Case Report

Taiwan J Ophthalmol 2023;13: 93-96

Access this article online

Quick Response Code:

Website:
www.e-tjo.org

DOI:
10.4103/tjo.TJO-D-22-00156

Herpes endotheliitis following laser-assisted *in situ* keratomileusis and photorefractive keratectomy

Majid Moshirfar[1,2,3]*, Melody Ziari[4], Christian Peterson[5], Neil Kelkar[6], Yasmyne Ronquillo[1], Phillip Hoopes[1]

Abstract:

Herpes endotheliitis is a less common manifestation of herpes keratitis, and characteristic examination findings include corneal edema and the presence of keratic precipitates. Infection may be primary or secondary to herpes virus reactivation following exposure to a potential trigger such as physiologic stress or environmental factors. Ocular surgery, including laser-assisted *in situ* keratomileusis (LASIK) and photorefractive keratectomy (PRK), can trigger reactivation in patients with or without a documented history of previous herpes infection. We present two patients with visually insignificant stromal scarring who denied a previous history of herpetic disease and developed herpes endotheliitis following LASIK and PRK. We demonstrate the importance of an appropriately thorough preoperative evaluation and further workup of any corneal abnormalities, even if such findings initially appear inconsequential.

Keywords:

Cornea, cytomegalovirus, herpes endotheliitis, herpes keratitis, herpes simplex virus, refractive surgery

Introduction

Herpes keratitis can arise as a primary infection or as a reactivation of latent disease.[1] Herpes simplex virus-1 (HSV-1) is a common cause of herpes keratitis and can affect the epithelial, stromal, or endothelial layer of the cornea.[1,2] We present two cases of herpetic endotheliitis in patients with insignificant paracentral stromal scarring who denied any history of ocular herpes and underwent photorefractive keratectomy (PRK) and laser-assisted *in situ* keratomileusis (LASIK) to highlight the potential risk of HSV reactivation after surgery.

Case Reports

Case 1

A 38-year-old male presented for refractive surgery evaluation. Medical history included Graves' disease treated with levothyroxine and sporadic herpes labialis. His ocular history was unremarkable apart from a small linear laceration in the right eye from childhood, and he denied any history of ocular herpetic disease. Manifest refraction was − 4.75, −0.75 × 004 OD, and − 2.50 − 175 × 001 OS, and corrected distance visual acuity (CDVA) was 20/20 OU. Slit-lamp examination was notable for a 1.5 mm × 1.5 mm area of paracentral stromal haze with corresponding mild corneal pannus and neovascularization at the 11 o'clock position in the right eye [Figure 1]. Due to concerns regarding his linear corneal laceration and potential disruption of the corneal pannus with LASIK, routine PRK was done in the right eye with a 6.5 mm optical zone and 1.25 mm transitional zone using WaveLight® EX500 Excimer Laser (Alcon Laboratories, Fort Worth, TX). He underwent uneventful femto-assisted LASIK in the left eye. Postoperative

[1]*Hoopes Vision Research Center, Hoopes Vision, Draper, UT, USA,* [2]*John A. Moran Eye Center, University of Utah School of Medicine, Salt Lake City, UT, USA,* [3]*Utah Lions Eye Bank, Murray, UT, USA,* [4]*University of Texas Health Science Center, McGovern Medical School, Houston, TX, USA,* [5]*University of Utah School of Medicine, Salt Lake City, UT, USA,* [6]*University of Arizona College of Medicine - Phoenix, Phoenix, AZ, USA*

***Address for correspondence:**
Dr. Majid Moshirfar, Hoopes Vision Research Center, 11820 S. State St. #200, Draper, UT 84020, USA.
E-mail: cornea2020@me.com

Submission: 07-11-2022
Accepted: 25-12-2022
Published: 20-02-2023

How to cite this article: Moshirfar M, Ziari M, Peterson C, Kelkar N, Ronquillo Y, Hoopes P. Herpes endotheliitis following laser-assisted *in situ* keratomileusis and photorefractive keratectomy. Taiwan J Ophthalmol 2023;13:93-6.

