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Dematiaceous fungal keratitis caused by *Cladophialophora boppii* — A case report

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ABSTRACT

Purpose: To report a rare case of dematiaceous fungal keratitis caused by *Cladophialophora boppii* (*C. boppii*) in an immunocompromised patient.

Observations: An 83-year-old male with chronic renal failure was referred to the Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan due to persistent corneal epithelial defects (PEDs) in his left eye. Initial examination revealed decreased central corneal sensitivity and decreased tear secretion in that eye, both thought to be associated with herpetic keratitis. Permanent punctal-plug surgery combined with therapeutic soft contact lens wear was performed to treat the PED, which initially healed, yet recurred. Follow-up examination revealed a 1.0-mm-diameter black lesion consistent with the PED site, which subsequently increased in size, so treatment with miconazole solution eye drops, natamycin ophthalmic ointment, and systemic itraconazole was initially performed. Since the region of the lesion had progressed to corneal perforation, corneal transplantation surgery under general anesthesia was scheduled, yet the patient refused to undergo surgery. Mycological testing via DNA sequencing of the internal transcribed spacer of ribosomal DNA regions revealed that the isolate or pathogen was *C. boppii*. Mycotic keratitis caused by *C. boppii* was found to be resistant to antifungal drugs.

Conclusion and importance: This is a rare case of fungal keratitis caused by *C. boppii* in an elderly immunocompromised patient.

1. Introduction

Dematiaceous fungal keratitis is a very rare disease reportedly caused by an opportunistic nosocomial pathogen in immunosuppressed patients. To date, there have only been a few published reports of human infection due to *Cladophialophora boppii* (*C. boppii*); i.e., two reported cases with cutaneous phaeohyphomycosis,[1,2] one reported case with subcutaneous phaeohyphomycosis,[3] one reported case with toenail infection,[4] and one reported case with pulmonary infection.[5] *Cladophialophora*, a genus of fungi in the Herpotrichiellaceae ascomycetous fungi family, is frequently encountered in human infections ranging from mild cutaneous lesions to fatal encephalitis.[6] *Cladophialophora* is morphologically characterized by one-celled, ellipsoidal to fusiform, dry conidia arising through blastic acropetal conidiogenesis and arranged in branched chains. *C. boppii*, which reportedly was first isolated by C. Bopp in 1983 from a Brazilian female with chromomycosis,[7] is a dematiaceous fungus that rarely causes infectious disease in humans. For treatment, terbinafine, an antifungal medication, was found to be effective in over 50% of those reported cases. However, cases of fungal keratitis caused by a black fungus are far less frequently reported.[8]

Here we report a rare case of dematiaceous fungus keratitis caused by *C. boppii* in an immunosuppressed elderly male with chronic renal failure.

2. Case report

An 83-year-old man with no history of ocular trauma was referred to the Department of Ophthalmology at Kyoto Prefectural University of Medicine, Kyoto, Japan due to a small persistent corneal epithelial defect (PED) in his left eye. At initial presentation, he was found to have had a history of cataract surgery, recurrent herpetic keratitis and uveitis in his left eye, and bilateral normal-tension glaucoma treated with

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topical eye-drop therapy; i.e., 0.03% bimatoprost (once daily) in both eyes, 0.1% fluorometholone (2-times daily), and 0.1% sodium hyaluronate (4-times daily) in his left eye, along with chronic kidney failure.

Upon initial examination, a calcium deposit in the center of the elliptical PED in his left eye was observed (Fig. 1A). The size of the PED was 0.7 mm × 0.5 mm, and no infiltration was observed. In the patient's right eye, other than the presence of an age-related cataract, the anterior segment was normal. Cochet-Bonnet esthesiometry and a Schirmer test without anesthesia revealed that the central corneal sensitivity and tear secretion in his left eye were decreased to less than 5 mm and 3 mm, respectively, thus resulting in a diagnosis of neurotrophic ulcer and decreased tear secretion due to his history of herpetic keratitis, while the right eye showed normal central corneal sensitivity (>30 mm) and tear secretion (10 mm). For treatment, smear and culture examinations of the corneal lesion including calcium deposits in his left eye were performed to confirm the absence of any microbes, followed by the insertion of permanent silicone punctal plugs (SUPEREAGLE®; Eagle Vision, Inc., Memphis, TN, USA) and the fitting of a therapeutic soft contact lens (SCL).

