Acute *Fusarium solani* endophthalmitis secondary to keratitis following cataract surgery

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We report a case of fungal endophthalmitis in a 73-year-old woman secondary to *Fusarium* keratitis, which developed 1 week after complicated cataract surgery. The culture of corneal scraping specimens revealed isolated methicillin-resistant coagulase-negative staphylococci, whereas vitreous culture results identified *Fusarium solani*, which had a high minimum inhibitory concentration (MIC) (MIC >32 μg/mL) to amphotericin B, itraconazole, posaconazole, and a relatively low MIC concentration (MIC ≥4 μg/mL) to voriconazole. The primary source of infection (keratitis) and the associated endophthalmitis was controlled after several intravitreal and corneal intrastromal voriconazole injections, but the cornea perforated in the melting area. Although fungal keratitis after cataract surgery is rare, it may mimic a bacterial infection and the eventual failure of the initial empirical therapy might result in endophthalmitis. It is important, therefore, to obtain specimens for both fungal and bacterial cultures in atypical cases.

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Endophthalmitis is an inflammatory reaction resulting from intraocular colonization by bacteria, fungi, or rarely parasites. It is a serious complication of cataract surgery that every ophthalmic surgeon and patient strive to avoid. The visual loss and debilitation that occur after a postoperative endophthalmitis can be severe and irreversible. Those most in need of cataract surgery are often those at greatest risk, such as the elderly. The microbiological spectrum of postoperative cataract endophthalmitis has wide geographical variations. While postoperative fungal endophthalmitis may be rare in the developed world, it is apparently not as infrequent as in developing countries. In a study from India, fungi accounted for up to 21.8% of all the culture-positive postoperative endophthalmitis cases. The most commonly seen pathogens causing postoperative phacoemulsification endophthalmitis are gram-positive (50.9% to 94.0%), gram-negative (6.0% to 42.0%), and fungal (up to 12.7%) microorganisms.

*Fusarium* species, which are filamentous fungi, have been described as the most common cause of fungal keratitis. Qiu et al. report that *Fusarium solani* was the most frequently isolated pathogen in 27 of 61 eyes in which fungal keratitis was diagnosed. Although *Fusarium* species are the most common fungal pathogens in some reported keratitis series, endophthalmitis secondary to keratitis is uncommon. This case report describes the clinical presentation, microbiological spectrum, outcome, and possible predictors in a case of early-onset *Fusarium* endophthalmitis secondary to keratitis following cataract surgery.

CASE REPORT

A 73-year-old woman with a history of regulated type 2 diabetes and hyperthyroidism was referred to our clinic due to endophthalmitis in her right eye after phacoemulsification surgery, which had been performed in another clinic 2 weeks earlier. She had a history of posterior capsule rupture during the cataract surgery. The right eye had...
been left aphakic, and the corneal phaco incision was sutured with a 10-0 nylon monofilament suture. The medical history noted complaints of blurred vision, pain, and conjunctival hyperemia 1 week after the surgery. A diagnosis of keratitis had been established by the operating surgeon based on the clinical findings, and moxifloxacin drops alternating hourly with gentamicin drops in addition to cyclopentolate HCL had been prescribed. Four days later, because of progression of the keratitis and clinical observation of an evolving endophthalmitis, a fungal agent was suspected and topical amphotericin B (every 2 hours for 1 day) was initiated.

At presentation to our clinic, the patient's visual acuity was hand motion (HM) perception and on biomicroscopic examination, a central corneal abscess, diffuse conjunctival injection, and hypopyon were noted. The fundus could not be visualized because of the corneal abscess (Figure 1). Microbiologic samples of the cornea, aqueous, and vitreous were taken in the operating room under aseptic conditions, and prophylactic intravitreal vancomycin (1 mg/0.1 mL) and ceftazidime (2.25 mg/0.1 mL) were administered in the same session. The specimens were first examined by light microscopy following Gram staining for bacteria and Giemsa staining for fungus. The corneal scraping samples were inoculated to Sabouraud dextrose agar for fungus culture and to fluid thioglycolate medium for aerobic and anaerobic bacteria culture. Aqueous and vitreous samples were inoculated to chocolate agar, sheep blood agar, and MacConkey agar for aerobes and Schaedler agar for anaerobes and Sabouraud dextrose agar for fungus to obtain pure cultures.

