

## Late-onset Diffuse Lamellar Keratitis

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**Background:** Diffuse lamellar keratitis (DLK) is marked by the presence of diffuse or multifocal infiltrates confined to the laser in situ keratomileusis (LASIK) interface. These infiltrates are culture-negative, and the etiology is thought to be noninfectious. Most cases of DLK occur within the first week or 2 following surgery.

**Cases:** We described 2 cases of DLK that occurred 3 months after LASIK. These patients were treated with intensive topical corticosteroids.

**Results:** Treatment with topical corticosteroid was instituted, with rapid improvement in patient symptoms, visual acuity, and slit-lamp biomicroscopic findings.

**Conclusion:** DLK may occur as late as 3 months after LASIK. **Jpn J Ophthalmol 2003;47:463–468** © 2003 Japanese Ophthalmological Society

**Key Words:** Diffuse lamellar keratitis, dry eye, laser in situ keratomileusis, meibomian gland dysfunction, Schirmer test.

### Introduction

Diffuse lamellar keratitis (DLK) is an early postoperative complication of laser in situ keratomileusis (LASIK), where a diffuse, white, progressive, and infiltrative opacity develops between the corneal flap and bed 1 or 2 days after surgery. It has been reported that the opacity disappears spontaneously within 1 or 2 weeks after the onset.<sup>1–3</sup> We report 2 cases of DLK, which developed in the third month after LASIK, with a brief review of the literature.

To the best of our knowledge, delayed DLK has never been reported in Japan.

### Case Reports

- Case 1: a 50-year-old female patient
- Chief complaint: Myopia to be surgically corrected

- First visit: May 16, 2000
- Past history and family history: nothing remarkable

Ophthalmological findings on the first visit: The visual acuity was 0.05 ( $1.2 \times -4.5$  D = cyl  $-3.00$  DA  $5^\circ$ ) in the right eye and 0.06 ( $1.2 \times -6.50$  D = cyl  $-0.75$  DA  $175^\circ$ ) in the left eye. No abnormalities were noted in the anterior ocular segment, optic media, or fundus of either eye. The corneal thickness (in the center) was  $510 \mu\text{m}$  in the right eye and  $525 \mu\text{m}$  in the left eye. The corneal endothelial cell density was  $2808 \text{ cells}/\text{mm}^2$  in the right eye and  $2976 \text{ cells}/\text{mm}^2$  in the left eye. The Schirmer test (modified type I) showed 6 mm and 10 mm of strip wetting in the right and left eyes, respectively. The tear-film breakup time (BUT) was 4 seconds in the right eye and 6 seconds in the left eye.

Surgical procedures: LASIK was performed in both eyes on June 22, 2000. The previously reported procedures were used.<sup>4,5</sup> As for the preoperative treatment, local application of oxytetracycline hydrochloride + polymyxin B sulfate (Terramycin) ointment once daily before sleep for 2 days before surgery was prescribed. On the day of surgery, the eyelid skin and conjunctiva

