A 52-year-old man underwent bilateral laser-assisted in situ keratomileusis. Eight months later, he sustained a penetrating corneal injury to the left eye. A dense white infiltrate, unresponsive to antimicrobial therapy, developed in the corneal stroma. Corneal biopsy and eventual penetrating keratoplasty were performed, and both specimens demonstrated fungal elements with branching, septate hyphae. Culture identified the organism as Acremonium atrogriseum. Histopathologic features of this organism and its differentiation from other, more common fungal organisms are discussed herein.

Fungal keratitis is a potentially devastating condition that, at best, is difficult to treat successfully. It occurs most commonly following an injury involving vegetable matter. More than 60 species of fungi have been reported to cause keratomycosis, with the causative organism varying by geographic locale. Candida species and Aspergillus species are most common in the northern United States and Fusarium species in the southern United States. Apergillus predominates worldwide. In one series, topical amphotericin B was preferentially used when a diagnosis of Candida species infection was made, while natamycin was more commonly used in non-candidal infections.

Laser-assisted in situ keratomileusis (LASIK) is a refractive surgical procedure that involves creation of a flap in the anterior cornea followed by excimer laser ablation of the resulting stromal bed. Infection is a known risk after refractive procedures. We describe the first case, to our knowledge, of fungal keratitis in an eye with previous LASIK surgery.

A 52-year-old white man underwent bilateral hyperopic LASIK 15 months before initial examination. Eight months after surgery he sustained a penetrating wood chip injury to the left cornea. He was treated 1 day after the injury by lifting the corneal LASIK flap and irrigating the stromal bed. On the second postoperative day, a deep white scar was noted at the site of injury. Medical therapy consisted of a topical combination of tobramycin and dexamethasone, fluorometholone, and a combination of sulfacetamide sodium and prednisolone acetate. The patient's condition worsened and he was referred to the Doheny Eye Institute, Los Angeles, Calif.

At initial examination, the patient was in severe pain with an uncorrected visual acuity of 20/100 OS. The LASIK flap was hazy, with multifocal infiltrates in the stromal bed at the border of the hyperopic ablation zone, at the flap-bed interface (Figure 1). To avoid relifting the flap and causing possible damage to it, the corneal surface was initially scraped for culture. The patient was started on an hourly regimen of topical vancomycin hydrochloride (25 mg/mL), tobramycin sulfate (14 mg/mL), and amphotericin B (2 mg/mL). By day 4 of treatment, the infiltrate extended to the Descemet membrane, a large plaque developed on the corneal endothelial surface, and a hypopyon had formed. All cultures were reported as negative. The LASIK flap was lifted and corneal biopsy and repeated culturing of the stromal bed were performed, followed by irrigation with amphotericin B, vancomycin, and tobramycin. All culture specimens were
plated onto Sabouraud agar and incubated at 30°C.

The biopsy specimen consisted of a 1 × 1–mm piece of firm white tissue. The corneal stroma showed necrosis and a few chronic inflammatory cells. Multiple mycelial elements consisting of septate hyphae were present.

Despite hourly treatment with topical amphotericin B, the patient’s condition failed to improve, prompting penetrating keratoplasty. Intraoperatively, the retro-corneal plaque was noted to be continuous with a fibrin sheet connected to the hypopyon.

The corneal button measured 7 mm in diameter. On the posterior surface was a 1 × 2–mm, dome-shaped white plaque, through which the specimen was bisected. Histopathologic examination disclosed an intact epithelium with focal thinning. Within the corneal stroma, parallel to the epithelium, a continuous space was present, extending the full width of the specimen. This space separated the anterior one eighth from the remainder of the cornea and contained epithelial cells (Figure 2 and Figure 3). Multiple organisms exhibiting septate hyphae with 45° and 90° branching were present within the stroma of the posterior cornea, extending to and involving the Descemet membrane (Figure 4). Adherent to the endothelial surface was a large collection of acute and chronic inflammatory cells (Figure 2) with fungal elements present.

