Current Fungal Infection Reports (2020) 14:384–390
https://doi.org/10.1007/s12281-020-00403-5

FUNGAL GENOMICS AND PATHOGENESIS (S SHOHAM, SECTION EDITOR)

Invasive Fungal Keratitis as an Uncommon Form of Mucormycosis Leading to Endophthalmitis: Report of Two Cases and Literature Review

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Published online: 20 July 2020

Abstract

Purpose of Review This study was conducted to report two cases of fungal keratitis caused by mucormycetes that led to endophthalmitis.

Recent Findings Case number 1: a 24-year-old male, with a known case of thalassemia major, presented with chief complaints of painful periorbital edema and redness in the left eye. Intravenous antibiotics were prescribed upon diagnosis of orbital cellulitis, but it progressed to the cornea and sclera and led to endophthalmitis, which was treated with penetrating keratoplasty (PK) combined with deep vitrectomy. Case number 2: a 6-year-old healthy boy presented to the ophthalmology emergency room with ocular pain and redness in his right eye. He had a history of swimming in a river 2 weeks prior to presentation. At the time of presentation, eye examinations showed a dense stromal infiltration with hypopyon. He underwent therapeutic PK due to progression of infiltration to the total cornea and limbus. After the first PK, the patient underwent combined Re-PK and deep vitrectomy, because of recurrence of infection on graft and development of endophthalmitis. The infection relapsed on corneal graft and visual acuity decreased to no light perception. For this patient, enucleation was performed in order to prevent spread of infection to the orbit and brain.

Summary Fungal keratitis caused by mucormycetes as an uncommon infection might occur in healthy individuals. Accordingly, timely diagnosis and administration of appropriate antimicrobial agents are vital. In fungal keratitis, patients who have intraocular involvement and are unresponsive to initial antifungal therapy should be evaluated regarding suspicion of mucormycetes.

Keywords Keratitis · Fungal · Endophthalmitis · Mucormycosis · Infection · Cornea

Introduction

Mucormycosis is an invasive fungal infection caused by the class of Mucormycetes, the order of Mucorales, and the family of Mucoraceae that as non-septate filamentous fungi include *Mucor*, *Rhizopus*, *Rhizomucor*, *Apophysomyces*, *Cunninghamella*, *Saksenaea*, *and Absidia* species [1, 2]. It has 6 clinical forms including rhino-orbito-cerebral (the most common form), pulmonary, cutaneous, gastrointestinal, disseminated, and focal forms. The focal form is very rare and may involve any organ, leading to endocarditis, mediastinitis, peritonitis, osteomyelitis, pyelonephritis, external otitis, keratitis, scleritis, and necrotizing fasciitis [2, 3]. Fungal keratitis and endophthalmitis caused by mucormycetes are very rare and sight-threatening conditions [4•, 5, 6••, 7•]. Herein, we report two cases of corneal mucormycosis that progressed to endophthalmitis.

This article is part of the Topical Collection on *Fungal Genomics and Pathogenesis*

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Case Presentation (Table 1)

Case 1

A 24-year-old male with thalassemia major presented to the ophthalmic emergency room with chief complaints of left

painful periorbital edema and erythema of 2 days' duration and without any history of ocular trauma or surgery. He had no signs of upper respiratory infection or sinusitis. Eye examinations revealed visual acuity (VA) of 20/100, superior eyelid swelling with erythema, limitation of motion on superior gaze, 16 mmHg intraocular pressure (IOP), conjunctival injection without discharge, and punctate epithelial erosion in the inferior part of the cornea. The anterior chamber (AC), lens, and vitreous were clear with normal optic disc and retina. He underwent orbital computed tomography (CT) scan, which showed inflammation of the orbital cavity and posterior sclera (Fig. 1). Intravenous (IV) ceftazidime (1 g q8 h) combined with vancomycin (1 g q12 h) and topical ciprofloxacin were prescribed upon diagnosis of orbital cellulitis.

After 48 h, symptoms and signs began to worsen, conjunctival chemosis increased, and limitations of motion in all positions of gaze developed. At the same time, VA decreased to 20/600, and ocular echography showed increased thickness in the posterior pole of sclera with posterior orbital inflammation (Fig. 2a). Consequently, IV dexamethasone (8 mg q8 h) was prescribed.