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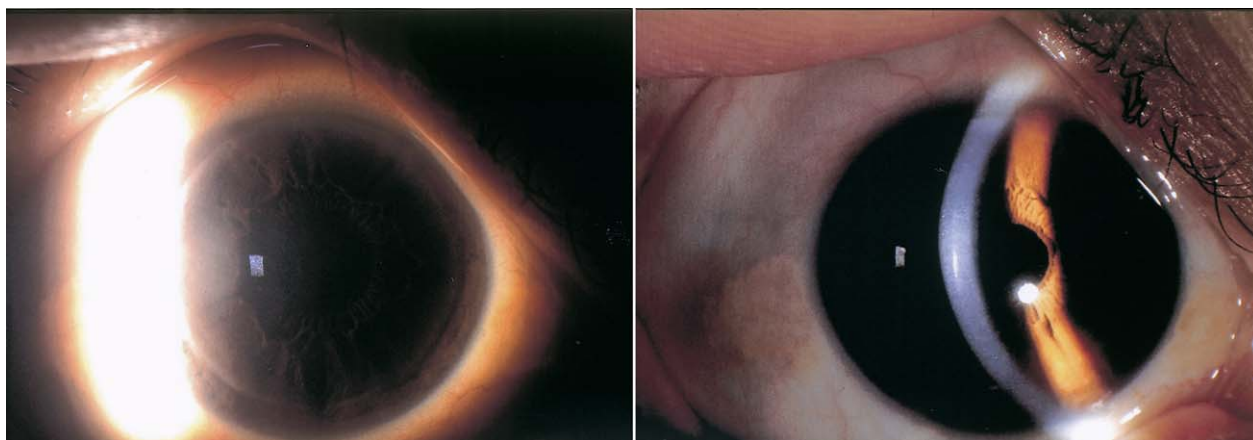
were washed with diluted povidone iodine (Isodine) and balanced salt solution (BSS) for disinfection after topical anesthesia with oxybuprocain hydrochloride (Benoxil). Eye drops of oxybuprocain hydrochloride (Minimus) were additionally instilled just before surgery.

Surgery was performed using a Moria LSK-ONE microkeratome (vacuum-ring: +2, stop-ring: 7.75 mm) with an aspiration time of 21 seconds in the right eye and 16 seconds in the left eye. A new blade was used in each eye. The microkeratome was sterilized in chlorhexidine gluconate (Hibiten) for 5 minutes and washed with distilled water. An excimer laser system (Smooth Scan S2; VisX, Sunnyvale, CA, USA) was used to obtain emmetropia with the spherical correction of  $-3.74$  D, astigmatic correction of  $-2.50$  D and axial correction of  $5^\circ$  in the right eye, and the spherical correction of  $-5.34$  D in the left eye. Surgery was first performed in the right eye and then in the left eye. The patient wore protective glasses after surgery. The visual acuity was measured 30 minutes after surgery. The postoperative condition of the corneal flap, intralamellar space and corneal bed was examined under a slit-lamp microscope. Abnormal findings, such as malpositioning of the flap, intralamellar foreign body and intralamellar hemorrhage, were not noted.

As for the postoperative treatment, instillation four times daily of eye drops, erythromycin lactobionate (Ecolicin), fluorometholone (0.1% Flumetholon), and diclofenac sodium (Diclod), was prescribed. Postoperative examination was scheduled 1 day, 1 week, 2 weeks, 1 month, and 2 months after surgery.

Postoperative course: The visual acuity 1 month after surgery was 0.8 ( $1.2 \times -0.25$  D = cyl  $-0.50$  DA  $100^\circ$ ) in the right eye and 1.5 (noncorrigunt) in the left eye. Ophthalmologic examination 2 months after surgery revealed no abnormal findings. However, the patient returned to our clinic on September 14, 2000 (12 weeks after surgery) complaining of foreign-body sensation, lacrimation, and decreased vision in the right eye. The visual acuity was 0.4 ( $1.2 \times -0.25$  D = cyl  $-3.50$  DA  $180^\circ$ ) in the right eye. Slit-lamp microscopy showed mild white opacity, with cellular infiltration in the intralamellar space including an edge of the corneal flap, and parenchymal edema in the flap and bed (Figures 1A and 1B). Based on these findings, a diagnosis of DLK at stage 2 was made. Instillation of eye drops of fluorometholone (0.1% Flumetholon) once an hour was prescribed. Considering the possibility of bacterial infection, instillation four times daily of levofloxacin (Cravit) eye drops also was prescribed. On November 1, the visual acuity improved to 0.7 ( $1.5 \times -1.50$  D = cyl  $-2.00$  DA  $180^\circ$ ) in the right eye. On January 17, 2001, the corneal opacity disappeared and the visual acuity improved to 0.2 ( $1.2 \times -1.00$  D = cyl  $-2.00$  DA  $180^\circ$ ) in the right eye, and the patient had no complaints. The left eye had no abnormalities throughout the postoperative course.

