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Case Report

Non-Pathogenic *Aspergillus oryzae* Acute Exogenous Endophthalmitis after Penetrating Keratoplasty: The First Case Report in the Literature

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Keywords
Anti-fungal agent · Case report · *Aspergillus oryzae* · Fungal endophthalmitis · Penetrating keratoplasty complications · Voriconazole

Abstract
The authors report a singular case of post-operative exogenous fungal endophthalmitis caused by a non-pathogenic fungal agent: *Aspergillus oryzae*. A 75-year-old Caucasian woman with post-penetrating keratoplasty fungal endophthalmitis due to a nonpathogenic *A. oryzae,* resistant to the current azoles anti-fungal agents, was treated with subtotal vitrectomy, intravitreal injection, and systemic voriconazole therapy. Complete resolution of the endophthalmitis occurred after two subsequent intravitreal injections and a 2-month-long systemic delivery of voriconazole. The quick identification of the fungal agent allowed immediate and targeted therapy. In the article, the safety and efficacy of both systemic and intravitreal voriconazole treatments are discussed.

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Introduction

Fungal exogenous endophthalmitis, defined as growth of any yeast or filamentous fungus from intraocular fluids associated with inflammatory reaction of globe tissues, has been nosographically classified as post-traumatic, post-keratitis, and postoperative [1]. Fungal endophthalmitis after keratoplasty tends to be rare with the incidence of 0.16% [2], which is 3 times higher than that of post-cataract surgery [3]. Within the surgery-related cases, a large amount (70%) follows cataract extraction with intraocular lens (IOL) implantation [1]: the genera *Aspergillus fumigatus, niger*, and *terreus* are the most common causal agents in this clinical category (with variation ranging from 50 to 91%, depending on geographic location) [1, 4]; in post-keratoplasty eyes is reported a strong association between exogenous endophthalmitis and candida species contamination [1, 3]. One recent study showed the increasing trend in fungal donor rim contamination with full correlation between the positive donor rim culture and cases of postoperative infection: local and oral steroid use as well as long-lasting broad-spectrum antibiotic postsurgical treatment may be contributing factors [2]. The only results for *A. oryzae* infection were rare cases of infective keratitis [5, 6]. To the best of our knowledge, the case reported in this article is the first nonpathogenic *A. oryzae* exogenous fungal endophthalmitis after penetrating keratoplasty (PKP) described in the literature. *A. oryzae* belongs to Aspergillus section Flavi. It is a non-aflatoxigenic filamentous fungus, widely used to ferment soybeans, saccharify rice in the making of sake, and product enzymes, although there have been reports of some strains identified as *A. oryzae* that were implicated in the production of aflatoxins or other toxic metabolites [7, 8].

The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531801).

Case Report

A 75-year-old Caucasian female with a history of previous herpetic uveitis underwent cataract surgery with subsequent anterior chamber (AC) IOL implantation in her right eye 20 years before. Because of a corneal decompensation, she underwent her first PKP with an AC IOL explant in February 2011; her early postoperative course was complicated by massive vitreous hemorrhage (for intraoperative choroidal effusion), hyphema, corneal edema, raised intraocular pressure (IOP), compensated with postoperative pharmacological therapy. One year later, in March 2012, a scleral fixation IOL was implanted. Then, in January 2014, for an unsatisfactory medical therapy control of IOP, a trabeculectomy was performed. Two years later, a new endothelial decompensation induced graft failure with visual impairment, and the patient was submitted to an endothelial keratoplasty (DSAEK) in November 2016. Approximately 2 weeks later, due to an early donor disc graft failure, an uneventful full-thickness corneal transplantation (PKP) was performed. Anterior chamber amoxicillin and sub-tenon corticosteroid injections were applied immediately after the surgery. The next day at postoperative control, the patient presented with massive corneal edema (Fig. 1a) with no red eye, no hypopyon, and no pain, so that regular postoperative therapy was delivered. Seven days later, the gravity of the clinical conditions – an evident graft failure (Fig. 1b), an increase in the corneal edema, and the emergence of corneal melting with AC involvement (Fig. 1c) – led to the suspicion of acute surgery-related exogenous endophthalmitis.