After 24 h, redness and conjunctival chemosis were reduced and VA increased to 20/100. However, after 24 h, the patient came back with significant eye pain, swelling, and redness and decreased VA to hand motion. Eye examinations showed multiple patchy, superficial stromal infiltrates of the cornea with corneal edema, and 1-mm hypopyon in AC (Fig. 3a), while IOP was elevated to 40 mmHg.

Corneal biopsy revealed presence of multiple non-septate hyphae (Fig. 4).

Rhizopus species grew in the culture prepared from a cornea sample. Topical natamycin 5% was prescribed, and then, the patient underwent intrastromal injection of voriconazole (50 μg/0.1 cc) and IV dexamethasone was discontinued after diagnosis of fungal corneal ulcer. After 24 h, eye examinations revealed near-total corneal infiltration and 6-mm hypopyon while VA decreased to light perception (Fig. 3b). Ocular echography revealed severe vitreous opacity and increased thickness of the sclera (Fig. 2b); hence, IV amphotericin B (50 mg Q12 h) was added to his medication. The patient underwent penetrating keratoplasty (PK) combined with deep vitrectomy and intravitreal injection of amphotericin B (10 μg/0.1 cc). One month after the surgery, eye examinations revealed total corneal opacity with peripheral vascularization (Fig. 3b).

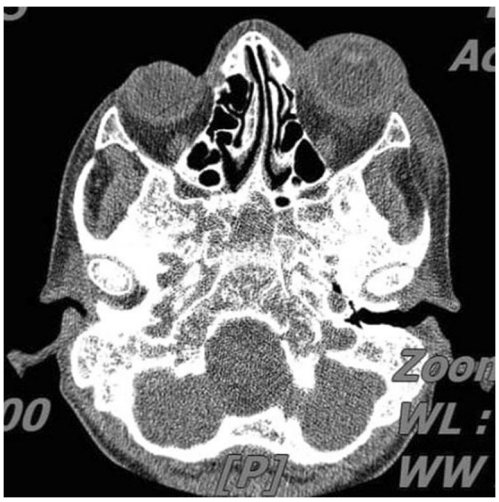

Fig. 1 A 24-year-old man, with a known case of thalassemia major; orbital CT scan with contrast coronal view at presentation revealed clear sinuses and mild proptosis of the left eye with increased thickness of the posterior sclera

Case 2

A 6-year-old healthy boy was referred to the ophthalmic emergency room with chief complaints of ocular pain and redness in his right eye. He had a history of swimming in a river 2 weeks before onset of symptoms. Nasal and oropharyngeal cavities were normal. Eye examinations revealed mild upper eyelid swelling, conjunctival injection, 5 × 6 mm corneal epithelium defect (CED) with dense central stromal infiltration, and 2-mm hypopyon (Fig. 5a). B-scan ocular echography showed no vitreous and retina involvement.

The VA was 20/400 in the right eye, and it was 20/20 in the left eye, which was unaffected. Radiological imaging was performed and initial CT scans of the brain, orbit, and paranasal sinuses were normal. Corneal biopsy was obtained, which revealed multiple non-septate fungal hyphae. No microorganism grew in culture after 2 days. Treatment was initiated with topical eye drop natamycin 5% (q2 h) and topical voriconazole 1% (q2 h). Despite initial treatment, the patient's conditions did not improve after 5 days; the infiltration progressed to involve the entire cornea and limbus. Consequently, the ophthalmology team performed a PK to prevent progression of infiltration to the sclera and vitreous. After PK, histopathology of recipient cornea revealed presence of many non-septate ribbon-like hyphae in the middle and deep stromal layer of the cornea (Fig. 6).

After the operation, antifungal therapy was continued, but corneal infiltration progressed onto the corneal graft 1 week after the initial PK (Fig. 5b). At that point, intrastromal voriconazole injection (50 μg/0.1 cc) was performed twice. However, the patient had no response and the corneal graft was infected and infection progressed to the vitreous cavity as detected in B-scan ultrasonography (Fig. 7).

