Diffuse lamellar keratitis after femtosecond laser refractive lenticule extraction

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We report 6 eyes (spherical refraction from −4.0 to −10.0 diopters) in 4 cases of diffuse lamellar keratitis (DLK) after femtosecond laser refractive lenticule extraction. A refractive lenticule was created using a femtosecond laser and then extracted through a 3.0 mm incision (5 eyes without a flap) and an approximately 20.0 mm incision (1 eye, flap thickness 100 μm). On the first postoperative day, Case 1 developed bilateral DLK (stage 1), Case 2 developed DLK (stage 2) with a small tear at the incision edge, Case 3 developed bilateral DLK (stage 2 in the right eye, stage 1 in the left eye). Case 4 developed late-onset DLK (stage 2) after 5 months. All cases were treated adequately with topical steroids and resolved completely without progression; no visual acuity loss occurred. The DLK may have occurred after refractive lenticule extraction. It is important to diagnose and treat timely and appropriately to avoid vision loss.

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The introduction of femtosecond laser technology has brought innovation to corneal refractive surgery. The femtosecond laser has been used successfully to create laser in situ keratomileusis (LASIK) flaps1,2 and was recently applied to an all-in-one refractive procedure called refractive lenticule extraction.3,4 Refractive lenticule extraction has been safe, predictable, and effective in treating myopia and myopic astigmatism, with few reports of complications.3–5

Diffuse lamellar keratitis (DLK), a relatively common complication after LASIK, is characterized by a noninfectious inflammatory cellular response at the interface, usually within several days of surgery.9–11 Because of the variety of inducing factors and unclear etiology and pathogenesis, the clinical appearance of DLK is not uniform. Most cases are asymptomatic, but more severe or advanced forms can cause symptoms such as blurred vision or pain and lead to stromal melting, interface scarring, and a permanent decrease in visual acuity if treated inadequately.11,12 Given the potential for severe consequences, vigilance and prompt treatment are required. We present what we believe is the first report of DLK after the refractive lenticule extraction procedure.

CASE REPORTS

Between December 1, 2011, and March 31, 2013, DLK developed in 6 eyes of 4 patients who had had refractive lenticule extraction procedures. Refractive lenticule extraction was performed in 2 modalities5: femtosecond lenticule extraction, which involves creating and lifting a hinged flap followed by manual removal of an intrastromal refractive lenticule11–9; and small-incision lenticule extraction, an alternative flapless procedure in which a flap is not made and lifted but the lenticule is separated and removed through a small incision, leaving an interface in the cornea and the upper arcade of the corneal tissue (equivalent to a flap) called a cap.6,7 Diffuse lamellar keratitis was graded clinically according to the staging described previously by Linebarger et al.11: Stage 1, faint white granular infiltrate located in flap periphery; stage 2, white granular infiltrate diffusely distributed in flap interface; stage 3, diffuse white granular infiltrate centrally more confluent and densely clumped, often with
relative peripheral clearing; stage 4, central striae, bullae formation, stromal melting, and permanent scarring. Table 1 presents the clinical characteristics of the 4 cases.

Case 1
A 20-year-old man with myopic astigmatism had uneventful small-incision lenticule extraction in both eyes. On the first postoperative day, he reported mild photophobia and tearing. The uncorrected distance visual acuity (UDVA) was 20/20 in both eyes. A faint infiltrate in the cap periphery was noted in both eyes under slitlamp examination (Figure 1, A). The central cornea was clear, and the infiltrate was confined to the peripheral interface with no anterior or posterior extension (Figure 1, B). Binocular confocal microscopy examination on the third postoperative day showed the epithelium, post-interface stroma, and endothelium were normal; there were no infiltrates in the central cornea. The site of the clinically visible infiltrate was similar in both eyes: Round or oval cells were arranged sparsely among keratocyte nuclei in the pre-interface stroma; some had highly reflective round nuclei, others had less reflective intracellular structures or appeared reflective in total (Figure 2, A). At the interface, clusters and lines of small, highly reflective cells were visible (Figure 2, B). Stage 1 DLK was diagnosed in both eyes. The infiltrate was presumed to be inflammatory but noninfectious so ofloxacin was discontinued after the third postoperative day and fluorometholone 0.1% 8 times a day and tobramycin and dexamethasone ointment were added to the routine therapy.