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A new surgery was planned as follows: the infected sutures were removed and the opacified, edematous graft with severe melting was replaced with a new donor cornea, the partially dislocated scleral fixation IOL was removed, and subtotal vitrectomy was performed (Fig. 1d). Cornea, AC exudates, and vitreous samples were taken and delivered for microbiology examination, as well as donor corneo-scleral ring tissue with the entire storage medium (that were conserved, as usual, after the first PKP at 4°C for microbiological purposes) and the explanted IOL. Intravitreal injections of 0.01 mg of vancomycin and 0.1 mg of amikacin were administered. Twenty-four hours later, microscopic observation of the corneal specimens with the potassium hydroxide (KOH) preparation revealed mycelial elements. Therefore, they were inoculated onto blood agar and Sabouraud dextrose agar isolation media with incubation at 29°C and daily observation: very fast colony growth occurred in both AC exudate samples and donor storage medium cultures (Fig. 2a, b, c). For identification of the pathogenic agent, a spectrometry method was used. Mass spectrum profile was acquired by MALDI-TOF mass spectrometry and identified as *A. oryzae* by matching against an in-house-implemented database [9] (Fig. 2d). Due to high sensitivity of this diagnostic tool, which collects species-specific spectra in order to reproducibly identify microorganisms, unequivocal correspondence was found with *A. oryzae* species. Intravenous amphotericin b 50 mg twice a day and amphotericin b 0.03% drops were administered until the resistance to this drug was confirmed by an antifungal susceptibility test. Voriconazole's minimal effective concentration was 0.25 μg/mL. Thus, intravenous voriconazole therapy of 200 mg twice a day was started and maintained for 1 week. B-scan ultrasonography demonstration of persistent vitreitis with inflammatory infiltrates led us to apply two intravitreal pars plana injections of voriconazole 100 μg/mL in a week. The concentration of intravitreal voriconazole injection was calculated based on a maximum-tolerant dose reported in previous safety studies [10]. No local adverse reactions were reported. Two months of oral voriconazole 200 mg twice-a-day regimen resulted in well-tolerated total clinical resolution of infection. Six months after intravitreal injections, a clear graft resulted (Fig. 3a) in a BSCVA of 20/100 with +11 = +3.50 × 140°. At fundus examination, no vitreous debris and no signs of retino-choroidal inflammation were found. The patient has given explicit, informed consent to publish this case.

Discussion

The last reviews of the medical literature had not revealed cases of exogenous ocular infections due to *A. oryzae* [4, 11]. Only one case of endogenous necrotizing scleritis following *A. oryzae* meningitis was reported in 1982 [12]. Moreover, A. oryzae infection was referred in rare cases of infective keratitis [5, 6]. Thus, to the best of our knowledge, this is the first case described of *A. oryzae* exogenous fungal endophthalmitis [6–11]. Fungal endophthalmitis is considered a dreadful infection due to the difficult identification by clinical presentation; the establishment of an adequate therapy is often delayed. In addition, the growing trend towards resistance to common antifungal agents and the lack of specific alternative treatment protocols make the management of these rare cases arduous. Amphotericin B has a limited effectiveness in invasive eye infections because of its minimal penetration into the vitreous; its retinal toxicity in case of intravitreal administration is well known, but it represents the only antifungal drug approved for intravitreal injections [13]; fluconazole achieves high concentration into the vitreous, also in inflamed eyes, it has a good safety profile, but rarely susceptible organisms cause severe endophthalmitis [10].