The SCL therapy was administered for a period of 2.5 months until epithelial healing was achieved. Follow-ups were conducted every 2 weeks for replacement with new SCLs. Although the PED ultimately healed post treatment, after the epithelial healing, the patient returned to the previous physician. Unfortunately, a recurrence of the PED occurred after a lapse of 2 months. Follow-up examination revealed a 1.0-mm-diameter black lesion consistent with the site of the corneal erosion that subsequently increased in size to approximately 3.0 mm in diameter after 3 months (Fig. 1B and C). Although upon initial observation the black lesion appeared to be an iris herniation, subsequent anterior segment optical coherence tomography (AS-OCT) imaging revealed that there was no iris herniation (Fig. 1D). It should be noted that since the color of an iris herniation and a fungal lesion are very similar, the use of AS-OCT in this present study was very useful for differentiating between the two. In the case of an iris herniation, the anterior chamber should be shallower around the iris herniation, as the area of the iris is continuous to the posterior surface of the cornea. In this present case, since the depth of the anterior chamber was still deep, we were able to diagnose a fungal infection in his eye. Thus, the black lesion was diagnosed as a corneal infection. Calcofluor staining (Fungi-Fluor® Staining Solution; Polysciences, Inc., Warrington, PA, USA) from scraping of the black lesion revealed a filamentous fungal-like substance (Fig. 2A). Culture examination of the specimen obtained via the corneal scraping on Sigma-Aldrich® Potato Dextrose Agar Culture Plates (EMD Millipore Corporation, Burlington, MA, USA) showed the growth of a black fungus (Fig. 2B and C). For the black fungus, DNA sequencing of the internal transcribed spacer (ITS)1/ITS4 regions was performed, and ultimately classified (the organism was identified as *C. boppii*).

Subsequently, the patient underwent treatment for fungal keratitis, with the initial treatment being a topical administration of 0.1% miconazole (6-times daily), 1.0% natamycin ophthalmic ointment (5-times daily), and systemic itraconazole (200mg) (dose adjustment recommended based on renal function). However, the systemic itraconazole treatment was stopped due to a drug-induced diarrhea that occurred over the 16-day administration period, and the condition of the patient's eye worsened, as evidenced by an increase in hypopyon (Fig. 1E). At 3 weeks of administration of the topical and ophthalmic ointment, a perforated corneal ulcer was ultimately observed. Thus, a corneal transplantation under general anesthesia was scheduled. However, the patient ultimately refused to undergo surgery and requested non-surgical follow-up examinations, as he feared that the general anesthesia would worsen his chronic renal failure and lead to the introduction of hemodialysis. Antifungal treatment was administered in a tapering regimen over 8 months due to the effectiveness of the eye drops in reducing congestion and lowering the activity of inflammation. Initially, for the first 4 months, the treatment was administered 6-times daily; for the following 2 months it was administered 4-times daily due to the observed improvements, and owing to the continued improvement the treatment was administered twice daily for the final 2 months. Following this regimen, the anti-fungal eye-drop treatment was stopped, and there has been no recurrence of fungal keratitis for more than 9