treatment regimen included prednisolone acetate 1% drops every 4 h for 1 week, ofloxacin 0.3% drops every 4 h for 1 week, and artificial tears. Postoperative visits at 1 day and 1 month were unremarkable. Three months following surgery, manifest refraction was + 0.25 D OU and uncorrected distance visual acuity (UDVA) was 20/20 OU. The patient was instructed to return for a routine follow-up in 6 months. However, he presented 3 weeks later with a 4-day history of redness and blurry vision OD. Examination revealed a small dendritic lesion on the right eye. The patient was started on valacyclovir 1000 mg TID and ganciclovir gel 5×/day (Zirgan, Bausch and Lomb, Tampa, FL). The dendritic lesion resolved in the following 4 days. However, disciform keratitis [Figure 2a] with central 4 mm × 5 mm stromal edema, and keratic precipitates (KPs), were noted, and prednisolone acetate 1% drops TID was initiated. These findings resolved in the following 3 months and the patient continued with a slow steroid taper and a maintenance dose of valacyclovir. Seven months after presentation, he continues to have central stromal haze without active KPs, and a beaten bronze-appearing endothelium [Figure 2b]. Manifest refraction was + 0.25–0. 25 × 104 OD with UDVA of 20/20 OU. He has not had any additional flare-ups and is on a regimen of once-weekly prednisolone 1% drops and valacyclovir 500 mg daily.

Case 2

A 27-year-old male patient presented seeking refractive surgery. He denied any medical or ocular history, including previous herpetic keratitis. Manifest refraction was – 3.00 – 1.50 × 90 OD and – 4.75 DS OS and CDVA was 20/15 OU. Slit-lamp examination demonstrated a 2.5 mm × 3 mm paracentral nummular scar of the corneal stroma at the 2 o'clock position in the right eye [Figure 3]. Following a detailed informed consent, uneventful AMO IntraLase femtosecond laser (iFS®)-assisted LASIK (Johnson and Johnson, Santa Ana, CA) was performed. Flap diameters were measured 8.4 mm in the right eye and 8.3 mm in the left eye, with a thickness of 100 µ. The optical zone was 6.5 mm with a transitional zone of 1.25 mm OU using WaveLight® EX500 Excimer Laser. The postoperative treatment regimen included ofloxacin 0.3% QID for one 1 week, ketorolac 0.5% drops BID for 3 days, and prednisolone acetate 1% drops QID for 1 month followed by a fluorometholone 0.1% drop slow taper, and artificial tears. The postoperative course in the first 3 months was unremarkable and manifest refraction was +0.25 – 0.25 × 101 OD and +0.50 – 0.50 × 41 OS with UDVA of 20/20 in both eyes.

Ten months following surgery, he presented with blurry vision in the right eye for several days. UDVA had declined to 20/50 OD and slit-lamp examination revealed fine KPs and diffuse corneal edema, [Figure 4a]

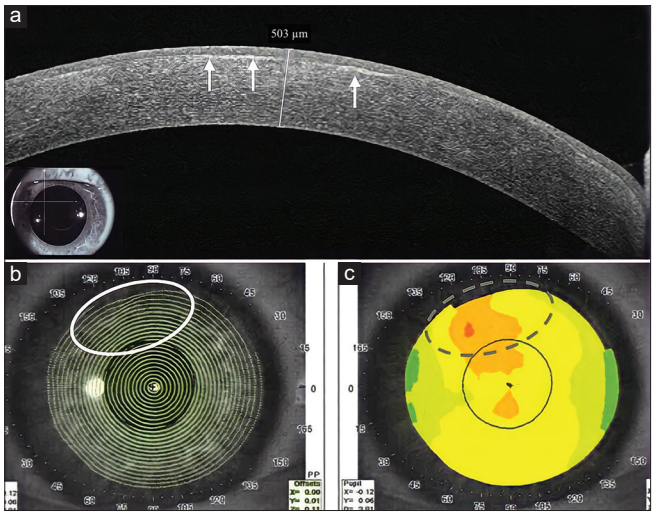

Figure 1: (a) Corneal hyperlucency on Anterior Segment Optical Coherence Tomography (AS-OCT) (white arrows). (b and c) Topographic distortion (white circle and gray dashed circle) corresponding to the location of the preoperative corneal pannus, stromal scar, and neovascularization

