Penetrating keratoplasty carries an infectious risk. Its requirement for topical corticosteroid therapy facilitates fungal growth with resulting keratitis. Although progression of fungal keratitis to intraocular infection is uncommon, endophthalmitis resulting from keratitis usually has a poor visual prognosis. Fungal infection under these circumstances remains a diagnostic and therapeutic challenge. We report a complicated case of recurrent fungal keratitis with endophthalmitis following a contaminated penetrating keratoplasty that ultimately was controlled with a new treatment modality. Intrastromal corneal injections combined with intravitreal injection of amphotericin B led to the eradication of the corneal fungal plaques and the intraocular infection. Intrastromal corneal injections of amphotericin B may offer a less invasive, in-office alternative to repeat penetrating keratoplasty.

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REPORT OF A CASE

An 85-year-old woman with Fuchs endothelial dystrophy and a history of pseudophakia came to the Emory University Eye Center, Atlanta, Ga, complaining of decreased vision in the right eye of 6 months' duration. She underwent penetrating keratoplasty (PK) for visually significant corneal edema secondary to Fuchs dystrophy. The donor corneal rim culture yielded the yeast Candida glabrata. The patient was prophylactically treated with oral fluconazole, 200 mg once daily, and topical 5% natamycin, 4 times daily (QID) for 6 weeks, and she continued treatment with topical 1% prednisolone acetate, 5 times daily. When no evidence of infection remained, the antifungal medications were discontinued and the topical corticosteroid was tapered to 3 times daily. Her best-corrected vision was 20/70 OD.

Five months after surgery, she returned with pain and decreased vision. On examination, a posterior corneal plaque, a hypopyon, and vitreous cells were noted. There was no epithelial defect. She was diagnosed as having late-onset endophthalmitis. Aqueous and vitreous taps were performed, and an intravitreal injection of amphotericin B, 5 µg, was given. Administration of oral fluconazole, 200 mg once daily, was restarted and topical corticosteroid therapy, 1% prednisolone acetate QID, was maintained. Although the aqueous and vitreous biopsy specimens did not disclose an infectious agent, the intraocular signs of infection cleared. A residual small, deep intrastromal white opacity remained at the corneal donor-host interface. The patient's vision improved to 20/50 OD with spectacles.

On follow-up 12 months after surgery, mild anterior inflammation was evident. Her visual acuity was 20/70 OD. She was treated with 1% prednisolone acetate, QID. The patient did not return for follow-up appointments until 3 months later (15 months after surgery), when she sought care for severe worsening of vision to hand motions. A hypopyon had developed with increased vitreous inflammation, and a fibrous plaque was noted to surround the intraocular lens. She underwent vitrectomy.

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and removal of the intraocular lens implant and capsule, and received intravitreal amphotericin B, 5 µg, and oral fluconazole, 200 mg once daily. The vitreous biopsy specimen yielded C glabrata.

The corneal plaques initially diminished in size with an intact epithelium, but 18 months after keratoplasty, the plaques grew, with extension into the endothelium and aqueous and increased intraocular inflammation (Figure, A). The patient declined repeat PK. After informed consent, she chose to undergo combined intracorneal and intravitreal therapeutic injections, for which institutional review board approval was obtained. Amphotericin B, 5 µg, was injected intravitreally, after a retrobulbar block with 2% lidocaine hydrochloride. In addition, concurrent intrastromal corneal injections were performed in the office with the patient in a supine position, using a 1-mL syringe with a 30-gauge needle while viewing the injection site through surgical loupes. Five midstromal injections were given in the areas surrounding the corneal plaques. Each time the needle was withdrawn after a 1-minute delay to minimize leakage of the drug. A total of approximately 0.05 mL of amphotericin B, 5 µg per 0.1 mL, was administered, resulting in hydration of the cornea. Within 3 months the eye became completely quiet and the stromal corneal plaques cleared.

On last follow-up, 18 months after the combined intravitreal and intrastromal injections, we found no signs of fungal recurrence. The patient had a best-corrected visual acuity of 20/400 OD. Her macula had marked traction with edema secondary to a visually significant epiretinal membrane. The patient declined vitrectomy surgery with membrane peeling. Biomicroscopic findings had been unchanged since 3 months after treatment and showed a clear cornea with minimal focal fibrosis at the donor-host interface (Figure, B).

