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CASE REPORT

Rare Persistent Corneal Infection by *Phoma* sp. - A Case Report

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ABSTRACT

We report a case of severe *Phoma* sp. corneal infection in a middle-aged, otherwise healthy, female patient who was using a soft contact lens. This is the first time that such an infection has been reported in Greece. Our case demonstrates the clinical difficulties and management challenges presented by these recalcitrant corneal infections. Management steps included corneal grafting, vitrectomy, and intravitreal antibiotics.

Keywords: Corneal infection; Fungal; *Phoma* sp.

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INTRODUCTION

Fungal eye infections are rare but can result in keratitis [1, 2] and even endophthalmitis. Many different types of fungi can cause eye infections, but the most common infections are caused by species of *Fusarium*, *Aspergillus*, *Curvularia*, and *Candida*. Trauma is the most frequent predisposing factor, although important contributors include ocular and systemic defects along with the prior application of corticosteroids [3]. Endophytic fungi are ubiquitous organisms found in plants. They usually reside intercellularly or intracellularly without causing any apparent symptoms of infection, while all plants are known to harbor endophytes [4]. *Phoma* is a genus of endophytic fungus which may also appear on plant foliage. In contrast to most fungal species that can cause eye infections, the involvement of any *Phoma* sp. in eye injury is previously unreported. In fact, *Phoma* sp. infection appears to be very rare: among 209 references retrieved in a search in PubMed (lemma: *Phoma* sp.; last accessed on September

19, 2019), only eight refer (mostly tangentially) to human infection [5–12] (mainly in immunocompromised hosts [8, 12]), and only one of those may be said to remotely implicate a *Phoma* sp. in eye infection [5]! Herein, we present a unique case of persistent corneal infection by a *Phoma* sp. in an immunocompetent adult with no clear origin of infection.

CASE (SUMMARY IN TABLE 1)

A 47-year-old female who was a long-time soft contact lens user and was meticulous with her lens hygiene presented to her ophthalmologist (March 2014) following a month of constant tearing and progressively worsening blurred vision in the right eye. Anamnesis indicated a preoccupation with gardening and the recent use of commercially available prepackaged plant seeds. The initial diagnosis was bacterial keratitis. She was referred to our center on June 4, 2014 due to a persistent infectious corneal ulcer with a central corneal ulcerative area (0.75 mm × 1 mm), mild stromal infiltration, and a reduced best-corrected visual acuity of 0.3. We interrupted topical treatment for 48 h to obtain culture material (corneal scrapings) and determine the causative agent and her sensitivity to antibiotics. We subsequently initiated treatment (coll. moxifloxacin, coll. azithromycin, washing with Betadine 5%) according to our standard therapy protocol.

Culture demonstrated the presence of *Staphylococcus epidermidis* only, while the clinical picture kept worsening. A satellite extension of the infiltration appeared. On June 24, 2014, we biopsied the limits of the infiltration, and local therapy was changed to coll. gentamicin and coll. vancomycin on July 8, 2014 (Fig. 1).

By July 31, 2014, incomplete healing inferiorly with fibrosis was evident. However, central melting ensued, and we sealed the descemetocele with a tectonic graft on August 9, 2014.

Microscopy (under KOH 15%) of the June 24, 2014 biopsy material revealed abundant narrow and septate fungal hyphae with an acute angle branching pattern. Specimens were inoculated on Sabouraud's dextrose agar with chloramphenicol (0.05%), malt extract agar, and Czapek–Dox agar at 30 °C and 35 °C, respectively. Following incubation (3–5 days), fungal growth (mold) was present in all cultures, with wrinkled colonies grayish to lightly tanned or light salmon-pink in color that grew at a moderately rapid pace. The mold grew at both 30 °C and 35 °C but not at 40 °C. Dark pycnidia with apical openings, abundant small fusiform conidia, and chlamydospores were present. The phenotype was identified as a *Phoma* sp.

By September 10, 2014, a second lunate extension appeared from the superior border of the tectonic graft. We again biopsied the borders of the new infiltrate, and mycology culture confirmed the previous phenotypic identification, while sequencing of the internal transcribed spacer (ITS1 and ITS2) regions of the isolate's ribosomal DNA presented the highest homology with *Phoma foliaceiphila*.

As susceptibility testing was not yet complete, we started treatment with ketoconazole 200 mg b.i.d. systemically and topical application of fluconazole hourly. By 15 Sept 2014, hypopyon developed (1.5 mm height) with paracentral ulceration and melting adjacent to the graft (Fig. 2).