A deep vitrectomy (vitreous sample sent for pathology) with silicon oil replacement and PK was done, and IV amphotericin B and topical voriconazole 1% and topical natamycin 5% were given. *Absidia* species grew in the culture of the vitreous sample. After 10 days, the infection relapsed in the corneal graft with diffuse involvement of sclera and severe eyelid swelling, redness, and purulent discharge. Visual acuity

Table 1 Clinical data of two patients

Case	Age/sex	Underlying disease	Origin of infection	Eye examination at presentation	Initial and final visual acuity	Treatment and outcome
1	24/M	Major thalassemia with repeated transfusion	Orbital cavity and sclera	Left painful periorbital edema and redness which progressed to superficial central corneal infiltration and hypopyon	20/100 and LP	Systemic and topical antifungal and combined PK + deep vitrectomy. Outcome was total corneal opacity with vascularization.
2	6/M	-	Following swimming in a river	Right corneal edema, 5 × 6 mm CED with dense central stromal infiltration and 2-mm hypopyon	20/400 and no light perception	Systemic and topical antifungal and combined PK + deep vitrectomy. Enucleation was ultimately required due to extension to sclera and optic nerve.

M male, *mm* millimeter, *LP* light perception, *FC* finger counting, *CED* corneal epithelial defect, *PK* penetrating keratoplasty

decreased to no light perception. The patient underwent enucleation and systemic antifungal therapy. After 3 days, eyelid swelling and proptosis reduced without any signs of cerebral involvement.

Discussion

Fungal keratitis is a less common cause of infectious keratitis (IK) in temperate climates (accounting for 5–10% of cases in the USA), but is responsible for 50% of cases in tropical regions [8••]. The most common predisposing risk factors for fungal keratitis are corneal trauma with organic materials such as plant and soil, use of contact lenses, long-standing use of topical corticosteroids, corneal surgery, and chronic keratitis [7•, 8••, 9•]. Fungal keratitis and endophthalmitis caused by mucormycetes are rare [3, 4•, 5, 6••, 7•]. Predisposing conditions reported for mucormycosis include hematological malignancies, hematopoietic stem cell transplantation, uncontrolled diabetes mellitus, long-term treatment with corticosteroids, autoimmune disease, HIV infection, IV drug use, iron overload and chelation therapy with deferoxamine, solid organ transplantation, and prolonged use of broad-spectrum antimicrobial agents [1, 2]. In our study, case 1 (N1) had iron overload due to repeated blood transfusions. Microorganisms such as mucormycetes need iron for their growth and proliferation. In iron overload conditions, the iron is attached to the non-specific receptors on the surface of fungal cells and is transported into the cells [2]. Patients without underlying conditions usually have primary mucormycosis associated with direct inoculation of microorganism secondary to trauma, bites, and burns [2]. In our second case (N2), the infection was most likely transmitted by inoculation of microorganisms during swimming in a river. In previous reports on keratitis and endophthalmitis caused by mucormycetes, the most common underlying disease was diabetes mellitus, and the common sources of infection were rhino-orbito-cerebral mucormycosis (ROCM) (as in our case N1), direct trauma,

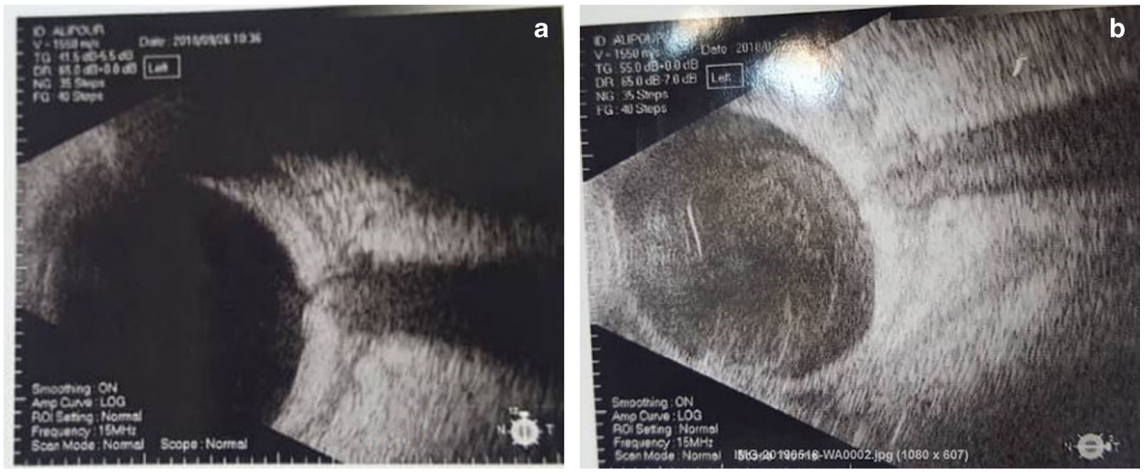

Fig. 2 B-scan ocular echography of the left eye; at presentation, **a** showed clear vitreous cavity with diffused thickening of the posterior sclera (typical T sign); 5 days after admission, **b** showed diffused vitreous opacity and inflammation

