CASE REPORT

Activation of *Cytomegalovirus* corneal endotheliitis following laser in situ keratomileusis

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SUMMARY

A case of *Cytomegalovirus* (CMV) corneal endotheliitis following laser in-situ keratomileusis (LASIK) is presented. A 32-year-old man presented 3 weeks after uncomplicated myopic LASIK with unilateral LASIK flap oedema, interface fluid accumulation, keratic precipitates, anterior uveitis and raised intraocular pressure. Despite treatment with topical corticosteroids, he had 3 further recurrent episodes. Specular microscopy showed decreased endothelial cell density and aqueous humour. Polymerase chain reaction (PCR) testing was positive for CMV DNA. He was treated with topical ganciclovir and ketorolac, and the inflammation and oedema resolved. Repeat aqueous humour PCR testing was negative for CMV DNA, and he remained well at last follow-up (3 months after stopping all medications). CMV corneal endotheliitis can be reactivated after LASIK, and CMV DNA PCR of aqueous humour samples can help in definitive diagnosis. Early recognition and treatment of this condition is important to prevent permanent endothelial cell loss and corneal decompensation.

BACKGROUND

Cytomegalovirus (CMV) is a ubiquitous human herpes virus that can cause ocular manifestations in immunocompromised and immunocompetent patients. Since the first report in 2006, CMV is now increasingly recognised as a cause of corneal endotheliitis.¹ We report a case of CMV corneal endotheliitis reactivation after laser in-situ keratomileusis (LASIK). To the best of our knowledge, this may be the first reported case of activation of CMV corneal endotheliitis directly after LASIK. A high index of suspicion is important for early recognition and diagnosis of this complication. Delayed diagnosis and treatment can lead to corneal decompensation and further morbidity.

CASE PRESENTATION

A 32-year-old man was referred to our centre for the management of right anterior uveitis after LASIK. In terms of general medical history, he was asthmatic, but had no other general medical conditions of note. Prior to his presentation to our centre, he had undergone bilateral myopic LASIK 15 weeks before (at another centre) and had already been treated for two episodes of anterior uveitis in his right eye.

Immediately after LASIK, he had received dexamethasone 0.1% (Maxidex; Alcon, Fort Worth, Texas, USA) eye drops in both eyes every 3 hours for 2 days, followed by four times a day for

another 5 days. The first episode of anterior uveitis occurred 3 weeks after LASIK. He presented to his ophthalmologist complaining of right eye blurring of vision, and was noted to have right anterior uveitis with a 'sentinel' keratic precipitate (KP) and intraocular pressure (IOP) of 32 mm Hg. This resolved with 2 weeks of treatment with topical dexamethasone 0.1%, moxifloxacin hydrochloride 0.5% (Vigamox; Alcon, Forth Worth, Texas, USA), latanoprost 0.005% (Xalatan; Pfizer, New York City, New York, USA) and brinzolamide/timolol 10 mg/mL+5 mg/mL (Azarga; Alcon, Forth Worth, Texas, USA) eye drops (exact medication frequency unclear). Eight weeks later (13 weeks after LASIK), he presented to his ophthalmologist with a second episode of right anterior uveitis. He was then treated with loteprednol etabonate 0.5% (Lotemax; Bausch & Lomb, Bridgewater, New Jersey, USA), moxifloxacin hydrochloride 0.5%, latanoprost 0.005% and brinzolamide/timolol 10 mg/mL+5 mg/mL (exact medication frequency unclear). The anterior uveitis persisted despite 2 weeks of treatment, and he was therefore referred to our centre for further management.

At presentation to our centre (15 weeks after LASIK), uncorrected distance visual acuity (UDVA) was 20/20 in both eyes. Right IOP was 13 mm Hg measured by Tono-Pen XL applanation tonometer (Reichert Technologies, Depew, New York, USA) outside the LASIK flap. The right eye showed inferior flap oedema, but no infiltrates or KPs. The anterior chamber (AC) was deep, with occasional cells. The posterior segment was unremarkable, and examination of the left eye was normal. Specular microscopy showed endothelial cell density (ECD) of 2155 cells/mm² in the right, and 2595 cells/mm² in the left, while central corneal thickness (CCT) was 407 µm in the right and 394 µm in the left. He was treated with topical prednisolone acetate 1% (Pred Forte; Allergan, Dublin, Ireland) eye drops three times a day, moxifloxacin hydrochloride 0.5% three times a day and brinzolamide/timolol 10 mg/mL+5 mg/mL two times a day. On review 1 week later, he improved, and prednisolone acetate 1% was tapered down to two times a day for 1 week, followed by one time a day for 1 week and then stopped completely.