A few gram-positive diplococci were seen with Gram stain on the light microscope in the corneal scraping. In addition, an abundant amount of fungus hyphae were observed with the light microscope in 3 different samples. The patient was started on fortified topical cephalosporin (50 mg/mL) every 2 hours for 1 day, natamycin 5% ointment 5 times a day topically, fortified amphotericin B drops (1.5 mg/mL) hourly each day, and oral itraconazole (100 mg) twice a day. The patient also received intravitreal amphotericin B (5 µg/0.1 mL) injection. During the early incubation period, methicillin-resistant coagulase-negative staphylococci were isolated on cultures obtained from the corneal scraping. Therefore, topical cephalosporin was stopped and fortified topical vancomycin (50 mg/mL) was started every 2 hours for 1 day, according to the antibiogram results. A second intravitreal amphotericin B injection was given 72 hours later. After a week, despite the ongoing therapy, the visual acuity decreased to light perception; eyelid edema and edema evolved (Figure 2).

After 2 weeks of incubation period, amphotericin B-resistant (minimum inhibitory concentration [MIC] >32 µg/mL), itraconazole-resistant (MIC >32 µg/mL), posaconazole-resistant (MIC >32 µg/mL), and voriconazole-sensitive (relatively low MIC) (MIC ≥4 µg/mL) Fusarium solani was isolated in vitreous cultures. Oral itraconazole was stopped, and intravenous voriconazole 400 mg was initiated twice daily. In addition, topical amphotericin B was replaced with topical vancomycin (50 mg/mL) ordered hourly each day. Intravitreal (100 µg/0.1 cc) and corneal intrastromal (50 µg/0.1 cc) voriconazole was injected.

After review of the patients' current therapy revealed that she had not been taking her antihyperthyroid medications in the past month. The patient was referred to an endocrinologist with her blood sample results and was reported to be in a hyperthyroid state of Graves disease. Antihyperthyroid medications were prescribed.

A second intravitreal and corneal intrastromal voriconazole injection was given 72 hours after the first injection. Spreading of the corneal infiltrates halted, and a reduction of vitreous opacities was observed in the B-scan ultrasonography. A third intravitreal and corneal intrastromal voriconazole injection was given 72 hours after the second injection. On the third day of the previous voriconazole

Figure 1. A: Central corneal abscess, diffuse conjunctival injection, and hypopyon are seen. B: B-scan ultrasonography shows mild vitreous opacities.

Figure 2. A: White satellite infiltrates are seen on the corneal surface. B: B-scan ultrasonography shows increased diffuse vitreous opacities.
injection, corneal infiltrates became smaller and the visual acuity improved from light perception to HM. However, corneal melting was observed in the upper temporal quadrant. On the tenth day of the onset of voriconazole, intravenous drug use was stopped because of elevated liver enzymes (alanine transaminase [ALT], aspartate transaminase [AST]). The clinical signs and symptoms of the endophthalmitis were successfully controlled, but the corneal melting area perforated (Figure 3). Amniotic membrane transplantation was performed (Figure 4). Topical antifungals were tapered and stopped in 8 weeks, and topical vancomycin was tapered and stopped in 4 weeks. After 6 months of follow-up, the cornea was diffusely opaque with significant thinning in the upper temporal quadrant. The visual acuity was HM, and the patient reported no pain.

**DISCUSSION**

The occurrence, severity, and clinical course of endophthalmitis is related to the virulence, inoculum of infecting microorganism, and the time of diagnosis, as well as the patient’s immune status. In our case, although an appropriate treatment was initiated based on the findings of the microbiological analysis, the delayed diagnosis is thought to be a major contributing factor to the progression of endophthalmitis that evolved secondary to keratitis. The progression despite full medication may also be related to profuse ocular invasion of *Fusarium spp* and the immune state of the patient.