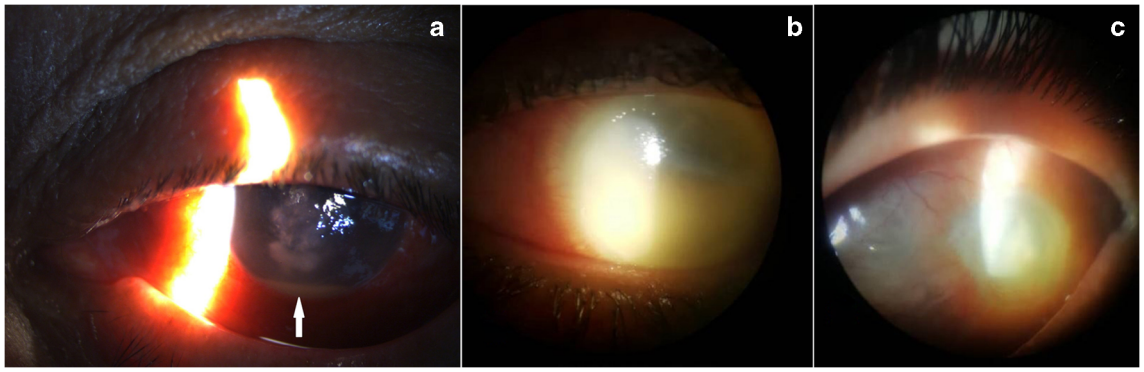

Fig. 3 Slit lamp photos of the left eye; after the 3rd day of admission, **a** showed conjunctival chemosis, central patchy corneal infiltrates, and 1-mm hypopyon (white arrow); after the 5th day of admission, **b** showed near-total corneal infiltration and edema and 6-mm hypopyon; and 1 month after penetrating keratoplasty + deep vitrectomy, **c** revealed diffuse corneal opacity with inferior and superior vascularization

and ocular surgery such as corneal graft [3, 4•, 5, 6••, 7•, 9•, 10, 11]. As shown in Table 2, there are few reported cases of keratitis and endophthalmitis caused by mucormycetes.

Corneal epithelial damage, secondary to eye trauma and long-standing use of topical steroids, can lead to invasion of the fungal spores of mucormycetes at the extracellular matrix and basement membrane. Secretion of lipolytic and proteolytic enzyme destroys the corneal stroma and intraocular tissue [12•, 13]. Mucormycetes invade the endothelial cells, such as in the corneal endothelium layer, by coat homolog (CotH) proteins. The CotH proteins help this organism to adhere to receptor glucose-regulator protein 78 (GRP78) on the endothelial cells, leading to endocytosis of fungi to the endothelial cells [12•]. For the two cases reported here, keratitis led to intraocular involvement and endophthalmitis, but, as demonstrated, one progressed to necrotizing scleritis [3] and one progressed to anterior segment involvement [11]. Some mucormycetes, such as *Absidia corymbifera*, can pass through healthy corneal epithelium by destructive action of the scalp keratin [7•, 12•]. Timely diagnosis of mucormycosis affects prognosis and may reduce morbidity and mortality [12•, 13, 14]. There are reports on various patterns of corneal involvement of mucormycosis; superior corneal and scleral infiltration with feathery border and small hypopyon [3]; CED with diffuse stromal infiltration and several Descemet's membrane folding [9•]; fluffy, white, irregular corneal infiltration with mucus plaque [6••]; central corneal infiltrate with finger-shaped extensions [7•]; and slight grayish infiltration in the central part of the cornea [10]. Thus, clinical diagnosis of fungal keratitis is difficult and requires additional microbiologic and pathologic testing. For the patients with corneal ulcer and infiltration, sampling (scraping or biopsy) and culture should be performed [8••]. To diagnose mucormycosis, classic laboratory methods include histopathology examination of tissue sample and culture. Typical histology patterns of mucormycetes are non-septate wide-angle branching hyphae that are variable in size (6 to 25 μm) and can be visualized by fungus-specific staining including periodic acid-Schiff and methenamine silver stains. Mucorales often fail to grow but may grow slowly (3–7 days) on some culture media, such as Sabouraud agar [1, 2, 12•, 13].