On April 13, 2001, photorefractive keratectomy (PRK) was performed to enhance the stability of the improved visual acuity and refraction. Eye drops of erythromycin lactobionate (Ecolicin), fluorometholone (0.1% Flumetholon), and diclofenac sodium (Diclod) were prescribed at four times a day for 3 months after the enhancement



**Figure 1.** Case 1: A 50-year-old woman in whom unilateral diffuse lamellar keratitis developed in the third month after laser in situ keratomileusis. An opacity at stage 2 and edema in the corneal flap are observed in the anterior ocular segment. Epithelial erosion and inflammation were not seen.

surgery. The visual acuity was 1.5 (noncorrigent) in the right eye and no abnormalities were noted 5 months after the enhancement surgery (Figure 2).

- Case 2: A 64-year-old male patient
- Chief complaint: Decreased vision in the left eye
- First visit: November 17, 2000

Ophthalmological findings on the first visit: The visual acuity was 0.02 ( $1.2 \times -7.25$  D) in the right eye and 0.01 ( $0.5$  P  $\times -16.0$  D) in the left eye. Nuclear cataract was noted in the left eye. The fundus in both eyes exhibited myopic changes. No marked difference was noted in the axial length between 26.0 mm in the right eye and 26.5 mm in the left eye. Cataract surgery was performed on January 11, 2001. The postoperative course was uneventful. The patient wanted to have his myopia corrected by surgery. On May 18, 2001, the visual acuity was 0.02 ( $1.2 \times -7.25$  D) in the right eye and 0.2 ( $1.2 \times -2.75$  D = cyl  $-1.00$  DA  $85^\circ$ ) in the left eye. The corneal thickness (in the center) was 567  $\mu$ m in the right eye and 564  $\mu$ m in the left eye. The corneal endothelial cell density was 3125 cells/mm<sup>2</sup> in the right eye and 2832 cells/mm<sup>2</sup> in the left eye. The Schirmer test (modified type I) showed 4 mm and 3 mm of strip wetting in the right and left eyes, respectively.

Surgical procedures: LASIK was performed in both eyes on May 18, 2001. Eye drops of levofloxacin (Cravit) were instilled the day before surgery. Disinfection of the eyelid skin and conjunctiva was performed in the same way as described for case 1. Surgery was performed

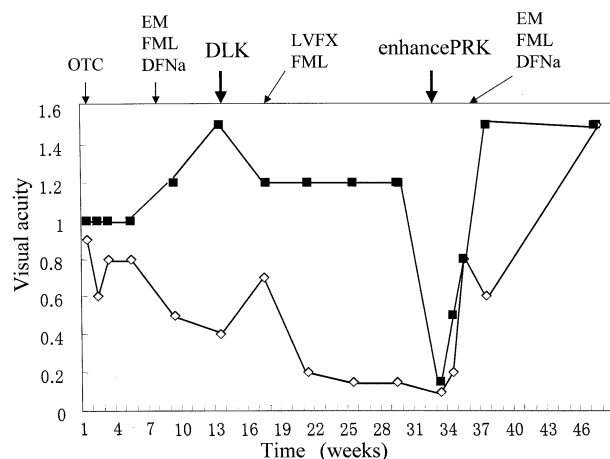


Figure 2. Case 1. Changes in the vision of the right eye. ■: corrected vision, □: uncorrected vision. OTC: oxytetracycline hydrochloride + polymyxin B sulfate (Terramycin), EM: eye drops of erythromycin lactobionate (Ecolicin), FML: eye drops of fluorometholone (0.1% Flumetholon), DFNa: eye drops of diclofenac (Diclod), LVFX: eye drops of levofloxacin (Cravit).

using the Moria LSK-ONE microkeratome (vacuum-ring: +2, stop-ring: 7.75 mm) with an aspiration time of 10 seconds in the right eye and 15 seconds in the left eye. A new blade was used in each eye. The microkeratome was sterilized in the same way as described for case 1. An excimer laser system (Tecknolas 217z; Bausch & Lomb, Rochester, NY, USA) was used with the correction of  $-6.75$  D in the right eye and  $-3.38$  D in the left eye. Surgery was successfully performed in the right eye first, and then in the left eye.