One week later, there was marked improvement and the infiltrate continued to resolve. Ten days after the extraction, the cornea was clear and the DLK had completely resolved (Figure 1, C). The UDVA was 20/16 and the manifest refraction was plano, providing a corrected distance visual acuity (CDVA) of 20/16 in both eyes.

Case 2
A 29-year-old woman had myopic small-incision lenticule extraction in both eyes. The procedure was performed uneventfully in the right eye, but separating the surfaces of the lenticule tissue from the stroma through a small incision was difficult in the left eye and required more time than usual. A small tear occurred unexpectedly at the incision edge during the manual operation (Figure 3, A). A bandage contact lens was applied after the procedure. On the first postoperative day, the patient reported mild pain, photophobia, blurred vision, and tearing in the left eye; there were no obvious symptoms in the contralateral eye. The UDVA was 20/25 in the left eye and 20/16 in the right eye. Slitlamp examination showed diffuse cellular infiltration in the interface with a superior corneal epithelial defect localized at the edge of the small incision and underlying localized stromal edema in the left eye (Figure 3, B). The highly reflective granular infiltrate in the interface of the cornea could also be visualized from the Scheimpflug image (Figure 3, C). Stage 2 DLK was diagnosed and more instillations of topical steroids (0.1% fluorometholone) together with tobramycin and dexamethasone ointment were added to the routine therapy.

On the third day, the pain and discomfort improved and the interface infiltrate was fading. A progressive regression of the interface inflammation occurred at the following visits; the steroids were slowly tapered over the following 3 weeks. The epithelial defect had healed and the DLK had completely resolved 3 weeks postoperatively (Figure 3, D). At the last resection, the UDVA was 20/16 and the CDVA was 20/12.5 in the left eye; the manifest refraction was +0.25 sphere, as in the right eye.

Case 3
A 23-year-old woman had uneventful myopic small-incision lenticule extraction in both eyes. One day after surgery, the patient presented with a complaint of blurred vision, constant photophobia, pain, and tearing in the right eye, with a UDVA of 20/32; there was mild pain and photophobia in the left eye, with a UDVA of 20/20. Slitlamp examination showed a powdery cellular infiltration of the interface in the right eye, with the typical Sands of Sahara appearance (Figure 4, A). Multiple fine granular collections of inflammation were scattered diffusely throughout the

| Case | Stage | Age (Y) | Sex | Eye Procedure | Pre-op CDVA (Refraction) | Post-op Day of DLK Onset (UDVA) | Symptoms | Time for DLK Resolution | UDVA (CDVA Refraction) at Resolution |
|------|-------|---------|-----|---------------|--------------------------|-------------------------------|----------|------------------------|----------------------------------|
| 1    | 1     | 20/M    | R   | SMILE         | 20/16 (−6.25 − 0.5 × 5) | 1 day (20/20)                 | Photophobia, tearing           | 10 days | 20/16 (20/16 plano)   |
| 1    | 1     | 20/M    | L   | SMILE         | 20/16 (−6.25 − 0.75 × 175) | 1 day (20/20)                 | Photophobia, tearing           | 10 days | 20/16 (20/16 plano)  |
| 2    | 2     | 29/F    | L   | SMILE         | 20/20 (−4.0 × 120) DS    | 1 day (20/25)                 | Pain, photophobia, blurred vision, tearing | 3 weeks | 20/16 (20/12.5 + 0.25) |
| 3    | 2     | 23/F    | R   | SMILE         | 20/20 (−4.0 − 0.5 × 175) | 1 day (20/32)                 | Blurred vision, photophobia, pain, tearing | 20 days | 20/20 (20/16 + 0.25 DS) |
| 3    | 1     | 23/F    | L   | SMILE         | 20/16 (−3.5 − 1.0 × 10)  | 1 day (20/20)                 | Photophobia, pain              | 1 week  | 20/16 (20/16 − 0.25) |
| 4    | 2     | 58/M    | L   | FLEX          | 20/25 (−10.25 − 0.5 × 90) | 5 months (20/32)              | Blurred vision                  | 2 weeks | 20/30 (20/25 − 0.25 × 180) |