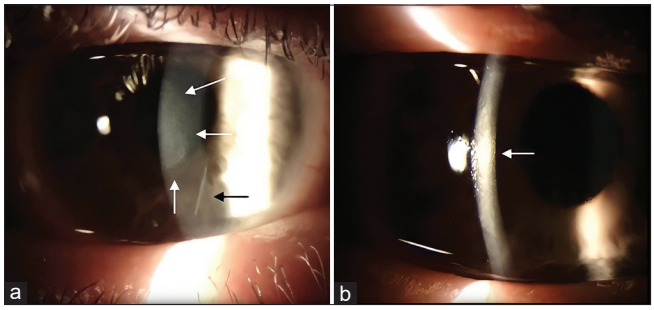

Figure 2: (a) Discrete region of edema consistent with disciform keratitis (white arrows) and previous laceration (black arrow). (b) Beaten bronze appearance of the endothelium (white arrows)

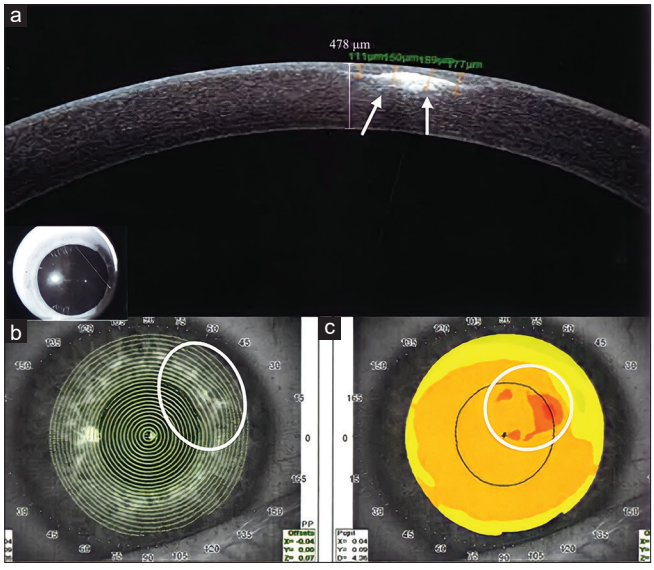

Figure 3: (a) Opacification of the cornea on Anterior Segment Optical Coherence Tomography (AS-OCT) (white arrow). (b and c) Distortion on corneal topography (white circle and gray dashed circle) in the area of the paracentral stromal scar

suggestive of herpes endotheliitis. Treatment with valacyclovir 500 mg TID and fluorometholone 0.1%

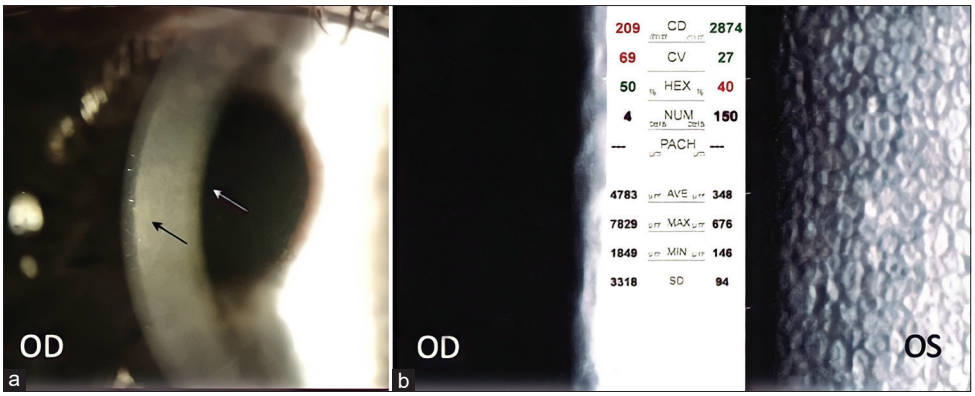

Figure 4: (a) Beaten bronze appearance of endothelial (white arrow) and KPs (black arrow). (b) Specular microscopy showing the inability to assess endothelial integrity in the right eye compared to the normal endothelium in the left eye, KPs: Keratic precipitates

eye drops TID was started, and symptoms appeared to improve. In the subsequent two years, the patient had fluctuating visual acuity with episodes of corneal edema. Improvements were noted with the administration of topical corticosteroids and antiviral medications. However, flare-ups would occur soon after treatment completion. Two years postoperative, UDVA and CDVA were 20/60 OD and 20/40 OD, respectively, and manifest refraction was + 1.00 – 1.25 × 53 OD. Specular microscopy imaging of the right eye endothelium was unsuccessful and failed to show good endothelial integrity compared to the left eye [Figure 4b]. He remains stable on maintenance therapy of valacyclovir 500 mg QD and fluorometholone 1% drops QID.

