Aspergillus fumigatus Keratitis After Laser In Situ Keratomileusis

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Purpose. To report a case of Aspergillus fumigatus keratitis after a laser in situ keratomileusis (LASIK) enhancement procedure. Method. Case report. Results. A 56-year-old woman developed an ulcer in the flap 13 days after LASIK enhancement. A 4-week course of fortified antibiotics for a presumed bacterial infection followed. The ulcer progressed, causing 60% thinning of the corneal stroma. A biopsy was performed 5 weeks after onset of symptoms, and antifungal agents were initiated. Cultures showed A. fumigatus. Her cornea perforated after the biopsy, requiring cyanoacrylate and lamellar overlay sutures, but the infiltrate resolved on antifungal agents. Conclusion. This report is the first description of Aspergillus keratitis after LASIK. We hypothesize that the infection became established on the stromal bed during surgery and led to melting, anteriorly through the flap and posteriorly through the stroma. Diagnosis was made by a corneal biopsy and inoculation of a wide array of media. This case demonstrates the need to consider atypical organisms, including fungi, in the differential diagnosis of post-LASIK infections when there is no response to therapy and highlights the role of corneal biopsy and flap lifting in the diagnosis of this condition. Key Words: LASIK—Infection—Keratitis—Aspergillus—Fungus—Cultures—Antibiotics.

Laser in situ keratomileusis (LASIK) has surpassed photorefractive keratectomy as the laser procedure of choice in correcting refractive errors, in part because of patient desires for both postoperative comfort and speed of visual recovery. The incidence of infectious keratitis after photorefractive keratectomy is estimated to be 1 in 1,000, and the incidence after LASIK is estimated to be 1 in 5,000; however, in separate published series of several thousand eyes, there has been no case of infectious keratitis, nor has there been a case reported among 100,000 eyes enrolled in the Clinical Research and Statistics—LASIK study and the Refractive Consultant Group (G. Kezirian, personal communication, December 2000). In addition, the Food and Drug Administration does not receive data regarding such complications (A.R. Rosenthal, Director, Division of Ophthalmic Devices, Food and Drug Administration, personal communication, December 2000); however, a detailed MedVyl-MEDLINE search yielded 12 cases of LASIK-associated keratitis of infectious etiology, including one case of fungal (Curvularia sp) keratitis. We describe a case of LASIK-associated Aspergillus fumigatus keratitis, which represents the second reported case of fungal keratitis after LASIK and the first case caused by Aspergillus.

CASE REPORT

In June 1999, a healthy 56-year-old woman underwent uncomplicated hyperopic LASIK in her left eye. She underwent an enhancement procedure on December 22, 1999, followed by a 5-day course of topical ciprofloxacin and topical steroids four times daily. On January 4, 2000, she developed redness and pain in this eye and her surgeon noted an ulcer with adjacent infiltrate and lamellar keratitis in the nasal aspect of the flap. The patient was treated initially with ciprofloxacin, and then fortified vancomycin and tobramycin; fluorometholone was added later. Cultures for bacteria, fungi, and acid fast bacilli were negative.

On January 26, she complained of marked worsening in vision, redness, photophobia, and tearing in the left eye. Her visual acuity was 20/200. There was a 1.1 × 1.0-mm ulcer with perforation of the flap and 60% overall thinning of the corneal stroma in the inferonasal quadrant of the cornea. The base of the ulcer was necrotic, and there was marked diffuse interface haze, in addition to epithelialization of the lamellar interface (“epithelial ingrowth”), from 4 to 8 o’clock. A 1+ anterior chamber reaction was present and the vitreous was quiet. The corneal ulcer was scraped and cultured, and 2 days later, the flap was lifted and irrigated with ciprofloxacin.

Over the next week, her condition worsened while on a treatment of topical fortified cephalosporins, vancomycin, and tobramycin; therefore, she was referred to the University of California, San Francisco (San Francisco, CA, U.S.A.) on February 4, 2000. Visual acuity was count fingers at 4 feet, the ulcer measured 2.5 × 2.5 mm, and the stromal thinning was unchanged. A dense stromal infiltrate with feathered edges was present adjacent to the ulcer (Fig. 1). Approximately 1 to 2 mm of epithelial ingrowth was noted in the interface over 9 clock hours and a small hypopyon was present while the vitreous remained quiet. A single colony of A. fumigatus was recovered from the corneal scraping on January 26, but to confirm the diagnosis, a 2.5-mm diameter corneal biopsy approximately 350 μm in depth was obtained. The flap was lifted, and the ingrowth from 4 to 9 o’clock was debrided. Three overlay
“bra” configuration sutures of 10-0 nylon were placed to secure the flap. The friable corneal tissue was suspended in sterile balanced salt solution and was inoculated onto blood agar, chocolate agar, noninhibitory potato flake agar, Lowenstein–Jensen slant, nonnutrient agar with Escherichia coli overlay, and cooked meat broth. Smears were obtained for Gram and Gomori methenamine silver stains.

Topical amphotericin 0.15% and natamycin 5% hourly by day were prescribed. Cultures confirmed A. fumigatus. Systematic evaluation of the patient was not performed; an endogenous source of the infection appeared to be unlikely given the location of the infection. On postoperative day 3, the biopsy site was Seidel-positive and a perforation was diagnosed. Cyanoacrylate (Histoacryl; B. Braun Petzold GmbH, Melsungen, Germany) glue was used to successfully seal the perforation, and a bandage soft contact lens was placed (Fig. 2). Cultures were not obtained. Topical natamycin 5%, vancomycin, and tobramycin were discontinued; topical ofloxacin, topical cyclopentolate 1%, and oral itraconazole 400 mg were added. Over the next few weeks, the infiltrate improved and the amphotericin dosing frequency was tapered. Anti-fungal susceptibility testing by the Fungus Testing Laboratory of the University of Texas Health Science Center (San Antonio, TX, U.S.A.) disclosed that the fungus was sensitive to amphotericin and itraconazole. The fungus was resistant to fluconazole and natamycin, and its susceptibility to itraconazole was intermediate.

