Delayed Diffuse Lamellar Keratitis After Small-Incision Lenticule Extraction related to IgA Nephropathy A Case Report

Abstract
BACKGROUND
Diffuse lamellar keratitis (DLK) is a complication of laser-assisted in situ keratomileusis (LASIK). This condition can also develop after small-incision lenticule extraction (SMILE) with a distinctive appearance. We report a case involving a female patient with delayed onset DLK accompanied by IgA nephropathy.

CASE SUMMARY
A 22-year-old woman was referred to our department for DLK and a decline in vision 1 mo after undergoing SMILE. The initial examination showed grade 2 DLK in the flap involving the central visual axis OD. She was immediately administered a large dose of a topical steroid for 30 days. However, the treatment was ineffective. Her vision deteriorated from 10/20 to 6/20, and DLK gradually worsened from grade 2 to 4. Eventually, interface washout was performed, after which her vision improved. DLK completely disappeared 2 mo after washout. Six months after SMILE, the patient was diagnosed with IgA nephropathy due to a 4-year history of interstitial hematuria.

CONCLUSION
DLK is a typical complication of LASIK but can also develop after SMILE. Topical steroid therapy was ineffective in our patient, and interface washout was required. IgA nephropathy could be one of the factors contributing to the development of delayed DLK after SMILE.

**Key Words:** DLK; SMILE; IgA nephropathy

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**Core Tip:** DLK is a typical complication of LASIK but could also develop after SMILE. Topical steroid therapy was ineffective in our patient, and interface washout was required. IgA nephropathy could be one of the factors contributing to the development of delayed DLK after SMILE.

**INTRODUCTION**
A 22-year-old woman was referred to our department for DLK and a decline in vision 1 mo after undergoing SMILE. The initial examination showed grade 2 DLK in the flap involving the central visual axis OD. She was immediately administered a large dose of a topical steroid for 30 days. However, the treatment was ineffective. Her vision deteriorated from 10/20 to 6/20, and DLK gradually worsened from grade 2 to 4. Eventually, interface washout was performed, after which her vision improved. DLK completely disappeared 2 mo after washout. Six months after SMILE, the patient was diagnosed with IgA nephropathy due to a 4-year history of interstitial hematuria.

**CASE PRESENTATION**

*Chief complaints*
A 22-year-old female patient presented with a 1-week history of gradual vision loss.
History of present illness
She had undergone bilateral SMILE 1 month ago and showed no other medical history.

History of past illness
Her medications did not contribute to her vision loss.

Personal and family history
Her personal and family history did not contribute to her vision loss.

Physical examination
The preoperative best-corrected distance visual acuity (DVA) was 20/20 in both eyes (OU) with refraction of -7.25 diopter sphere (DS) -0.5 diopter cylinder (DC)*20 in the right eye (OD) and -6.50 DS -0.50 DC*148 in the left eye (OS). The results of slit-lamp and dilated fundus examinations were normal, with no sign of dryness or superficial punctate keratopathy. The intraocular pressure (IOP) was 11.3 mmHg OD and 17 mmHg OS. Central corneal thickness (CCT) was 650 μm OD and 642 μm OS. Specular microscopy revealed an endothelial cell density of 2756 cells/mm² OD and 2929 cells/mm² OS with a uniform endothelial cell pattern without any sign of abnormalities.

Laboratory examinations
Her laboratory findings, including those of routine blood examination and tests for HBV, HCV, HIV, and RPR, were unremarkable.

Imaging examinations

Figure 1 Slit-lamp photograph examination of the Grade 2 DLK OD and Pentcam image of cornea density average OU postoperative SMILE 1 mo.

FINAL DIAGNOSIS
DLK after SMILE

TREATMENT

Her postoperative regimen consisted of topical levofloxacin 0.3% and artificial tears 4 times a day hourly OU, and topical fluorometholone 0.1% OU 4 times daily for the first week with the daily dose reducing by one drop every week. At her 1-week postoperative visit, the uncorrected DVA (UDVA) was 16/20 OD and 16/20 OS. The manifest refraction at 1 wk was +0.5 DS OD and +0.25 OS. At this point, the IOP was 11.3 mmHg OD and 17 mmHg OS. She was told to continue tapering her medication regimen and return for her 1-month follow-up visit.