UDVA = uncorrected distance visual acuity; CDVA = corrected distance visual acuity; FLEX = femtosecond lenticule extraction; SMILE = small-incision lenticule extraction; DLK = dissecting lamellar keratitis.
interface, without extending beyond the edge of the cap (Figure 4, B). The infiltration was confined to the interface and did not spread into the cap or extend into the stromal bed (Figure 4, C). The cellular infiltration in the left eye was faint. Anterior segment Fourier-domain optical coherence tomography (OCT) images showed a highly reflective structure on the interface partly due to the cellular infiltration (Figure 5, A), which was also confirmed by the Scheimpflug image in the right eye (Figure 5, B). On the third postoperative day, confocal microscopy showed singular mononuclear cells in the anterior stroma in the right eye (Figure 6, A). A large amount of a reflective granular substance was detectable in the interface, and conspicuous spindle-shaped structures were also detected adjacent to the infiltrate (Figure 6, B). Diffuse lamellar keratitis stage 2 was diagnosed in the right eye and stage 1 in the left eye. Instillations of fluorometholone 0.1% were prescribed every 2 hours, and tobramycin and dexamethasone ointment at bedtime were added to the routine therapy.

After 1 week, the subjective symptoms had improved. The UDVA in the left eye improved to 20/16 with complete DLK resolution. The manifest refraction was −0.25 −0.25 × 170 with a CDVA of 20/16. The fluorometholone was tapered slowly over the following 2 weeks. At 20 days, the interface in the right eye was clear and the UDVA was 20/20. The manifest refraction was +0.25 diopter sphere with a CDVA of 20/16.

Case 4

A 58-year-old man who had had uneventful femtosecond lenticule extraction in the left eye 5 months earlier returned to our clinic complaining of a 1-week history of blurred vision. No traumatic or infectious event was reported. The UDVA and CDVA in the left eye was 20/32 and 20/30, respectively. The intraocular pressure was normal. The slitlamp examination showed a diffuse fine granular infiltrate confined to the paracentral flap interface involving the visual axis as well as a mild conjunctival injection (Figure 7, A). No epithelial defect of the cornea or inflammation in the anterior chamber was observed. Corneal topography with Scheimpflug imaging showed a smooth and regular corneal surface.

Figure 1. Slitlamp photograph of Case 1. A: Faint infiltrate in the cap periphery was noted on the first postoperative day. B: Central cornea was clear and the infiltrate was confined to the peripheral interface on the first day. C: Cornea was clear and DLK completely resolved on day 10.

Figure 2. Confocal microscopy photograph of Case 1 on the third postoperative day. A: Round or oval cells were arranged sparsely among keratocyte nuclei in the preinterface stroma. Some cells had highly reflective round nuclei, others had less reflective intracellular structures or appeared reflective in total. B: Clusters and lines of small, highly reflective cells were visible at the interface.
without signs of postoperative abnormality (Figure 7, B). Fourier-domain OCT showed a uniform flap well attached to the stromal bed, with minimal interface reflection and no interface fluid in that eye (Figure 7, C). Other ophthalmic examinations were unremarkable. Corneal and conjunctival microbiology cultures were negative. Late-onset DLK (stage 2) was diagnosed, and the patient was treated topically with instillations of fluorometholone 0.1% every 2 hours, 4 instillations of levofloxacin 0.5%, and artificial tears each day, with tobramycin and dexamethasone ointment at bedtime.

Two weeks after treatment, the granular infiltrate in the flap interface had almost disappeared, subjective visual complaints completely resolved, and the CDVA improved to 20/25. Topical medication was gradually tapered over the next 2 weeks. The DLK did not recur during the 1-year follow-up.
DISCUSSION

Femtosecond laser-assisted LASIK flap creation has been reported to have a higher risk for DLK than microkeratome flap creation.\textsuperscript{13,14} With the advent of all-in-one femtosecond-laser refractive surgery, the occurrence of DLK after refractive lenticule extraction should also be noted. To our knowledge, these are the first cases of DLK after refractive lenticule extraction to be reported.