Postoperative course: The visual acuity 1 month after surgery was 0.5 ( $1.5 \times -2.00$  D = cyl  $-0.25$  DA  $150^\circ$ ) in the right eye and 1.0 ( $1.5 \times -0.25$  D = cyl  $-1.25$  DA  $25^\circ$ ) in the left eye. On July 24, the patient returned to our clinic complaining of haze in the left eye. The visual acuity on that day was 0.5 ( $1.2 \times -2.25$  D = cyl  $-0.25$  DA  $160^\circ$ ) in the right eye and 0.4 ( $0.6 \times -0.75$  D = cyl  $-0.5$  DA  $110^\circ$ ) in the left eye. Slit-lamp microscopy showed a white opacity with cellular infiltration in the intralamellar space corresponding to the laser irradiation site and parenchymal edema in the flap and bed (Figure 3). These findings suggested the corneal opacity was at stage 3. Oral prednisolone (Predonin) at a dose of 30 mg/day for 3 days was prescribed, and eye drops of betamethasone sodium phosphate (Rinderon) once an hour were also prescribed. Eye drops of levofloxacin (Cravit) were also to be instilled four times daily. The subepithelial opacity was still observed with the visual acuity of 0.3 ( $0.7 \times -1.75$  D = cyl  $-1.25$  DA  $70^\circ$ ) on July 26. The space under the corneal flap was washed with BSS and

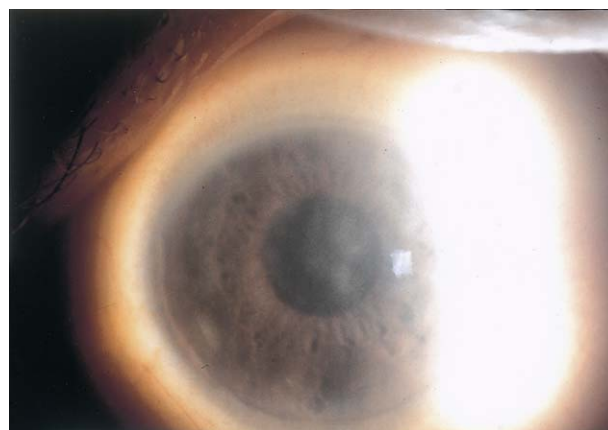


Figure 3. Case 2: A 64-year-old male patient who developed diffuse lamellar keratitis unilaterally after laser in situ keratomileusis (LASIK). Microscopic photography of the anterior ocular segment in the left eye 3 months after LASIK. An opacity at stage 3 extending to the pupillary area and edema in the corneal flap are observed. Epithelial erosion is not seen. Transparency of the anterior ocular segment is poor.

a sample for bacterial culture was taken. It was negative. Subconjunctival injection of betamethasone sodium phosphate (Rinderon) was performed. Eye drops of betamethasone sodium phosphate (Rinderon) once an hour and levofloxacin (Cravit) four times daily were continued at decreasing frequencies with the improvement of the corneal opacity. The visual acuity in the left eye improved to 0.1 ( $1.0 \times \text{cyl } -3.00 \text{ DA } 20^\circ$ ) 5 days after the flap washing procedure. The subepithelial opacity markedly decreased with the disappearance of symptoms. The visual acuity was 0.8 ( $1.2 -0.50 \text{ D} = \text{cyl } -1.25 \text{ DA } 20^\circ$ ) in the right eye 1 month after the flap washing procedure (Figure 4). The right eye had no abnormalities throughout the postoperative course (Figure 5).