However, one month later, she presented with sudden worsening of symptoms; her vision was hazy and she did not experience pain or any other sensation, which she started experiencing 1 wk before the visit. The UDVA was 10/20 OD and 16/20 OS, and the manifest refraction was -1.25 DS = 16/20 OD. OD showed large focal infiltrates in the flap involving the central 6-mm visual axis (grade 2 DLK). OS was slightly infiltrated (grade 1 DLK). The IOP was 7.5 mmHg OD and 8.0 mmHg OS. A Pentacam assessment showed that the average optical density was 18.4 (Figure 1) OD and 13.8 OS. On the basis of these findings, she was diagnosed as showing DLK with myopia OD. She was advised fluorometholone 0.1% OD 6 times daily 1 wk later. Her symptoms did not improve; therefore, she was prescribed 1% prednisolone acetate eye drops OD 8 times daily instead of TobraDex, the frequency of which was gradually reduced to 6 times daily for 1 wk. Two weeks later, i.e., 2 mo after the operation, she presented with worsening of symptoms and cloudy vision OD. UDVA declined to 6/20 OD. The manifest refraction was -1.50 DS = 14/20 OD with more large focal infiltrates in the flap involving the central 6-mm visual axis compared to before (grade 4 DLK). The IOP was 8.5 mmHg, and a Pentacam assessment showed that the average optical density was 19.5 D (Figure 2). Interface washout was eventually performed with a balanced salt solution and 0.1mg dexamethasone. Her treatment regimen then consisted of topical fluorometholone 0.1% OD 4 times daily for the first week with the daily dose reducing
by one drop every week. Thirteen days later, the UDVA was 10/20 -0.75 DS -0.75 DC\(^\circ\)38 = 16/20 OD, and there were little focal infiltrates in the flap involving the central 6-mm visual axis (grade 2 DLK). The IOP was 9 mmHg. The densitometry value was 18.4 D. A bacterial smear test showed no positive findings.

OUTCOME AND FOLLOW-UP
Two months later, the patient reported a subjective improvement in VA; the UDVA was 16/20, and the DLK severity was grade 1. The average optical density was 19.6 D, and the IOP was 8.7 mmHg. Five months later, the UDVA was 16/20 and the DLK had completely disappeared (Figure 3). The densitometry value (12.6 D) was similar to that before the operation, 12 D. The patient has diagnosed as showing IgA nephropathy due to "interstitial hematuria for 4 years" at 6 mo after SMILE. Biochemical examination showed a serum albumin level of 30.0 g/L (reference values is 35-55 g/L). Routine urine examination showed the following findings: urine albumin (+++) and occult blood (+++). Protein electrophoresis yielded the following findings: albumin: 55.1% (reference values is 53.8-66.1%); \(\alpha 1\) globulin: 5% (reference values is 1.1-3.7%); \(\alpha 2\) -globulin: 14.3% (reference values is 3.2-6.5%). Renal biopsy showed aortic arteriosclerosis, IgM (++); IgA (++); C3d (+++); and C4d (+). The patient was eventually diagnosed as Postoperation SMILE OU, Delayed DLK with myopia OD, IgA nephropathy.

DISCUSSION
DLK is rare occurs in SMILE surgery. The incidences of DLK after microkeratome LASIK, femtosecond laser-assisted LASIK, and SMILE range from 0.1% to 12.1% \(^{4-5}\), 0.4% to 37.5\(^{6-7}\), and 0.2% -0.45\(^{8-9}\), respectively. The 2-4 mm corneal stroma incision in SMILE may reduce the risk of introduction of various foreign bodies into the corneal interface in comparison with that associated with the 20-mm corneal stroma incision in LASIK. However, SMILE may also have specific features that may lead to DLK. For example, (1) the femtosecond laser bubbles increase antigen composition and space to
stimulate inflammation \[\text{[10]}\]; (2) the excessive manipulation in thinner lenticules and the larger diameter may stimulate the secretion of inflammatory factors and increase the incidence of DLK\[2\]; (3) the higher laser energy may cause severe corneal stroma damage \[\text{[11]}\]; (4) the repeated use of negative pressure suction during surgery may cause epithelial damage leading to DLK; (5) other agents such as meibomian gland secretions \[\text{[12-13]}\], oil, irrigating fluid, talc powder, traumatic flap dislocation, air dust, and other stimulating inflammatory factors may be associated \[\text{[9][14]}\] with DLK; and (6) individual patient differences in sensitivity to lasers.