Ten days after corneal transplant, the organism was identified as Acremonium atrogriseum from the culture of the original corneal scraping, obtained at initial examination 22 days earlier. Postoperatively, the patient was maintained on a regimen of topical amphotericin B (2 mg/mL) and oral fluconazole, 200 mg twice daily, for 1 month. Topical 2% cyclosporine was continued for 2 months, at which point topical fluorometholone was substituted when no recurrence of fungal infection was noted. The graft has remained clear and the hypopyon has not returned after 5 months of follow-up, with a visual acuity of 20/80 + 3 with pinhole (Figure 5).
Acremonium is an uncommon cause of human infection.1 While several different species of Acremonium have been reported in human disease, we could find no previously published report of A atrogriseum. Found in soil, decaying vegetation, and foodstuffs,1 Acremonium is frequently misidentified as Aspergillus or Candida on histopathologic examination because of their similar configurations.9 Distinction is important, since resistance to several of the currently available antimycotic agents has been reported in Acremonium.1,9 In general, Aspergillus hyphae have a more consistent diameter, with 45° branching and rare 90° branching. In contrast, Acremonium exhibits both 45° and 90° branching, with hyphae of varying diameter. Candida species can be differentiated by the presence of nonbranching pseudohyphae and blastocysts. Differentiation of Acremonium from Fusarium and Paecilomyces requires culture, since all show similar configurations in tissue sections.9 In culture the differentiation is based on colony configuration and structure of the reproductive organs, including fertile cells known as phialides, and the conidia (spores) that arise from the apical orifice of each phialide.9 Acremonium species produce colonies that are white to lightly pigmented, fast growing, and floccose to funiculose. The conidia are produced in a ball at the mouth of the phialides without a flared collarette. Fusarium species resemble Aspergillus species in size, branching, and seption, but the hyphal wall is less rigid; therefore, ribbonlike or twisted filaments are more commonly seen. The colonies are floccose and vary in color from lavender to pink, salmon, gray, or white. Fusiform macroconidia are present with “foot cells with some type of heel.” Paecilomyces species produce phialides with a swollen base and a long tapered neck bearing chains of conidia.1

Numerous risk factors have been identified for the development of fungal keratitis, including trauma and topical corticosteroids, among others.2 In this case, a combination of factors resulted in the development of a severe fungal infection. Corticosteroids are well-known suppressors of immune function, and their use most likely resulted in a localized decrease in the ability to clear fungal elements. Lifting of the corneal flap in the immediate postinjury period conceivably could allow fungal organisms present on the surface access to deeper layers of the corneal stroma than would be possible otherwise. It is impossible in this case to know whether this was a contributing factor, as precise patient records of the location of the infiltrate in the immediate postinjury period are not available to us. Some authors5,7 have attributed a successful outcome in infectious keratitis following LASIK to flap lifting and debridement, although none was fungal in origin.

Definitive organism identification requires culture, which should be held a minimum of 4 weeks before being declared negative, as evidenced by this case in which identification of the organism was not reported until 22 days after culture. In the face of strong clinical suspicion, negative cultures, and worsening condition, corneal biopsy with repeated culture and histopathologic examination is indicated.

Once a definitive diagnosis of fungal infection is made, therapy should be aggressive. Penetrating keratoplasty may be considered in recalcitrant cases to remove the focus of infection. After penetrating keratoplasty, Killingsworth and associates10 reported cure in 15 of 15 eyes with fungal keratitis refractory to medical therapy. Of the 15 grafts, 9

Figure 4. Histopathologic examination of corneal button shows multiple fungal elements with 45° (arrow) and 90° (small arrowhead) branching. Descemet membrane is involved (large arrowhead) (Grocott methenamine–silver nitrate stain, original magnification ×200).

Figure 5. Postoperative biomicroscopic view of clear corneal graft.
(60%) remained clear after a mean follow-up of 9.2 months. Postoperative corticosteroid use could result in a recurrence of infection. In our patient, topical cyclosporine was used with the intent to control postoperative inflammation without increasing the risk of recurrence of the corneal infiltrate or hypopyon.

In summary, LASIK presents a unique set of problems when complicated by infection. The location of infectious organisms within the stroma makes access for culture difficult and potentially decreases effective penetration of antimicrobial therapy. When infiltrates can already be seen within the stroma, lifting of the flap may be required to obtain sufficient material for culture or biopsy, or both. This allows for direct irrigation of the stroma with antimicrobial agents as well. Fungal keratitis requires a high index of suspicion and aggressive management when present. A history of injury with vegetable matter or a persistent infiltrate unresponsive to antibacterial therapy, especially in the setting of corticosteroid use, should prompt evaluation for a fungal cause.

Histopathologic examination can be of value to confirm the presence of fungal elements and may be able to implicate certain organisms, but definitive identification requires culture. Infection may be caused by a myriad of organisms, including uncommon ones such as A. atrogiure.

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REFERENCES


A look at the past . . .

Dr Charles A. Perera: Theoretically, the ideal corneoscleral suture is an appositional one, and the safest corneoscleral suture is one placed before the eyeball has been opened, because the structures are firm and the danger of damage to the interior of the eye and dislocation of the lens is absent. The next safest suture in one placed after a small incision has been made.