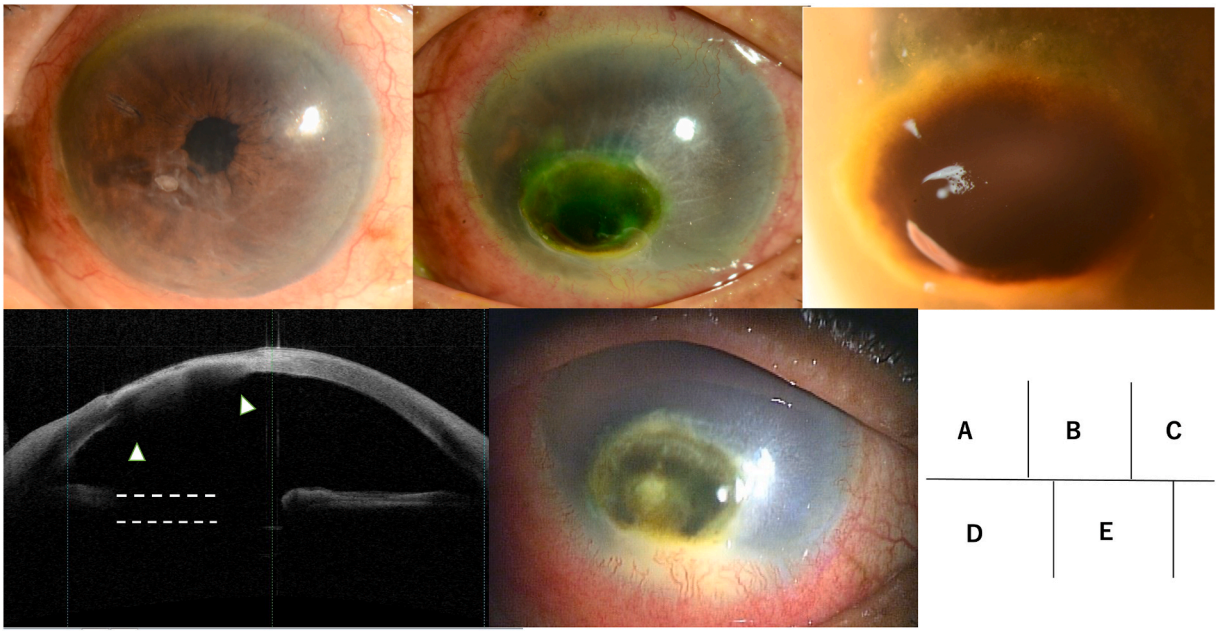

Fig. 1. Photographs and anterior segment optical coherence tomography (AS-OCT) image of the patient's left eye. A) Image obtained at initial presentation showing a calcium deposit in the center of the persistent epithelial defect (PED) in the patient's left cornea. B) Image obtained at the initial fungus treatment visit showing a black lesion measuring approximately 3.0-mm in diameter. C) An enlargement of image B showing an augmented black lesion. D) AS-OCT image of the patient's eye obtained at the initial fungus treatment in which it was possible to see the fungal mass at all corneal layers with a shadow (white arrowheads). As can be seen in the AS-OCT image, there was no iris herniation (white dotted lines). E) Image obtained during the course of treatment for fungal keratitis, showing a decrease in the black corneal lesion and an increase in the hypopyon.

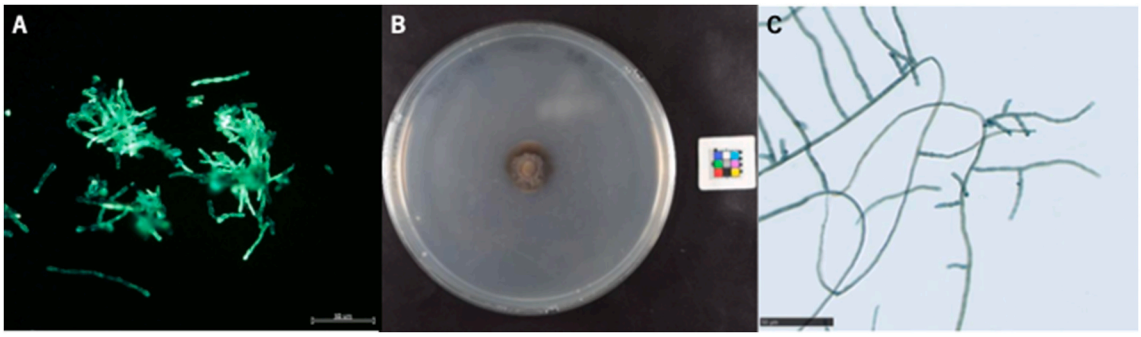

Fig. 2. Microscopic images of the growth of *Cladophialophora boppii* (*C. boppii*). A) Image of the corneal scraping showing a yeast-like fungus shaped ellipsoidal to fusiform, and arranged in branched chains [Calcofluor staining (Fungi-Flour® Staining Solution), ×100 magnification]. B) Image showing growth of *C. boppii* on Potato Dextrose Agar Culture Plates incubated at 28 °C for 14 days. C) Microscopic image of the slide culture showing growth of *C. boppii* on Potato Dextrose Agar Culture Plates incubated at 28 °C for 8 days (lactophenol cotton blue, ×400 magnification).

