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Grand Rounds

A 24-year-old contact lens wearer with unilateral vision loss requiring penetrating keratoplasty

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History

A 24-year-old myopic woman from rural Victoria who wore extended-wear soft contact lenses presented at Alfred Health, Melbourne, Australia, with a 2-week history of left eye irritation, redness, photophobia, and reduced visual acuity. She denied sleeping while wearing lenses, trauma, or agricultural exposure. She had been treated with topical ciprofloxacin 0.3% drops without improvement. There was a history of travel to Vietnam but only to coastal city centers. Initial symptoms developed in Australia prior to traveling to Vietnam, where they became progressively worse.

Examination

On initial examination, best-corrected visual acuity was 20/16 in the right eye and 20/80 in the left eye. Pupils were equal and reactive, with no afferent pupillary defect. Slit-lamp examination of the left eye revealed a dense 2.4 × 3.7 mm corneal infiltrate, with a surrounding 8.0 mm immune ring (Figure 1A). There was 2+ anterior chamber cell and flare, with associated ciliary injection. Posterior segment examination showed no vitreous cells and healthy fundus. Intraocular pressure was 9 mm Hg in the affected left eye. The fellow eye was unremarkable.

Treatment

On suspicion of a fungal infection, the patient was admitted for hourly topical cefazolin 5%, tobramycin 0.3%, and voriconazole 1% drops. Initial corneal scrapings did not elicit microbial growth at 8 days. A corneal biopsy was performed, and filamentous fungal elements were identified. Intrastromal voriconazole (50 μg/0.1 mL) was injected circumferentially around the edge of the infiltrate to midcorneal depth, and twice daily oral voriconazole 200 mg and hourly topical natamycin 5% were introduced to replace the antibiotics.

Seven days following admission, visual acuity in the left eye deteriorated to counting fingers. Examination revealed a 2.0 × 2.0 mm corneal perforation. A 4.0 mm Tenon's capsule patch graft was applied under general anesthesia. Three days postoperatively, visual acuity remained unchanged, and there was interval development of 4+ anterior chamber inflammation and a small hypopyon. Anterior chamber paracentesis was performed, with injections of intracameral and intrastromal voriconazole (50 μg/0.1 mL) as well as intracameral amphotericin B (5 μg/0.1 mL). Oral voriconazole was increased to 300 mg twice daily after consultation with the Infectious Diseases unit.

Isolates from the corneal biopsy grew olivaceous green colonies consistent with *Metarhizium anisopliae* after 10 days at 25° C on potato dextrose agar (Figure 2). Minimum inhibitory concentrations of several antifungal drugs were determined (Table 1).

Seventeen days following admission, the corneal glue patch dislodged. A 5.5 mm peripheral therapeutic penetrating keratoplasty was performed, with repeat intracameral, intrastromal, and subconjunctival voriconazole injections (50 μg/0.1 mL). A small iridectomy was performed where iris tissue was adherent to the perforation site.

Postoperative assessments were satisfactory with a clear graft and quiet anterior chamber. On discharge, the patient was commenced on topical cyclosporine A 1% drops 4 times daily and continued on her regular dose of topical and systemic voriconazole. The eye remained

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Digital Journal of Ophthalmology, Vol. 25