However, 1 week after stopping topical prednisolone acetate 1%, he suffered a third episode of anterior uveitis. In the right eye, there was inferior flap oedema, small-to-medium pigmented KPs and occasional AC cells (figure 1). IOP was 36 mm Hg. Anterior segment optical coherence tomography showed flap interface fluid (figure 1). Topical

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Figure 1 (A) Slit-lamp photograph showing flap oedema and pigmented small-to-medium keratic precipitates. (B) Anterior segment optical coherence tomography showing flap interface fluid.

prednisolone acetate 1% eye drops were restarted three times a day, and he was started on oral acetazolamide 250 mg three times a day. On subsequent review, he improved, and topical prednisolone acetate 1% was continued at three times a day for 2 weeks, then decreased to two times a day for another 2 weeks. Oral acetazolamide was reduced to two times a day for 1 week and then stopped, and he was restarted on topical brinzolamide/timolol 10 mg/mL+5 mg/mL two times a day. Four weeks later, he had improved, and the prednisolone acetate 1% was continued at two times a day for 2 weeks, and then reduced to one time a day. Specular microscopy performed showed right ECD of 1835 cells/mm² and CCT of 427 µm. One week after reducing the frequency of prednisolone acetate 1% to one time a day, the patient suffered a fourth episode of anterior uveitis, with an IOP of 27 mm Hg.

INVESTIGATIONS

During the fourth episode of anterior uveitis, an AC paracentesis was performed and aqueous humour was sent for polymerase chain reaction testing for CMV, herpes simplex virus (HSV), varicella zoster virus (VZV) and *Toxoplasma gondii* DNA. The result was positive for CMV DNA, with 29 929 copies/mL (4.48 log) detected by quantitative PCR, and negative for the others. Serum CMV *pp65* antigen immunofluorescence, CMV IgM antibody, and human immunodeficiency virus (HIV) testing were negative, while CMV IgG antibody was positive.

DIFFERENTIAL DIAGNOSIS

The diagnosis of corneal endotheliitis was made clinically because the patient showed typical signs, such as corneal oedema, coin-shaped KPs, mild AC inflammation with raised IOP and corneal endothelial cell loss.¹ CMV was identified as the causative agent based on the aqueous humour PCR result. However, prior to this result, the differential diagnosis included other viruses that commonly cause corneal endotheliitis, such as HSV and VZV.¹ The differential diagnosis also included non-infective aetiologies, such as Human leukocyte antigen B27 (HLA-B27)-related anterior uveitis.

TREATMENT

Once the diagnosis of CMV corneal endotheliitis was made, topical prednisolone acetate 1% was stopped. The patient was started on topical ketorolac tromethamine 0.5% (Acular; Allergan, Dublin, Ireland) eye drops four times a day and ganciclovir 0.15% (Virgan; Thea, Keele, England) gel five times a day. The patient was offered oral valganciclovir but declined due to financial reasons. For IOP, the patient was also continued on topical brinzolamide/timolol 10 mg/mL+5 mg/mL two times a day and oral acetazolamide one time a day.

OUTCOME AND FOLLOW-UP

The corneal oedema, KPs, and AC inflammation gradually resolved over the next 6 months, and IOP-lowering medications were completely stopped after 6 months. Topical ketorolac tromethamine 0.5% eye drops four times a day and ganciclovir 0.15% gel five times a day were continued for 8 months. Repeat aqueous PCR 8 months after the fourth episode of anterior uveitis was negative for CMV. At that point, topical ketorolac tromethamine 0.5% was decreased to three times a day for 1 month, then two times a day for 1 month, and then one time a day for 1 month, and then stopped completely. Ganciclovir 0.15% gel was decreased to three times a day, and then stopped 4 months later.

The patient had no further recurrences. At last follow-up, 3 months after stopping all medications, the patient was asymptomatic, with right UDVA of 20/20, and IOP of 16 mm Hg. In the right eye, there was a faint inferior corneal stromal scar, with a few small remnant KPs. The cornea was otherwise clear and the AC was quiet. Specular microscopy showed right ECD of 1163 cells/mm² and CCT of 425 µm.