months post treatment. Of note, the results of an anti-fungal susceptibility test for *C. boppii* performed after the treatment period are shown in Table 1.

3. Discussion

To the best of our knowledge, this is a unique reported case of fungal keratitis caused by *C. boppii*. This rare case involved an opportunistic infection that occurred due to a neurotrophic ulcer and an immunosuppressed state with chronic renal failure and low-dose steroid eye drops, which ultimately led to fungal keratitis.

In this present case, the dematiaceous fungus was identified as *C. boppii* via DNA sequencing. Molecular phylogenetic studies have shown that the term *Taeniolella boppii*, which was described by Borelli,[7] has subsequently been changed to *C. boppii* in a report by de Hoog et al.[9] The Cladophialophora group is comprised of melanized catenate hyphomycetes that are prevalently found on the human host.[9]

Herpetic keratitis, a herpes simplex virus corneal infection, reportedly causes decreased central corneal sensation that can lead to the occurrence of a PED and a neurotrophic ulcer.[10] In addition to this, our present case had chronic renal failure, which leads to an immunocompromised condition due to impaired cell-mediated and humoral immunity, thus reducing activities of the immune system cells.[11] Hence, we theorize that the case in this present study suffered from an opportunistic infection that occurred through both associations.

In our present case, we planned to perform corneal transplantation surgery under general anesthesia to remove the corneal stroma with the fungus in the patient's left eye. As stated above, the patient refused to undergo surgery. However, and even though the anti-fungal eye-drop treatment was tapered, there has been no recurrence of fungal keratitis for more than 9 months post treatment. In vitro, *C. boppii* appeared to be susceptible to micafungin and flucytosine at the mean minimal inhibitory concentrations of 0.015 μg/ml and 0.5 μg/ml, respectively, yet unsusceptible to miconazole and itraconazole at the mean minimal inhibitory concentrations of 16 μg/ml and 8 μg/ml, respectively. Retrospectively, we believe that systemic itraconazole may be ineffective, while local natamycin ointment or high concentrations (i.e., 1000 μg/ml) of 0.1% miconazole eye drops may be effective in this case. It should be noted that fungal keratitis usually tends to be difficult to diagnose. In this present case, AS-OCT was found to be especially useful in differentiating between an iris herniation and a fungal lesion due to their color being similar.

In conclusion, here we report a rare case of fungal keratitis caused by *C. boppii* identified via DNA sequencing that was initially difficult to diagnose.

Table 1
Results of an antifungal susceptibility test for *Cladophialophora boppii*.

	(μg/mL)
MCFG	≤0.015
CPFG	8
AMPH	1
5-FC	0.5
FLCZ	>64
ITCZ	>8
VRCZ	>8
MCZ	>16

MCFG: micafungin; CPFG: caspofungin; AMPH: amphotericin B; 5-FC: flucytosine; FLCZ: fluconazole; ITCZ: itraconazole; VRCZ: voriconazole; MCZ: miconazole.

Patient consent

Consent to publish this case report has been obtained from the patient in writing. This case report does not contain any personally identifying information.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Funding disclosure

None to disclose.

CRediT authorship contribution statement

Hideki Fukuoka: Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Norihiko Yokoi:** Writing – review & editing, Supervision, Investigation, Data curation, Conceptualization. **Aya Komori:** Writing – review & editing, Validation, Methodology, Formal analysis, Data curation. **Koichi Makimura:** Writing – review & editing, Supervision, Investigation, Data curation. **Chie Sotozono:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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