## Discussion

Recently, various surgical procedures for correcting refractive errors have been developed and applied to a large number of clinical cases. Compared with PRK, LASIK has the advantage that postoperative corneal opacities are rarely encountered because of the preservation of Bowman's membrane, although the surgical procedure of LASIK is more complicated. It has been reported that LASIK can be indicated for severe myopia with tolerable pain after surgery and early recovery of the visual acuity.<sup>5-8</sup> Among LASIK-specific complications, DLK has been attracting attention since it was first reported by Smith and Maloney in 1998.<sup>3</sup>

DLK is an early postoperative complication of LASIK presenting with decreased vision, redness and pain in the

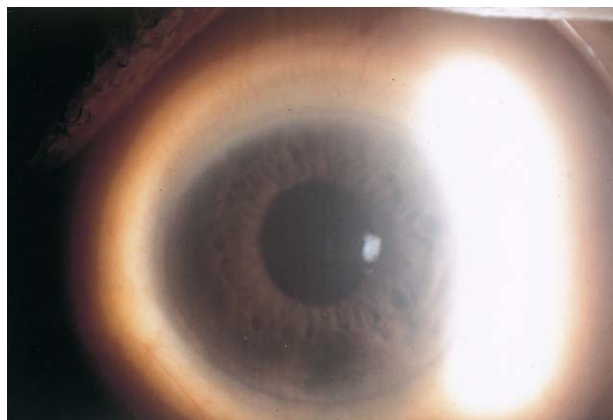


Figure 4. Case 2. Microscopic photography of the anterior ocular segment in the left eye 1 month after corneal lavage. The opacity at stage 3 extending to the pupillary area and edema in the corneal flap have disappeared with recovery of visual acuity.

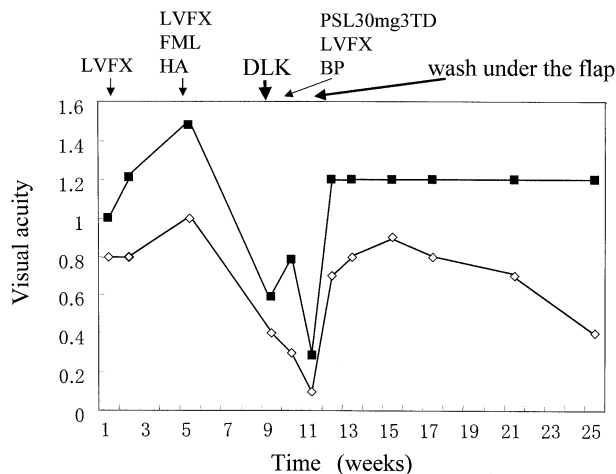


Figure 5. Case 2. Changes in vision of the left eye. ■: corrected vision, □: uncorrected vision. LVFX: eye drops of levofloxacin (Cravit), FML: eye drops of fluorometholone (0.1% Flumetholon), HA: eye drops of hyaluronate (Hyalein), BP: eye drops of betamethasone sodium phosphate (Rinderon), PSL: oral administration of prednisolone (Predonin).

operated eye, which usually occurs within 1 week after surgery.<sup>1-3</sup> Inflammation between the corneal flap and bed, which is considered to be responsible for the complication, is caused by intralamellar foreign bodies, such as keratome oil, airborne dust, powder on surgical gloves, metallic debris, and bacteria of normal flora in the meibomian gland.<sup>8-10</sup> Allergic response, rather than inflammation, can be a causal factor of DLK.<sup>1-3,8-10</sup> Peters et al<sup>11</sup> reported that DLK could be classified into either the sporadic type or the epidemic type, based on the clinical features. They speculated that epidemic DLK was caused by endotoxin of Gram-negative rods. However, the etiology of DLK remains unclear.<sup>12,13</sup>

Cases of delayed DLK after LASIK<sup>14-16</sup> have been reported in Europe and America. However, delayed DLK has not been reported in Japan. Seven of the 9 reported cases of delayed DLK<sup>14-16</sup> included the 6 male cases in the series reported by Weldon and Edward<sup>16</sup> In our experience, they were 1 male and 1 female patient.