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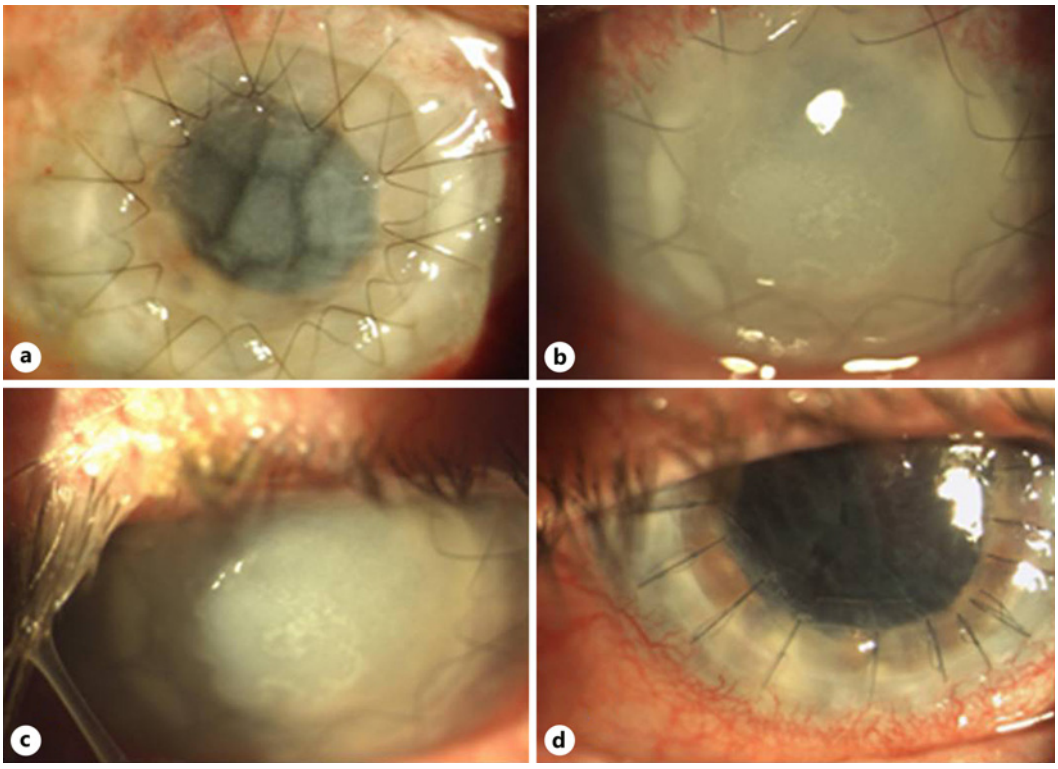

Fig. 1. Acute infection course: massive corneal edema with no red eye, no hypopyon, and no pain at the first postoperative day (**a**); graft failure with corneal edema, corneal melting, and AC involvement 1 week later (**b**, **c**); the new clear cornea sutured in place (**d**) 10 days postoperatively.

Since the US Food and Drug Administration and the European Medicines Agency approved the systemic use of voriconazole in 2002 for the prevention or treatment of refractory fungal infections, such as severe aspergillosis in immunocompromised patients, there has been an increasing interest in testing this novel agent in fungal eye infections. Voriconazole is a synthetic triazole showing higher affinity to sterols biosynthesis enzymes with consequently more potent inhibition activity compared with first-generation antifungal agents; in addition to 14α demethylase inhibition, voriconazole causes the ergosterol depletion and cell wall destruction also by preventing 24-methylene dihydrolanosterol demethylation in some yeasts and filamentous fungi such as Aspergillus species [14]; some bioavailability studies showed achievement of significant vitreous and aqueous humor concentrations after oral and intravenous administration in non-inflamed eyes [14]. Successful intracameral administration led rapidly to experimentation of first intravitreal injection of voriconazole after the endogenous fungal endophthalmitis conventional treatment failure in 2006. Despite the Infectious Diseases Society of America 2008 guidelines suggesting oral and intravitreal voriconazole administration as an alternative treatment of aspergillus endogenous endophthalmitis, many authors recommend voriconazole as a first-line intravitreal drug [13–15] because of its safety on retinal tissue and its efficacy as reported in several in vitro and in vivo studies [14]. Our clinical report on this rare nonpathogenic fungal infection encourages the oral and intravitreal voriconazole use in exogenous fungal endophthalmitis; it is also intended to alert on the relevance of the fast identification of the pathogen for an immediate and targeted therapy.