The infiltrate disappeared over the next few weeks, but neovascularization of the interface developed. Her visual acuity was 20/200. Topical steroids were initiated 2 weeks later when the cyanoacrylate was removed. Four months after the biopsy, uncorrected and best spectacle-corrected visual acuity (BSCVA) was 20/200, and a rigid contact lens corrected the acuity to 20/40.

**DISCUSSION**

This case report is the first description of A. keratitis after LASIK. The apparent failure to consider and diagnose a fungal etiology for the infectious keratitis led to eventual corneal perforation and a poor outcome.

Unlike the other case report of fungal keratitis in which the initial infection appeared at the ocular surface, this case appears to have evolved from infection at the interface. Two lines of evidence support this hypothesis. First, there was no report of an epithelial defect at any time after the LASIK enhancement. Epithelial ingrowth might have induced overlying flap necrosis and may have led to flap perforation, but the ingrowth did not extend to the ulcer. Second, the pattern of haze and white-cell infiltration in the flap interface supports the hypothesis that the infection started in the interface. The haze and infiltrate would not be expected to be most dense in the interface if the infection had started in the epithelium.

Although interface infections after LASIK are uncommon, once an organism is established, the infection may be extremely difficult to eradicate because the nidus of infection is sequestered from the ocular surface defenses and because the epithelium serves as a relative barrier to penetration of antimicrobial agents. In this respect, this patient’s keratitis might be better classified as an abscess, and the patient might have benefited from early lifting of the flap and debridement. Steroid use also could have affected the course of this infection. This patient instilled topical fluorometholone for 5 days after the enhancement, then for 10 days before the second corneal scraping.

The 12 cases of LASIK-associated infectious keratitis in the literature include 6 cases of Staphylococcus aureus (two patients with bilateral involvement), 8-8 1 case of Nocardia asteroides, 9 1 case of Streptococcus pneumoniae, 10 1 case of viridans Streptococcus, 11 2 cases of Mycobacterium chelonae, 12,13 and 1 case of Curvularia sp. 4 The Curvularia keratitis followed a LASIK enhancement after which there was a persistent epithelial defect; all others were primary LASIK procedures. One patient with bilateral S. aureus infection was infected with the human immunodeficiency virus, 5 but all other patients were presumed to be immunocompetent. Two eyes of two patients required penetrating keratoplasty. One eye had dense corneal scarring from S. aureus infection that limited the BSCVA to 20/200. 8 The other eye, from which M. chelonae grew, underwent a penetrating keratoplasty as there was no response to topical and systemic medications. 12 The LASIK flap had to be removed from the second patient who grew M. chelonae to improve antibiotic penetration. 13 The final BSCVA of 10 of the 12 patients ranged from 20/20 to 20/25. The patient with Curvularia had an uncorrected visual acuity of 20/30, and the patient requiring flap removal for M. chelonae had a BSCVA of 20/50. There has been one reported case of traumatic fungal keratitis after LASIK. 14 This patient sustained a wood chip injury to his cornea 8 months after LASIK, and Acremonium atrogriseum was...
cultured from a corneal scraping. This patient required a penetrating keratoplasty (her BSCVA was 20/80); however, this case differs from the ones mentioned above as it was precipitated by late trauma to a well-healed LASIK flap.

Aspergillus species are the most common cause of fungal keratitis worldwide. Trauma is the most common antecedent event in fungal keratitis, but how such fungi become established in the corneal stroma after minor trauma is not adequately understood. A case series of Aspergillus endophthalmitis after cataract extraction associated with hospital construction has been described, but there were no special environmental factors in the current patient’s case, nor have there been concurrent cases of Aspergillus infectious keratitis reported in the area. Clinical manifestations of keratomycosis may become evident as quickly as 24 to 48 hours or may be delayed (as in our case) for 10 to 20 days. Invasion is characteristically deep in the stroma, and fungi can penetrate Descemet’s membrane. For this reason, deep corneal scrapings or biopsies are needed to establish the diagnosis in cases of presumed keratomycosis. One might have expected the infection in this patient to spread intraocularly after perforation. We attribute the lack of spread to the 6 days of intense topical antifungal therapy before the event and to the addition of oral itraconazole. It has been suggested that cyanoacrylate may have weak activity against Gram-positive organisms in vitro, but antifungal properties of the adhesive have not been described.

Corneal penetration of antifungal agents, such as amphotericin and natamycin, is poor in comparison to antibacterial therapy. There are few studies that correlate in vitro susceptibility testing of antifungal therapy with the in vivo therapeutic response. Sensitivities to antifungal agents are not easily obtained and are not well-standardized; very few fungus testing laboratories remain in this country.

In conclusion, we describe a case of LASIK-associated Aspergillus keratitis complicated by flap perforation and epithelial ingrowth, followed by corneal perforation after biopsy. Post-LASIK corneas might be considered compromised because of lack of ocular surface protection in the interface. Given the appearance of the ulcer and the pattern of necrosis, we hypothesize that the infection started in the interface. In retrospect, this patient may have benefited from early lifting of the flap and debridement, with concomitant microbiologic evaluation, as the patient was not responding to antibacterial agents. Although post-LASIK infections are rare, they are potentially vision-threatening, and fungal organisms and other nonbacterial organisms must be actively sought in the differential diagnosis and microbiologic workup.

REFERENCES