Digital Journal of Ophthalmology, Vol. 25

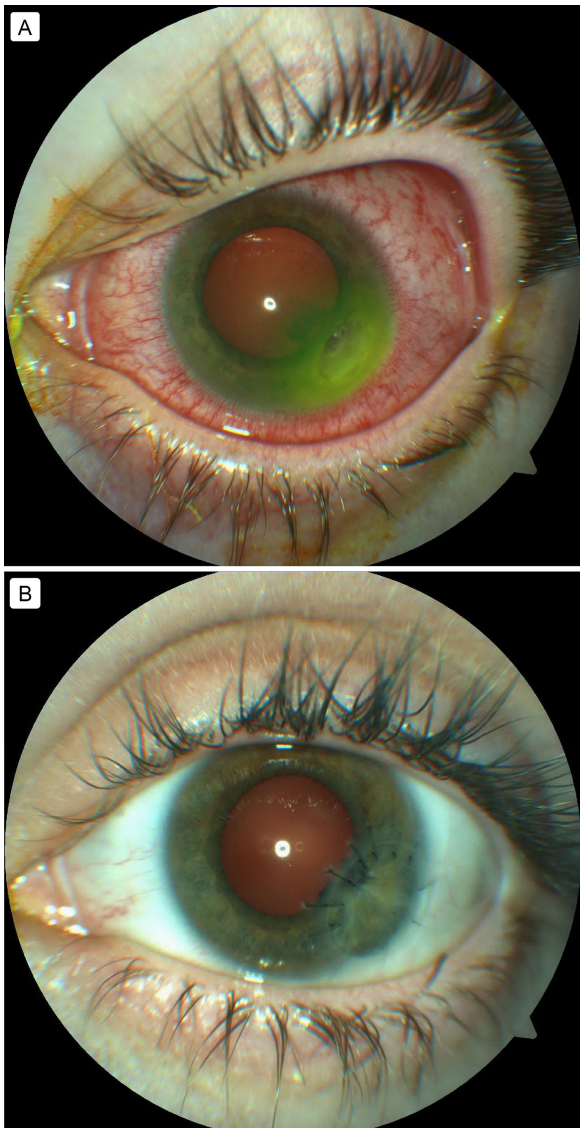

Figure 1. A, Dense corneal infiltrate with conjunctival injection at presentation. B, Clear corneal graft 9 weeks after penetrating keratoplasty. Best-corrected visual acuity was 20/40.

quiet; hence, topical dexamethasone 0.1% drops 4 times a day was introduced on day eleven post-keratoplasty for prevention of rejection. A 5-week course of oral voriconazole was completed, and topical voriconazole was gradually weaned over 9 weeks (Figure 1B). Fifteen months after keratoplasty best-corrected visual acuity in the left eye was 20/20, with refraction of −3.50 −1.00 ×60, with no evidence of infective recurrence or graft rejection.

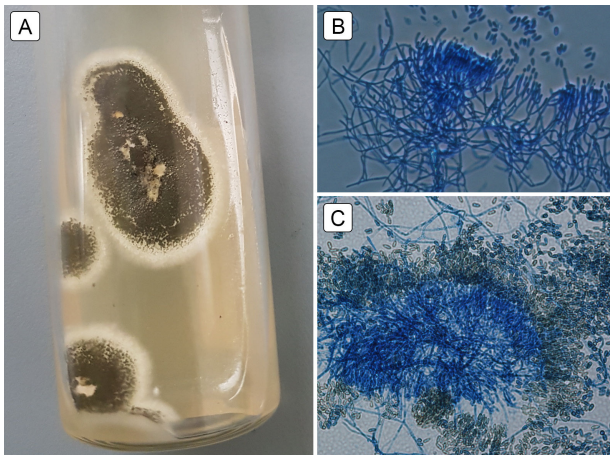

Figure 2. *Metarhizium anisopliae* strain isolated in the present case. A, Olivaceous-green colonies grown on potato dextrose agar at 25° C for 10 days. B, Specialized fungal stalks (conidiophores) aggregated in dense tufts with verticillate branching. C, Yellow-green cylindrical-shaped fungal spores (conidia), produced in long chains on conidiophores.

Differential Diagnosis

The differential diagnosis for infectious keratitis is broad, particularly for contact lens wearers who are at an increased risk for bacterial and fungal ulcers. Prompt diagnosis with Gram stain and cultures of corneal samples are essential to determine treatment direction. In many cases, it may be difficult to differentiate early keratomycoses clinically from corneal ulcers caused by bacteria, viruses or *Acanthamoeba*, and broad-spectrum treatment is often initiated prior to microbe identification. In the present case, the indolent course, lack of response to topical ciprofloxacin, dense gray-white stromal infiltrate, and immune ring were suggestive of a filamentous fungal pathogen. Principal causes of filamentous keratitis include species of *Fusarium*, *Aspergillus*, *Scedosporium apiospermum*, and *Paecilomyces*, although many other species have been implicated.[1] *Metarhizium anisopliae* is a ubiquitous and parasitic, soilborne, filamentous fungus with a worldwide distribution; it has only rarely been reported as a human pathogen.