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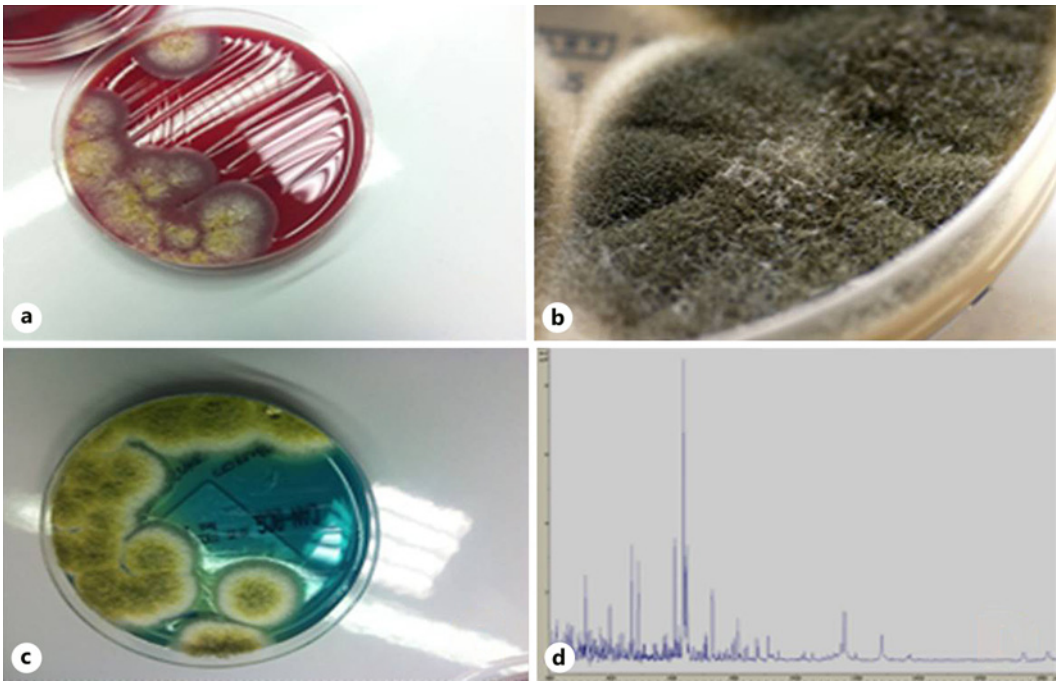

Fig. 2. Three-day-old *A. oryzae* colonies grown on solid medium: tryptic soy agar (TSA) (**a**), Candida bromocresol green (BCG) agar (**b**), Sabouraud agar (**c**). Mass spectrum profile of *A. oryzae* using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI TOF MS) (**d**).

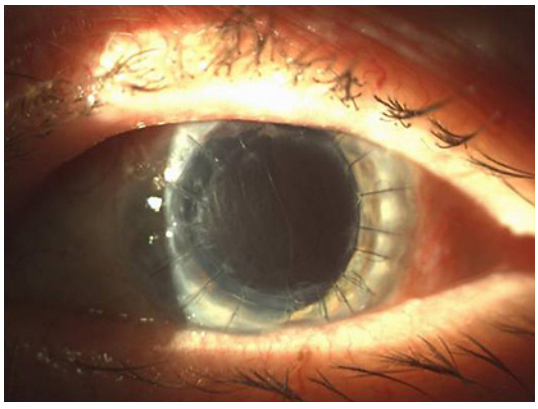

Fig. 3. Six months follow-up after voriconazole intravitreal injections a clear graft resulted with a BSCVA of 20/100 with +11 = +3.50 ×140° (Aphakia).

Statement of Ethics

All procedures performed in the study were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study has been evaluated by the Catholic University/A. Gemelli University Polyclinic Foundation-IRCCS Institutional Ethics Committee and deemed not to require ethics approval, in accordance with local guidelines. Written informed consent was obtained from the patient for publication of the details of the medical case and any accompanying images.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

L.M. designed the study, analyzed the data, wrote the article, and performed the final revision; M.E.T. and R.T. collected, analyzed the data, and wrote the article; L.S., R.F., and LG collected the data and performed a critical revision; and M.S. and S.R. performed a critical revision. All authors read and approved the final manuscript.

Data Availability Statement

The main part of the data used for this study is included within the article. Other data are available from the corresponding author upon request.

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