Discussion

Herpes keratitis following corneal refractive surgery has been well documented in the literature. Of the reported cases, 13 involved epithelial keratitis, six had stromal keratitis, and five were herpes endotheliitis which include the two cases presented in this article.[3] The patients with endotheliitis were predominantly male (80%), between 25 and 52 years old, and had a final CDVA ranging from 20/20 to 20/200.[4-6] Interestingly, of the five cases of herpes endotheliitis, only one had a known history of ocular herpes. The first patient's findings were consistent with epithelial keratitis followed by disciform endotheliitis, whereas the second patient's presentation was characteristic of diffuse endotheliitis. The cases presented underscore a key point – seemingly insignificant corneal scarring cannot be overlooked even if the patient denies a history of ocular infection.

Primary infection is often asymptomatic, and reactivation frequently elicits the first manifestation of ocular herpes.[1] Ocular HSV results from the reactivation of HSV previously dormant in the maxillary branch of the trigeminal ganglion.[1] Triggers for reactivation include physiologic and emotional stress as well as environmental exposure such as ultraviolet (UV) light.[1,3] Surgical trauma and postoperative topical steroid use are also potential causes of herpes reactivation.[7] While the exact mechanism of reactivation following ocular surgery is unknown, studies suggest cytokines such as interleukin-6 and ciliary neurotrophic factor may play a role. Disruption of the corneal nerve, which can occur following photorefractive procedures, has also been a strong stimulus for HSV-1 reactivation.[7] In addition, animal models have demonstrated that excimer lasers, such as those used in LASIK and PRK, can induce HSV reactivation.[8] The duration between refractive surgery and reactivation is variable and is about 15 weeks for patients who underwent PRK and ranging from 1 day to 28 months after LASIK.[3] Both patients spent a significant time outdoors, which likely contributed to their relapsing course. Patients were instructed to limit UV exposure and use proper sun protection.

Diagnosis of herpes endotheliitis can be made clinically, but anterior chamber (AC) paracentesis can be performed to confirm HSV or identify other causative agents. The rate of HSV positivity in AC paracentesis with polymerase chain reaction is approximately 8% and may require multiple paracenteses before obtaining a positive sample.[9] Studies have found that paracentesis results rarely alter the diagnosis and treatment of herpetic disease.[9,10] Given the low negative predictive value, a negative result does not rule out herpetic endotheliitis.[9]

Findings suggestive of herpes endotheliitis may warrant initiation of antiviral prophylaxis pre- or perioperatively to decrease the likelihood of reactivation following surgery.[11] Studies investigating preoperative antiviral prophylaxis most commonly assessed the use of valacyclovir and acyclovir. Animal models have demonstrated decreased rates of HSV-1 reactivation following LASIK in mice treated with acyclovir (6.2% of eyes) compared to the control group (35.3% of eyes). Additional animal model studies using valacyclovir

showed no reactivation following LASIK. Human studies have assessed various antivirals (valacyclovir, acyclovir, and famciclovir) with varying regimens such as acyclovir 800 mg TID and valacyclovir 500 mg BID and found no reactivation.[3] For example, de Rojas Silva *et al*. conducted a study investigating herpes keratitis reactivation in patients following LASIK. Patients were given preoperative valacyclovir 500 mg for 1 week before surgery and 2 weeks after surgery in addition to postoperative dexamethasone 0.1% and tobramycin 0.3% QID for 1 week following surgery, and none of the eyes developed herpes keratitis postoperatively.[12] Clinicians should maintain a high level of suspicion for possible prior ocular infection in such cases, even in the absence of previous history. Herpes keratitis is often self-resolving; however, treatment can shorten the disease course.[1] Treatment options include an antiviral, such as oral acyclovir 400 mg 3–5 times daily or valacyclovir 500 mg TID,[1] and steroid therapy to reduce corneal inflammation.[13] Although oral acyclovir (ACV) and valacyclovir have comparative efficacy in preventing recurrence, valacyclovir has higher bioavailability and fewer side effects.[14]

