Logarithm of the Minimum Angle of Resolution, *NA* not applicable, *FBS* foreign body sensation; *Staph* staphylococcus

suffered from blepharitis with dry eye symptoms. It is reasonable to think that the combination of these two contributed to instability of the corneal epithelium following LASIK leading to an increased risk of developing a corneal ulcer at the edge of the LASIK flap. Thus, LASIK may have long-term effects on the cornea, rendering it vulnerable to flap margin-related corneal ulcers.

Corneal flaps created with mechanical microkeratomers are reported to be less predictable and reproducible than femtosecond laser flaps [35–37]. This could potentially make a difference in the long-term risk of flap stability. Unfortunately, we could not obtain the LASIK surgery reports of our patients (all surgeries were performed years ago and in different medical centers) and examine the differences.

This study has several limitations; these include the comparably small number of patients, the retrospective design, lack of comprehensive data for all patients and lack of a control group. As such we cannot comment as to whether LASIK has increased the risk of corneal ulcers in this context.

Nevertheless, in the current study, we report the largest case series to date of very late onset flap margin-related corneal ulcers following LASIK. It may be prudent to inform patients, particularly those with blepharitis or dry eye disease, of the risk of very late onset flap margin-related corneal ulcers. Such patients should also be advised to maintain a long-term follow-up, including a strict control of blepharitis and dry eye disease.

Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was waived due to the retrospective nature of this study.

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