DLK occurred 3 months after LASIK in our 2 patients. The interval between the onset of delayed DLK and surgery ranged between 2 and 12 months (mean = 5.9 months) in the previously reported cases.<sup>14-16</sup>

It has been reported that delayed DLK is often associated with epithelial erosion.<sup>16</sup> Epithelial erosion is considered to enhance the spread of inflammatory substances from the tear film to the cornea, resulting in the development of DLK.<sup>16</sup> The 2 cases of DLK that we are reporting developed in the third month after surgery. Epithelial erosion was not noted in either case. The development of DLK could have been anticipated if intralamellar foreign

bodies had been found during or early after surgery. No abnormal findings were noted in the corneal epithelium or flap interface in our patients after surgery.

Various factors may participate in the development of delayed DLK. In the present 2 cases, eye drops were instilled in the same way as in other cases undergoing LASIK at our institution. Surgery was performed uneventfully. No abnormal findings suggestive of ocular inflammation were noted 1–2 weeks after surgery, the most likely period for DLK to develop. In case 2, bacterial culture was negative in the space under the flap after lavage. The negative result of the bacterial culture is an important finding to differentiate DLK from delayed inflammation. Postoperative inflammation is characterized by topical parenchymal liquefaction, irregular astigmatism, and decentration. In the present cases, findings by slit-lamp microscopy also supported the diagnosis of DLK.

The present 2 cases had the following two characteristics. (1) The patients were aged over 50 years. The mean age of patients who underwent LASIK at our institution was 34 years. The mean age of the 9 previously reported cases of delayed DLK<sup>14–16</sup> was 46.8 years. Therefore, special attention should be paid to the development of DLK in patients undergoing LASIK who are middle-aged or older. (2) The Schirmer test (modified type I) showed lacrimal hypofunction in both our cases. Abnormal results of the Schirmer test and BUT suggested the presence of mild dry eye in case 1, where DLK developed in the right eye with more severe lacrimal hypofunction. In case 2, the patient also had dry eye based on the results of the Schirmer test, which showed <5 mm of strip wetting. No corneal damage was noted throughout the clinical course of each case. However, a strong correlation has been reported between dry eye and hypofunction of the meibomian gland.<sup>17</sup> Hypofunction of the meibomian gland with aging was also reported.<sup>18</sup> Another report<sup>19</sup> suggested that the secretion of the meibomian gland played an important role in the development of DLK. The meibomian gland function should be evaluated preoperatively in elderly patients with dry eye. Attention should be paid to delayed DLK in patients with poor results in the Schirmer test, even if they have no corneal damage.

LASIK was performed to obtain emmetropia in the present 2 cases. Visual regression with astigmatism has been noted in eyes developing DLK. In case 1, enhanced PRK was performed to obtain good vision. It has been reported that haze and regression are often encountered after PRK following LASIK.<sup>20</sup> The correction rate is larger in patients with postoperative haze than in those without this complication. Considering the high risk of re-lifting the corneal flap, we performed PRK because

the correction was small in case 1. However, we have encountered cases of severe opacity developing after PRK in eyes with history of refractive surgery, such as radial keratotomy (RK) and PRK.<sup>21</sup> Careful follow-up should be performed after additional PRK. Enhancement surgery was not scheduled in case 2 because the patient was satisfied with his near vision.

Fortunately, the visual prognosis was good in the present 2 cases because of the effectiveness of steroid therapy. Early treatment with steroids is considered to be important for obtaining a good therapeutic outcome of DLK after LASIK. The patients returned to our clinic early after the onset of ocular symptoms. We reconfirmed the importance of informed consent in patients undergoing LASIK.

LASIK was performed after cataract surgery in case 2. The number of patients undergoing LASIK (Bi-optics) after cataract surgery is expected to increase in the future (Kimiya Shimizu: Basic and clinical features in refractive surgery, Refractive surgery in phakic intraocular lens: The 55th Congress of Clinical Ophthalmology of Japan in 2001, Kyoto). Responses different from those after lamellar keratopathy may occur in patients after LASIK. Long-term and careful follow-up is required to prevent delayed DLK in older patients with a higher risk of corneal erosion and in patients undergoing LASIK after cataract surgery.

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