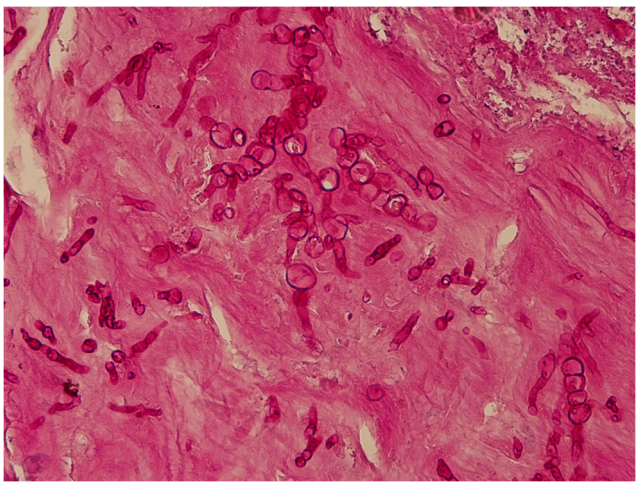

Fig. 4 Slide photo of corneal biopsy revealed many fragments of non-septate fungus in PAS staining (PAS, × 400)

The available data on corneal mucormycosis treatment is limited. Generally, natamycin 5% is the first recommended topical antifungal treatment for filamentous fungal keratitis, but its effectiveness is limited due to poor penetration into the corneal stroma [7•, 8••]. According to several studies, in the case of superficial fungal keratitis, mechanical debridement can lead to the increase in penetration of topical antifungal agent into the corneal stroma [8••]. Although voriconazole has good ocular penetration and is effective for mold and yeast fungal keratitis, it is not effective for mucormycosis and in vitro studies reported that many mucormycetes are resistant to it [2, 14]. Among the azoles, posaconazole and isavuconazole possess good in vitro good activity against many mucormycetes and are recommended for salvage or maintenance therapy [14]. Although itraconazole has activity against some strains of *Rhizomucor* and *Lichtheimia*, it is not effective for the treatment of mucormycosis [1, 2, 14]. Topical

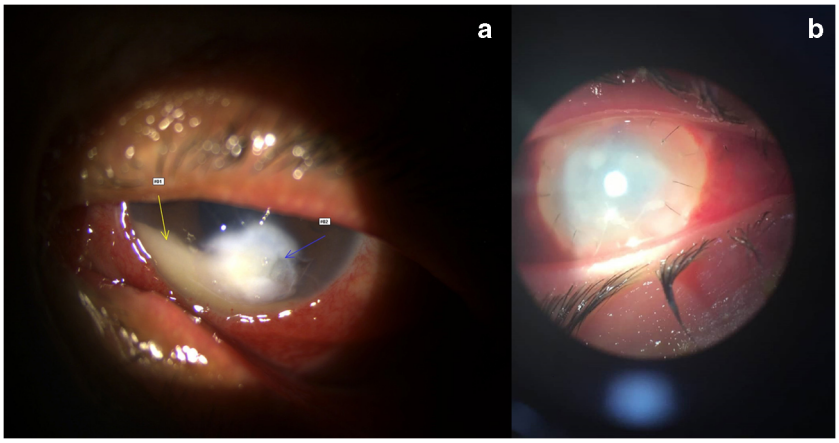

Fig. 5 A 6-year-old boy presented with right eye pain and redness; **a** slit lamp photos of the right eye at presentation revealed conjunctival chemosis, dense central stromal infiltration (blue arrow), and 2-mm hypopyon (yellow arrow); 1 week after first PK, **b** revealed severe conjunctival injection and purulent discharge with diffuse corneal edema and infiltration of sutures