By October 5, 2014, despite antifungal treatment, the whitish infiltrate at the superior border of the graft had enlarged, and there was paracentral melting. We changed treatment to topical amphotericin 0.015% hourly and to intrastromal injections of amphotericin in order to overcome the limited permeability of the intact epithelium.

On October 15, 2014, we proceeded with a tectonic 7.5 mm diameter full-thickness keratoplasty, anterior chamber washing, and intrastromal injection of amphotericin B at the graft edges. Additionally, we performed a corneal biopsy and sent specimens to facilitate the identification of the fungus.

Susceptibility results became available on November 7, 2014, which showed in vitro susceptibility to amphotericin B, itraconazole, voriconazole, posaconazole, and micafungin, and resistance to flucytosine and caspofungin. We changed treatment to voriconazole 400 mg, twice daily systemically.

The graft remained clear for 2 months with no clinical signs of infection. However, by

Table 1 Timeline of the case

February 2014	Initial symptoms appear
March 2014	Visit to ophthalmologist
June 4, 2014	Referral to Ophthalmica; persistent infectious corneal ulcer with a central corneal ulcerative area (0.75 mm × 1 mm), mild stromal infiltration, VA: 3/10
June 6, 2014	Corneal scrapings obtained (*Staphylococcus epidermidis*); coll. moxifloxacin, coll. azithromycin, washing with Betadine 5%
June 24, 2014	Lunate extension of the infiltration; biopsy of its limits (*Phoma* sp.)
July 8, 2014	Coll. gentamicin, coll. vancomycin
July 30, 2014	Incomplete healing inferiorly with fibrosis
August 9, 2014	Central melting; sealed descemetocele with tectonic graft
September 10, 2014	New lunate extension at superior border of the tectonic graft; biopsy of its limits (*Phoma* sp.); ketoconazole 200 mg b.i.d. systemically and topical application of fluconazole hourly
September 15, 2014	Hypopyon (1.5 mm) with paracentral ulceration and melting adjacent to the graft
October 5, 2014	Enlarged whitish infiltrate at superior border of the graft and paracentral melting; topical amphotericin 0.015% hourly and intrastromal injections of amphotericin
October 15, 2014	Tectonic 7.5 mm diameter full-thickness keratoplasty, anterior chamber washing and intrastromal injection of amphotericin B at the graft edges; corneal biopsy (*Phoma foliaceiphila*)
~ November 7, 2014	Susceptibility results: susceptible to amphotericin B, itraconazole, voriconazole, posaconazole, and micafungin; resistant to flucytosine and caspofungin; voriconazole 400 mg, s: 1 × 2
November 21, 2014	Small suture infiltration appears; immediate suture removal and intrastromal injection
December 19, 2014	Infiltration has invaded the graft and enlarged, despite continuing systemic voriconazole administration
December 25, 2014 to January 1, 2015	Infiltrate has developed central melting with hypopyon and perforation
January 2, 2015	Second graft. Reconstruction of anterior chamber, removal of crystalline lens, anterior segment wash-on and core (open sky) vitrectomy, with removal of retroiridic inflammatory membranes and injection of combination of amphotericin-voriconazole into the vitreal cavity; systemic treatment with voriconazole (200 mg b.i.d.) and posaconazole started, initially for three months
March 16, 2015	Clear graft; diminished peripheral neovascularization. Best-corrected VA: 5/10
June 10, 2015	Discontinued systemic voriconazole
July 1, 2015	Infiltrate arising from the posterior surface of the iris
July 2, 2015	Panophthalmitis with hypopyon and posterior vitritis

Table 1 continued

July 5, 2015	Emergency PP vitrectomy and silicon oil; restarted systemic voriconazole
August 2016	Discontinued systemic voriconazole
January 2017	Infection is under control

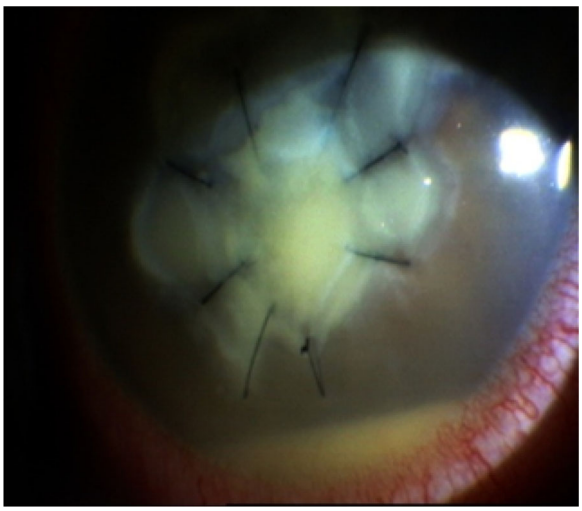

Fig. 1 Right cornea with the initial infiltration and the added lunate infiltration 20 days later. The central corneal ulcer with the stromal infiltration and hypopyon are clearly seen