According to previous descriptions,\textsuperscript{9,11,15} the natural course of DLK is variable and the intensity of the infiltrates can differ. In our cases, the infiltrates were mild, between stage 1 and stage 2. This is most likely because of the new generation Visumax FS laser (Carl Zeiss Meditec AG) that we used, with higher pulse frequency and lower pulse energy applied in refractive lenticule extraction procedures. Previous studies have demonstrated that high laser energy levels with the ensuing photodisruption-induced tissue injury and accumulation of gas bubbles can lead to an increased cellular inflammatory response and DLK.\textsuperscript{13-16} Riau et al.\textsuperscript{17} suggested that refractive lenticule extraction stimulated a lower degree of inflammation than excimer laser treatment in LASIK by releasing fewer cytokines and chemokines, which recruit the inflammatory cells to the injury site. This may also contribute to the phenomenon.

The etiology of DLK is unclear. It has been associated with numerous factors such as bacterial endotoxins, chemicals or debris, surgical gloves, meibomian gland secretions, peripheral immune infiltrates, atopy, and epithelial defects.\textsuperscript{11,15,18} In Case 2, a small tear occurred unexpectedly at the incision edge during manual separation. Accordingly, we suspected that the incomplete cap integrity and iatrogenic epithelial defect might allow more diffusion of inflammatory mediators from the tear film or might alter the permeability of the limbal vasculature, which led to an accumulation of inflammatory cells at the interface, resulting in onset of DLK on postoperative day 1. Although the inducing factors in Case 1 and Case 3 were not apparent, the intraoperative irrigation without lifting the flap during the small-incision lenticule extraction procedure was presumed to be incomplete and a possible cause. Although numerous etiologies contribute to the occurrence of DLK in the early postoperative period, cases have also been reported in the late postoperative period.\textsuperscript{19,20} Case 4 was a late-onset DLK, occurring 5 months after the femtosecond lenticule extraction procedure. Although the inciting agent was unclear, we assumed that the patient’s older age, with more meibomian gland secretions, or an allergic reaction might be the contributor.

Fortunately, DLK was diagnosed in a timely fashion in all 4 cases and treated adequately with topical steroids; no case progressed to the advanced stages of DLK. This was based on the clinical appearance and therapy guidelines relative to the intensity of the inflammation.\textsuperscript{11} From our experience, careful slitlamp examination on the first postoperative day is crucial in identifying DLK after refractive lenticule extraction, as the cellular reaction presented within the first 24 hours (Cases 1 to 3), similar to post LASIK.\textsuperscript{11} Other ophthalmic examinations such as confocal microscopy,\textsuperscript{21}
anterior segment OCT examination, corneal topography, and microbiology cultures might confirm the diagnosis. Our DLK cases were treatable with intensive topical steroids, and there was little impact on the visual acuity due to the prompt treatment. Both eyes of Case 1 and the left eye of Case 3 with stage 1 represented mild inflammation and resolved completely after 10 days and 1 week, respectively. Case 2 and Case 4, as well as the right eye of Case 3 with stage 2, required no more than 3 weeks for resolution with little sequelae. All cases with DLK achieved a CDVA of 20/25 or better at resolution time. No CDVA was lost.

In summary, this report indicated that DLK after the refractive lenticule extraction procedure may be possible and it is important to diagnose and treat it in a timely and appropriate way to prevent vision loss. Early postoperative slitlamp examination is mandatory, and long-term follow-up after this surgery should not be ignored.