Penetrating keratoplasty carries an infectious risk. Its requirement for topical corticosteroid therapy facilitates fungal growth with resulting keratitis.1 Although progression of fungal keratitis to intraocular infection is uncommon, endophthalmitis resulting from keratitis usually has a poor visual prognosis.2 The incidence of endophthalmitis following PK has been found to range between 0.2% and 0.77%,3,4 and the rate of endophthalmitis increases 22-fold when the donor rim culture indicates contamination.3 There is an approximately 50% correlation between the infecting organism isolated from the endophthalmitis aspirate and that cultured from the donor tissue.5,6 However, others6 have offered data questioning whether rim cultures have any useful value, since so often no infection develops despite positive culture results. Microbial contamination of corneal donor tissue is not an infrequent finding because of the difficulty in fully sterilizing the tissue without affecting its viability. Detection of microorganisms in posttransplant cultures of donor corneal rim ranges from 4% to 43%, with higher culture yields often explained by the use of more thorough culture techniques.3,5,6 Despite relatively high rates of contamination of donor tissue, the clinical occurrence of bacterial keratitis and/or endophthalmitis is low. Routine topical antimicrobial therapy given postoperatively to all patients after PK probably decreases the incidence of intraocular infection. Contamination with fungus is less frequently found in routine cultures of donor corneal rim, with a reported rate of approximately 6.5% of the identified organisms, although the rate can be as high as 50%.6,7 The role of prophylactic treatment is not firmly established in patients whose graft rim has been positive for fungi.

The initial therapy for the first episode of endophthalmitis in our patient was intravitreal amphotericin B and oral fluconazole. This resulted in resolution of all signs of infection for 7 months. When the patient returned with endophthalmitis, the source of the fungus was thought to be the large feathery, fibrotic white plaques between the lens capsule and the intraocular lens. Because the plaques in the cornea were small and posterior in the corneal stroma, they were considered not to be the source of recurrence but rather to be sites of infection secondary to the endophthalmitis. The possibility of concurrent PK and vitrectomy was thought unnecessary. Instead, the patient underwent vitrectomy with removal of the intraocular lens and lens capsule.

Figure. Biomicroscopic photographs of the patient’s right anterior segment before intrastromal amphotericin B injection (A) and 1 year after treatment (B). A, Endothelial and deep stromal corneal white plaques with feathery borders are seen at the donor-host interface, accompanied by anterior chamber inflammation and conjunctival vascular reaction. B, The resolution of infectious and inflammatory signs is apparent, with minimal residual localized endothelial fibrosis. (The green coloration is fluorescein, which had been used for tonometry immediately prior to this photograph.)
and received intravitreal amphotericin B and oral fluconazole.

At the third recurrence of endophthalmitis, frank white corneal plaques were also evident. These sites of corneal growth then became the primary suspects behind the fungal relapses. Penetrating keratoplasty is often considered when keratitis continues to progress with increasing hypopyon and peripheral corneal involvement.\(^8\) Penetrating keratoplasty is an effective way to remove infected cornea, as well as immune-complex precipitates that provide a stimulus for inflammation. The desired effect of therapeutic PK is to remove all infected tissue and leave a disease-free margin of at least 1 mm.\(^8\) Our patient was offered PK combined with vitrectomy and intravitreal amphotericin B, but she declined to have any complex ocular procedures.

As an alternative, we hypothesized that amphotericin B, given intravitreally in combination with intracorneal injections in the vicinity of the stromal site of fungal growth, would raise the local concentration of the antifungal agent enough to be effective in the eradication of the deep corneal infection. Intracorneal drug delivery has been performed previously on animals in an experimental setting.\(^7\) A literature search produced one report of a bioassay in rabbits in which several antifungal agents were evaluated in an effort to achieve therapeutic corneal levels.\(^10\)

Our patient received several amphotericin B intrastromal injections in addition to concomitant intravitreal amphotericin B to ensure that all fungal plaques were properly surrounded by the medication. This approach proved effective, with total elimination of the infection at the last follow-up (18 months after treatment). Corneal clarity was not compromised further by intrastromal amphotericin B. Recently, we studied the toxicity of intrastromal corneal amphotericin B in rabbits (Henia Lichter, MD, Batool Jafri, MD, Hans E. Grossniklaus, MD, Chris Banning, MD, C.D.S., E.G.-V., Henry Edelhauser, PhD; unpublished data; September 2004). Consistent with our experience reported herein, intrastromal injections of amphotericin B at a concentration of 5 µg per 0.1 mL do not appear to be deleterious to corneal kerocytes or endothelial cells.

In summary, we present a case of Candida endophthalmitis with multiple recurrences due to an inability to clear the corneal stromal infiltrate. To our knowledge, this is the first report of intracorneal delivery of a therapeutic agent in a patient. Intrastromal injection of amphotericin B combined with intravitreal injection of amphotericin B cleared the nidus of infection from the cornea. We suggest this as a treatment option that can successfully eradicate recurrent fungal keratitis with endophthalmitis. Although further experience is required, intrastromal corneal injections of amphotericin B may offer a less invasive, in-office alternative to repeat PK.

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