Diagnosis and Discussion

The fungus *Metarhizium anisopliae* was first described nearly 140 years ago and is a common insect pathogen, with a wide range of hosts comprising 200 insect species.[2] It is used commercially as a natural pesticide for biocontrol of many insect populations across the world. It is typically considered safe to humans, because opti-

Digital Journal of Ophthalmology, Vol. 25

Table 1. Antifungal minimum inhibitory concentrations for ophthalmic isolates of Metarhizium anisopliae

Antifungal susceptibility	Current report	Eguchi et al[5]	Dorin et al[6]	Derhy et al[7]
Method	E-test[a]	Broth dilution[b]	E-test[a]	Not reported
Agents, MIC, μg/mL				
Amphotericin B	>8	16	>32	Resistant
Anidulafungin	4	NT	NT	NT
Caspofungin	1	NT	0.19	Susceptible
Fluconazole	>256	8	>256	NT
Flucytosine	>64	>64	>32	NT
Itraconazole	>16	1	>32	Resistant
Micafungin	4	<0.015	0.23	NT
Miconazole	NT	1	NT	NT
Posaconazole	1	NT	0.064	Resistant
Voriconazole	1	0.5	0.125	Susceptible

MIC, minimum inhibitory concentration; NT, test not performed.

[a]BioMérieux, France.
[b]Clinical and Laboratory Standards Institute, USA.

mal temperature for growth is between 25° C and 30° C, but isolates that are able to grow at temperatures near 35° C exist, particularly in tropical regions.[2]

Our search of the English-language literature yielded fewer than 10 reported cases of *Metarhizium anisopliae* ocular infection worldwide.[3–9] Mode of transmission typically involves agricultural exposure, with a history of vegetal trauma or soft contact lens wear. Although fungal keratitis is thought to be more common in tropical regions,[1] most published cases of *Metarhizium anisopliae* keratitis have arisen in temperate or extratropical climates, including Japan,[5] France,[6,7] the United States,[8] and Australia.[4] In this case, initial symptoms developed in Australia, but it is possible that the keratomycosis only became established on travel to Vietnam, which has a tropical climate and high relative humidity.

Management of filamentous fungal keratitis requires prompt identification through corneal scrapings or biopsy to aid directed therapy. The prognosis of *Metarhizium anisopliae* keratitis may be favorable with early administration of topical natamycin.[3,8,9] However, factors that contribute to poor visual outcomes include anterior chamber inflammation, large ulcer size, or scleral involvement.[4–7] In cases of deeper fungal invasion into the underlying corneal stroma, intraocular and systemic antifungals are recommended, and ideally tailored according to in vitro antifungal susceptibility testing.[1] Antifungal therapy should be maintained for at least 6 weeks, because negative scrapings during treatment may not exclude deep-seated fungal infection.

Surgical intervention may be required in up to 35% of patients with fungal keratitis refractory to maximal medical therapy.[10] Ideally, medical management should be provided to reduce the microbial burden, but surgery may be necessary in cases of progressive keratitis approaching the limbus or when perforation is imminent. The aim of surgery is to completely remove all infectious elements and involved tissue, and this may involve debridement, conjunctival flap, lamellar keratectomy, or penetrating keratoplasty, depending on the depth and severity of infection.[1,10] This may also include an iridectomy when the iris is involved. The poor surgical outcomes previously reported for *Metarhizium anisopliae* keratomycosis are likely attributable to advanced disease with associated scleral necrosis[4,5] or endophthalmitis[7] at the time of operation.

We report a case of *Metarhizium anisopliae* ocular infection with a favorable visual outcome following keratoplasty. Several reasons may account for the successful response in this patient, including the peripheral location of the infiltrate, aggressive targeted antifungal therapy (topical, intraocular, and systemic) based on isolate susceptibilities, and keratoplasty before scleral involvement. Fungal infections of the cornea are a challenging disease entity, and early recognition remains crucial to facilitate appropriate treatment and avoid potentially devastating outcomes.

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Digital Journal of Ophthalmology, Vol. 25