Many aspects of fungal keratitis have not been fully elucidated, and its pathogenesis may be multifactorial with various risk factors. Regulatory T cells, responsible for both recognition of self antigens and microorganisms, may be a link between emergence of autoimmune disorders and infections. Previously, regulatory T cells have been associated with systemic and local immune responses in fungal infection. Additionally, defective function of regulatory T cells in peripheral blood and thyroid gland have been identified in cases with autoimmune thyroid disease, namely Graves disease. Until today, no direct evidence has been proposed for increased risk for infection in cases with Graves disease. However, we speculate that due to a common underlying pathogenesis, involving defective immune mechanisms, certain infections and autoimmunity in Graves disease may be related. Therefore, the presence of Graves disease in this case may have interfered with the immune state of the patient and influenced the outcome of fungal keratitis, despite the absence of Graves orbitopathy. In addition, Gupta et al. report that diabetes mellitus was also found to be a significant risk factor for unfavorable outcomes in post-cataract surgery endophthalmitis.

The European Society of Cataract and Refractive Surgeons study demonstrates that surgical complications contribute to a higher risk for contracting endophthalmitis following phacoemulsification cataract surgery. Patients experiencing complications at the time of surgery had a 4.95 times higher risk for

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**Figure 3.** A: Corneal upper temporal perforation. B: Choroidal detachment.

**Figure 4.** A: One week following amniotic membrane transplantation. B: Choroidal detachment reattached.
infection. In our case, posterior capsule rupture and the resultant aphasis might have contributed to the development of endophthalmitis by facilitating the access of fungus into the vitreous.

_Fusarium_ endophthalmitis can result from penetrating trauma, keratitis, and intraocular surgery in immunocompetent individuals. It can also occur endogenously in immunocompromised patients. In our case, a _Fusarium_ keratitis that developed after a complicated cataract surgery evolved into an endophthalmitis. Eradicating _Fusarium_ endophthalmitis is notoriously difficult. Persistence of the infection despite standard treatments or delayed recurrence of infection can occur for multiple reasons. _Fusarium_ has high rates of resistance to some antifungal medications.

Voriconazole, with broad-spectrum antifungal properties, high oral bioavailability, and rapid systemic absorption, was approved by the U.S. Food and Drug Administration in 2002 for invasive _Aspergillus_, _Fusarium_, and _Scedosporium_ infections. Several small descriptive reports have suggested that it is safe and effective when directed against _Fusarium_ infections in human eyes. The MIC of voriconazole for ocular _Fusarium_ isolates usually ranges between 2 \( \mu \text{g/mL} \) and 8 \( \mu \text{g/mL} \). Poor susceptibility to voriconazole is less common, with only a few cases of resistance reported. By contrast, _Fusarium_ exhibits relatively high resistance rates to fluconazole, itraconazole, miconazole, ketoconazole, posaconazole, flucytosine, and amphoteracin B deoxycholate. Voriconazole also demonstrates time-dependent activity, which suggests that maximizing the duration of exposure might optimize fungistatic activity. We attempted to achieve an intraocular concentration of voriconazole consistently in excess of the typical MIC by using systemic, corneal intrastromal, and intravitreal routes. In some cases due to poor systemic tolerance, voriconazole had to be stopped. In our case, systemic voriconazole led to an increase in hepatic enzymes (ALT, AST). Therefore, the systemic dose was stopped.

Once the infection reaches the vitreous, surgery is often needed to augment therapy. Dursun et al. report that 9 of 10 patients with endophthalmitis secondary to _Fusarium_ keratitis (90%) required penetrating keratoplasty (PKP), 40% required vitrectomy, 50% required lensectomy, 10% required iridectomy, and 30% were left with no light perception vision. Our case required a PKP to reduce the load of the infectious agent, but the patient rejected having any surgery.

In conclusion, this case report describes an isolated case of endophthalmitis secondary to _Fusarium solani_ keratitis following cataract surgery with a clinical presentation that mimicked bacterial endophthalmitis. The early-onset and rapidly progressive corneal involvement in the present case is indicative of a high load of the fungal inoculum being introduced intraoperatively into the eye. Apart from the virulence, inoculum of the infecting microorganism, the time of the diagnosis, and the patient’s immune status should be taken into account in the evaluation of endophthalmitis patients.

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