REFERENCES

1. Salomao MQ, Wilson SE. Femtosecond laser in laser in situ keratomileusis. J Cataract Refract Surg 2010; 36:1024–1032
2. Lubatschowski H. Overview of commercially available femtosecond lasers in refractive surgery. J Refract Surg 2008; 24:S102–S107
3. Blum M, Kunert K, Schröder M, Sekundo W. Femtosecond lenticule extraction for the correction of myopia: preliminary 6-month results. Graefes Arch Clin Exp Ophthalmol 2010; 248:1019–1027
4. Sekundo W, Kunert K, Russmann C, Gille A, Bissmann W, Stobrawa G, Sticker M, Bischoff M, Blum M. First efficacy and safety study of femtosecond lenticule extraction for the correction of myopia: six-month results. J Cataract Refract Surg 2008; 34:1513–1520; erratum, 1819
5. Blum M, Sekundo W. Femtosekunden-Lentikel-Extraktion (FLEEx) [Femtosecond lenticule extraction (FLEEx)]. Ophthalmologie 2010; 107:967–970
6. Sekundo W, Kunert KS, Blum M. Small incision corneal refractive surgery using the small incision lenticule extraction (SMILE) procedure for the correction of myopia and myopic astigmatism: results of a 6 month prospective study. Br J Ophthalmol 2011; 95:335–339
7. Shah R, Shah S, Sengupta S. Results of small incision lenticule extraction: all-in-one femtosecond laser refractive surgery. J Cataract Refract Surg 2011; 37:127–137
8. Shah R, Shah S. Effect of scanning patterns on the results of femtosecond laser lenticule extraction refractive surgery. J Cataract Refract Surg 2011; 37:1636–1647
9. Smith RJ, Maloney RK. Diffuse lamellar keratitis; a new syndrome in lamellar refractive surgery. Ophthalmology 1998; 105:1721–1726
10. Lin RT, Maloney RK. Flap complications associated with lamellar refractive surgery. Am J Ophthalmol 1999; 127:129–136
11. Linebarger EJ, Hardten DR, Lindstrom RL. Diffuse lamellar keratitis: diagnosis and management. J Cataract Refract Surg 2000; 26:1072–1077
12. Parolini B, Marcon G, Panozzo GA. Central necrotic lamellar inflammation after laser in situ keratomileusis. J Refract Surg 2001; 17:110–112

13. Gil-Cazorla R, Teus MA, de Benito-Llopis L, Fuentes I. Incidence of diffuse lamellar keratitis after laser in situ keratomileusis associated with the IntraLase 15 kHz femtosecond laser and Moria M2 microkeratome. J Cataract Refract Surg 2008; 34:28–31

14. Moshirfar M, Gardiner JP, Schliesser JA, Espandar L, Feiz V, Mifflin MD, Chang JC. Laser in situ keratomileusis flap complications using mechanical microkeratome versus femtosecond laser: retrospective comparison. J Cataract Refract Surg 2010; 36:1925–1933

15. de Paula FH, Khairallah CG, Niziol LM, Musch DC, Shtein RM. Diffuse lamellar keratitis after laser in situ keratomileusis with femtosecond laser flap creation. J Cataract Refract Surg 2012; 38:1014–1019

16. Binder PS. One thousand consecutive IntraLase laser in situ keratomileusis flaps. J Cataract Refract Surg 2006; 32:962–969

17. Riau AK, Angunawela RI, Chaurasia SS, Lee WS, Tan DT, Mehta JS. Early corneal wound healing and inflammatory responses after refractive lenticule extraction (ReLEx). Invest Ophthalmol Vis Sci 2011; 52:6213–6221. Available at: http://www.iovs.org/content/52/9/6213.full.pdf. Accessed May 16, 2013

18. Choe CH, Guss C, Musch DC, Niziol LM, Shtein RM. Incidence of diffuse lamellar keratitis after LASIK with 15 KHz, 30 KHz, and 60 KHz femtosecond laser flap creation. J Cataract Refract Surg 2010; 36:1912–1918

19. Kamiya K, Ikeda T, Aizawa D, Shimizu K. A case of late-onset diffuse lamellar keratitis 12 years after laser in situ keratomileusis [letter]. Jpn J Ophthalmol 2010; 54:163–164

20. Iovieno A, Amiran MD, Légaré ME, Slomovic AR. Diffuse lamellar keratitis 8 years after LASIK caused by corneal epithelial defect. J Cataract Refract Surg 2011; 37:418–419

21. Bühren J, Baumeister M, Cichocki M, Kohnen T. Confocal microscopic characteristics of stage of 1 to 4 diffuse lamellar keratitis after laser in situ keratomileusis. J Cataract Refract Surg 2002; 28:1390–1399