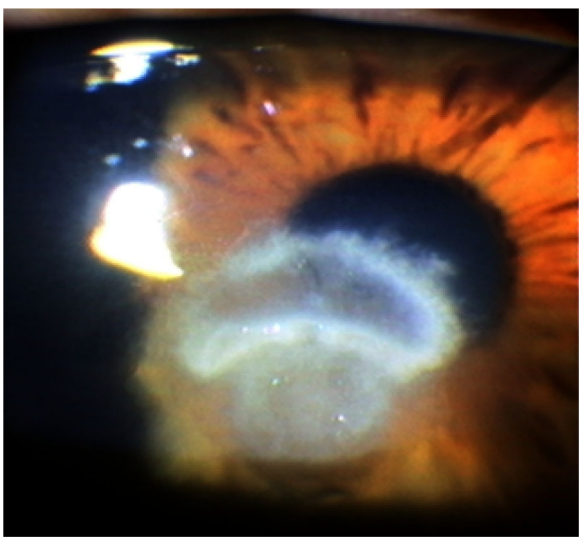

Fig. 2 Appearance of the treated ulcer

November 21, 2014, a small suture infiltration had appeared, which had invaded the graft and enlarged by December 19, 2014 despite systemic voriconazole administration, immediate suture removal, and intrastromal injection.

Between December 25, 2014 and January 1, 2015, the infiltrate developed central melting with hypopyon, and perforation occurred. At this point, a dilemma arose as to whether we should perform enucleation, given the risk of dissemination of the fungal infection to the brain. We decided against it. On January 2, 2015, we proceeded with a second graft, despite the active, uncontrolled infection. We reconstructed the anterior chamber, removed the crystalline lens, and performed anterior segment wash-on and core (open sky) vitrectomy, with the removal of retroiridic inflammatory membranes and the injection of a combination of amphotericin-voriconazole into the vitreal cavity. Systemic treatment with voriconazole (200 mg b.i.d.) and posaconazole was initiated for an initial period of 3 months, and biweekly liver and kidney function tests were ordered.

By March 15, 2015, the graft remained clear while peripheral neovascularization diminished following two subconjunctival injections of steroid and bevacizumab. Best-corrected VA improved to 0.5.

On June 10, 2015, we discontinued systemic voriconazole. However, on July 1, 2015, an infiltrate arose from the posterior surface of the iris. By July 2, 2015, panophthalmitis had developed with hypopyon and posterior vitritis, in spite of a clear graft. Consequently, on July 5, 2015, we proceeded with emergency pars plana (PP) vitrectomy and silicon oil. We also restarted systemic voriconazole administration.

As of January 2017, the infection is under control. Systemic voriconazole was

discontinued 14 months after the last operation (vitrectomy), and silicone oil gradually filled the anterior chamber, damaging the endothelium. This case is reported with the informed consent of the patient.

DISCUSSION

Based on the literature reported in PubMed, human *Phoma* ssp. infections are extremely rare, and those reported in the literature involve the lung interstitium [6], the exposed skin of farmers [7, 10], or immunocompromised patients [8, 11]. In addition, in the two cases where the investigation determined (either empirically [7] or through culturing [8]) a *Phoma* ssp., antibiotic susceptibility pointed to the same basic treatment options: itraconazole, ketoconazole, and amphotericin B [7, 8]. Fluconazole may sometimes be effective [7], although a *Phoma* ssp. has been reported to be resistant to both fluconazole as well as 5-flucytosine [8]. It should also be noted that targeted delivery of voriconazole by intrastromal corneal injection is considered a safe and highly effective way to treat deep recalcitrant fungal keratitis [12].

A prominent feature of our case was the apparent low susceptibility of the *Phoma* sp. to antibiotic/antifungal treatment. However, *Phoma* ssp. isolated from different medicinal plants has been reported to be a promising source of antimicrobial compounds [13]. This could explain the low susceptibility of the *Phoma* sp. in our case, as it is reasonable to expect that it must have evolved resistance to its own antibiotic products and related compounds.

We have not been able to determine our patient's infection route. However, the occurrence of major fungi varies with season or with leaf age. The occurrence of *Phoma* ssp. has been reported to be strongly correlated with season, reaching its maximum—in at least one meticulously investigated case—between the months of February and May [14]. Although this provides only a circumstantial indication, our patient's anamnesis indicated that her infection correlated well with the seasonal peak in *Phoma* sp. occurrence!

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Compliance with Ethics Guidelines. This case is reported with the informed consent of the patient.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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