Refractory cases may require an increase in treatment dosage or a broadening of therapy to cover additional infectious etiologies such as *Acanthamoeba*, varicella-zoster virus, *Cytomegalovirus*, and bacterial causes. ACV-resistant HSV should be considered in patients who are unresponsive to a trial of ACV or other acyclic guanosine analog antivirals. Although resistance is more common in immunosuppressed individuals, spontaneous resistance in immunocompetent patients has been documented.[15] ACV resistance should also be suspected in patients with severe HSV manifestations atypical for immunocompetent individuals or patients with recurrent HSV episodes despite ACV maintenance therapy. First-line treatment includes a trial of IV foscarnet.[15] Herpes keratitis can have a profound impact on a patient's vision. Preoperative stromal scarring, regardless of size, and ocular history cannot be overlooked in patients seeking refractive surgery. Appropriate workup, including a detailed eye examination, a thorough ocular history, and a review of pertinent medical history, should be done before surgery to assess the risk of potential reactivation and guide management.

Ethical approval and declaration of patient consent

This article does not contain any studies with human participants or animals performed by any of the authors. We have approval from the Biomedical Research Alliance of New York IRB (reference number: 20–12-547–823) for the use of deidentified patient information. Both patients' written and informed consent were obtained for their anonymized information to be published in this article.

Financial support and sponsorship

This article is supported by Research to Prevent Blindness, New York, USA.

Conflicts of interest

The authors declare that there are no conflicts of interest in this article.

References

1. Zhu L, Zhu H. Ocular herpes: The pathophysiology, management and treatment of herpetic eye diseases. Virol Sin 2014;29:327-42.
2. Kalezic T, Mazen M, Kuklinski E, Asbell P. Herpetic eye disease study: Lessons learned. Curr Opin Ophthalmol 2018;29:340-6.
3. Moshirfar M, Milner DC, Baker PA, McCabe SE, Ronquillo YC, Hoopes PC. Corneal refractive surgery in patients with a history of herpes simplex keratitis: A narrative review. Clin Ophthalmol 2020;14:3891-901.
4. Moshirfar M, Welling JD, Feiz V, Holz H, Clinch TE. Infectious and noninfectious keratitis after laser *in situ* keratomileusis Occurrence, management, and visual outcomes. J Cataract Refract Surg 2007;33:474-83.
5. Jain V, Pineda R. Reactivated herpetic keratitis following laser *in situ* keratomileusis. J Cataract Refract Surg 2009;35:946-8.
6. Oruçoğlu F, Birinci AA, Hastanesi G. Late disciform endotheliitis after LASIK. Turk J Ophthalmol 2013;43:282.
7. Kanclerz P, Alio JL. Ocular surgery after herpes simplex and herpes zoster keratitis. Int Ophthalmol 2020;40:3599-612.
8. Dhaliwal DK, Romanowski EG, Yates KA, Hu D, Goldstein M, Gordon YJ. Experimental laser-assisted *in situ* keratomileusis induces the reactivation of latent herpes simplex virus. Am J Ophthalmol 2001;131:506-7.
9. Anwar Z, Galor A, Albini TA, Miller D, Perez V, Davis JL. The diagnostic utility of anterior chamber paracentesis with polymerase chain reaction in anterior uveitis. Am J Ophthalmol 2013;155:781-6.
10. Chronopoulos A, Roquelaure D, Souteyrand G, Seebach JD, Schutz JS, Thumann G. Aqueous humor polymerase chain reaction in uveitis – Utility and safety. BMC Ophthalmol 2016;16:189.
11. Levy J, Lapid-Gortzak R, Klemperer I, Lifshitz T. Herpes simplex virus keratitis after laser *in situ* keratomileusis. J Refract Surg 2005;21:400-2.
12. de Rojas Silva MV, Díez-Feijóo E, Javaloy J, Sánchez-Salorio M. Prophylactic perioperative antiviral therapy for LASIK in patients with inactive herpetic keratitis. J Refract Surg 2006;22:404-6.
13. Lobo AM, Agelidis AM, Shukla D. Pathogenesis of herpes simplex keratitis: The host cell response and ocular surface sequelae to infection and inflammation. Ocul Surf 2019;17:40-9.
14. Arshad S, Petsoglou C, Lee T, Al-Tamimi A, Carnt NA. 20 years since the Herpetic Eye Disease Study: Lessons, developments and applications to clinical practice. Clin Exp Optom 2021;104:396-405.
15. Piret J, Boivin G. Antiviral resistance in herpes simplex virus and varicella-zoster virus infections: Diagnosis and management. Curr Opin Infect Dis 2016;29:654-62.