DISCUSSION

Anterior uveitis occurs infrequently after LASIK, with an incidence of 0.18%.² It is postulated that most cases are due to uveal trauma during LASIK, when the suction ring causes acute compression and decompression.² However, there are other less benign causes, such as HLA-B27 uveitis or herpetic keratouveitis.^{3,4}

In addition to anterior uveitis, our patient also developed typical signs of corneal endotheliitis, namely corneal oedema, coin-shaped KPs, mild AC inflammation with raised IOP and corneal endothelial cell loss.¹ Most cases are caused by HSV and VZV. However, recently, CMV has been recognised as an important cause of corneal endotheliitis. Aqueous humour testing is important to correctly identify the causative organism and to make a definitive diagnosis. The largest case series of CMV corneal endotheliitis was reported in Japan, and identified male gender, and middle-to-elderly age as risk factors.¹ Also, for reasons currently unknown, it appears to be more common in Asians.⁵ CMV corneal endotheliitis has also been reported after cataract surgery or corneal transplantation, which may be related to prolonged use of topical corticosteroids causing local immunosuppression.⁶⁻⁸ We speculate that our case may have been similarly triggered by topical corticosteroid use after LASIK, allowing reactivation of pre-existing latent CMV infection. Our patient had evidence of prior infection in the form of serum IgG antibodies against CMV, but no evidence of active systemic infection at the time of presentation (negative serum IgM antibodies and CMV *pp65* antigen). Our case is unusual having reactivation following a short course of steroids (1 week). However, the patient was a known asthmatic and we cannot exclude the possibility that previous use of steroid

inhalers may have triggered a subclinical ocular inflammation in the past. Perhaps patients at high risk for CMV corneal endotheliitis should be given non-steroidals after LASIK instead. To the best of our knowledge, this may be the first reported case of activation of CMV corneal endotheliitis directly after LASIK. A previous report documented a patient with CMV corneal endotheliitis 2 months after LASIK.⁹ However, considering the lengthy duration this may not have been related to the LASIK procedure.

CMV corneal endotheliitis has been treated with both topical and/or systemic ganciclovir (or valganciclovir), but there is currently no consensus on optimal treatment. Manufacturers recommend no more than 21 days of treatment with topical ganciclovir 0.15% gel, and no more than 14 days of topical ketorolac tromethamine 0.5% eye drops. However, while our patient showed clear improvement in AC activity and reduction in KPs after the initiation of ganciclovir and ketorolac, the resolution was gradual over a period of 6 months. We were therefore unable to taper off the ganciclovir and ketorolac that quickly, and had to continue until the AC activity resolved completely and IOP normalised. We eventually had to continue ganciclovir gel five times a day for 8 months before tapering down to three times a day for another 4 months. Topical ketorolac was similarly continued at four times a day for 8 months before being gradually tapered down over another 3 months. Perhaps if our patient had also been on oral valganciclovir, his resolution would have been faster, and the topical medications could have been tapered off earlier.

In terms of prognosis, with appropriate antivirals, the inflammation and oedema usually resolve, but there is often a permanent reduction in ECD. This is likely due to endothelial cell loss that occurs due to inflammation and raised IOP, especially prior to diagnosis and the initiation of appropriate treatment. In more severe cases with delayed presentation or diagnosis, patients may suffer persistent corneal decompensation due to permanent endothelial cell loss from cytopathic damage.¹⁻⁵ Risk factors for poorer visual outcome include severe pre-treatment corneal oedema, older age, previous corneal graft, and glaucomatous optic neuropathy.¹⁰

Our report highlights the importance of early recognition of CMV corneal endotheliitis in post-LASIK patients presenting with flap oedema, interface fluid, KPs, anterior uveitis and/or raised IOP. We recommend testing aqueous humour for CMV in such patients if they present with two or more episodes. Early diagnosis and treatment is crucial to avoid endothelial cell loss and corneal decompensation.

Contributors All three authors have made substantial contributions towards conception and design, acquisition of data, analysis and interpretation of data, as well as drafting of the article and revising it critically. JSM and CMGC made substantial contributions towards conception and design. TET, JSM and CMGC made

Learning points

- ▶ Latent *Cytomegalovirus* (CMV) infection can be reactivated after ocular surgery, including laser in situ keratomileusis (LASIK) which may be related to local immunosuppression from short periods of topical corticosteroid use.
- ▶ CMV corneal endotheliitis should be suspected in post-LASIK patients presenting with LASIK flap oedema, interface fluid, keratic precipitates, anterior uveitis and/or raised intraocular pressure.
- ▶ Aqueous humour polymerase chain reaction testing for CMV can be useful to make a definitive diagnosis.
- ▶ Early diagnosis and treatment in CMV endotheliitis helps to prevent corneal decompensation.

substantial contributions towards acquisition of data, analysis and interpretation of data. TET, JSM and CMGC made substantial contributions towards drafting of the manuscript and critical revision. All three authors approve of the version submitted, and all are accountable for the article and will ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved. JSM is responsible for the overall content as guarantor.

Competing interests None declared.

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