DLK usually occurs within 24 h and rarely appears 5 days after SMILE \[\text{[9]}\]. In this case, the surgical procedure was performed smoothly, and the patient’s vision improved at 1 mo after the procedure, consistent with the findings reported by Lin Kejies \[\text{[15]}\]. DLK is highly sensitive to steroid therapy, and the majority of cases can be managed with aggressive topical steroid treatment \[\text{[16-17]}\]. Therefore, steroid therapy and topical steroid treatment are routinely administered. Previous data showed that interface washout may increase the risk of corneal melting associated with focal infiltrates \[\text{[18]}\]. Therefore, in our case, interface washout was eventually performed after two months, not one month, of hormone therapy. Thus, once topical steroid therapy showed no efficacy, interface washout should be performed.

In this case, DLK was delayed and lasted for more than 4 mo. In addition to treatment-related factors, the patient’s systemic factors may have been responsible for the atypical presentation. The patient had been diagnosed with IgA nephropathy due to "interstitial hematuria for 4 years" at 6 mo after SMILE. IgA nephropathy is a form of glomerulonephritis characterized by deposition of the IgA antibody in the glomerular mesangial area, and the typical clinical presentation is gross hematuria. The specific etiology and mechanism of this condition are complex and include immune complex deposition, mucosal immunodeficiency, IgA molecular abnormalities, and microbial factors. Ocular involvement in patients with IgA nephropathy is rare, however, the most frequent association occurs with scleritis, episcleritis keratoconjunctivitis,
uveitis, retinal vasculopathy. To our knowledge, there are no study that directly shows delayed DLK after smile and IgA nephropathy. Tears contain a large number of SIgA and small amounts of IgA, tear SIgA and serum IgA has the common antigenicity. IgA of tears is 3-8 times than of the blood. IgA abnormalities in plasma affected by abnormal blood may result in slgA and IgM abnormalities in tears to ocular corneal and conjunctival inflammation. Unfortunately, we did not detect the IgA in tears and interface washing fluid. Meiyan Li reported a DLK occurring 4 years after SMILE because of trauma and it had cured by intensive topical corticosteroids eyedrops. As we know IgA nephropathy need sufficient dose of glucocorticoid therapy, in our case glucocorticoid is too little to get curative effect and ocular surface drugs cannot reach the flap interface in early time. Until 2 years later this patient is still received a maintenance dose of glucocorticoid.

In addition to these factors, plasma albumin, complement, and inflammatory factors may be related to the presentation of DLK. Corneal nutrition is derived from aqueous humor, tears, and the limbal sclera, and laser postoperative healing may result in inflammatory cell-mediated interference via multiple antibiotic factors. Changes in the albumin, complement, and inflammatory factor content in the plasma can cause changes in the lymphocytes, plasma cells, complement, and inflammatory overexpression in the corneal epithelium, tears, and scleral edge as well, directly or indirectly triggering an indirect immune response to the corneal gland and resulting in DLK. It has been proven that the aggregation of inflammatory cells along with interface debris presence under the corneal confocal microscopy in DLK patient’s corneal after SMILE.

**CONCLUSION**

Autoimmune diseases are relative contraindications to SMILE. The hidden onset, the patient's lack of consciousness, and the absence of preoperative urine and kidney function examinations as routine tests led to a missed diagnosis. The patient had a 4-
year history of hematuria, so her kidney disease was not controlled when she underwent surgery. Despite the long treatment process, she had good treatment and achieved satisfactory results for in this special case. This case indicates that IgA nephropathy in patients may be one of the factors related to delayed DLK in patient safter SMILE. Moreover, the preoperative history cannot be ignored, especially a history of autoimmune diseases.
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