amphotericin B (0.15% and 0.30%) is the first recommended topical antifungal for treatment of yeast fungal keratitis [8••]. Varona et al. reported a case of keratitis caused by *Absidia corymbifera* that was treated with topical amphotericin B 0.15% and oral posaconazole [7•]. Intrastromal injections of voriconazole (50–100 μg/0.1 cc) and amphotericin B (5–10 μg/0.1 cc) are generally recommended for treatment of deep and invasive fungal keratitis and fungal keratitis with intraocular involvement, and in patients who do not respond to primary treatment [7•, 8••]. Based on previous reports, systemic antifungal therapy has been recommended for severe fungal keratitis and keratitis with intraocular involvement [8••]. Amphotericin B is the most common systemic antifungal drug used for the treatment of mucormycosis [14]. Ho et al. reported a case of endogenous fungal endophthalmitis caused by *Rhizopus* species secondary to RCOM that was successfully treated with systemic and intravitreal amphotericin B [4•]. Therefore, we recommend that fungal keratitis caused by mucormycetes be treated with a topical antifungal with good activity against mucormycetes and good penetration into the cornea and intraocular tissues, such as amphotericin B 0.15 or 0.30%, and systemic antifungal drugs like posaconazole and IV amphotericin B.

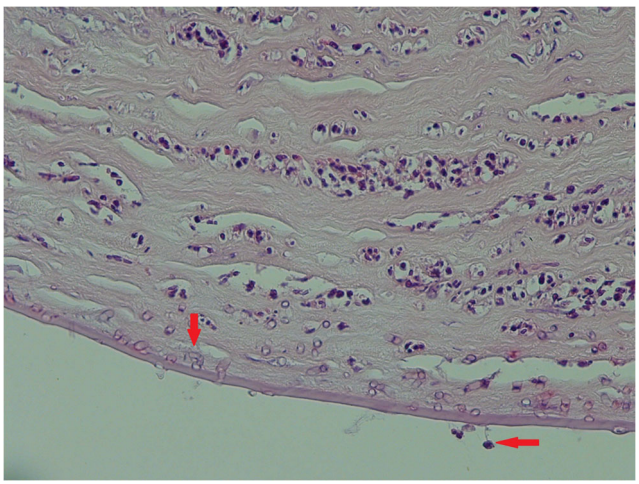

Fig. 6 Slide photo of recipient cornea after PK revealed inflammatory cell infiltration of deep stroma with many hyphae penetrating through Descemet's membrane (red arrows) and entering anterior chamber (hematoxylin and eosin, × 400)

Conclusion

Fungal keratitis caused by mucormycetes is a rare and vision-threatening condition that might occur in otherwise healthy individuals. Mucormycetes can pass through the cornea and invade the intraocular structures, leading to endophthalmitis. Thus, timely detection and initiation of appropriate antimicrobial agents are essential. In fungal keratitis, patients with intraocular involvement and those who are not responsive to initial antifungal therapy should be evaluated regarding suspicion for mucormycetes. Treatment should include topical and systemic antifungal drugs with good activity against mucormycetes and good penetration into the cornea and intraocular tissues.

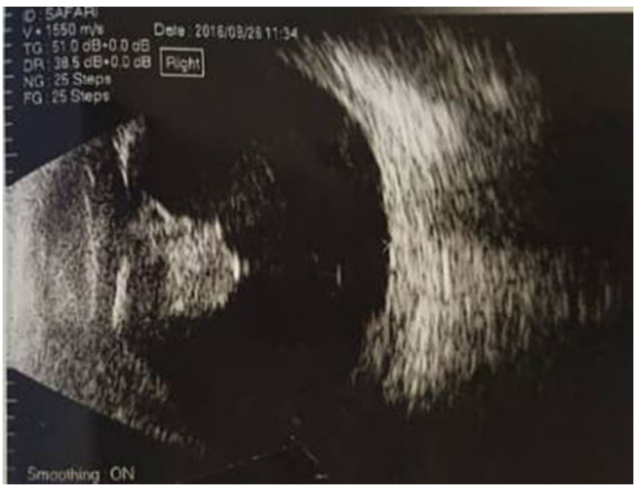

Fig. 7 B-scan echography of the right eye 1 week after first PK showed dense vitreous opacity in the anterior part of the vitreous cavity

Table 2 Summary of reported cases of keratitis and endophthalmitis caused by zygomycetes

Author	Age/sex	Type of ocular infection	Source of infection	Underlying condition(s)	Outcome
Ho [4•]	63/F	Endogenous endophthalmitis caused by *Rhizopus* species	ROCM	Diabetes	Complete resolution of chorioretinitis and vitritis. Final BCVA 6/9
Bhansali [5]	64/M	Endophthalmitis	ROCM (was detected on autopsy)	Diabetes	Died
Feizi [9•]	19/M	Keratitis after corneal transplantation (DALK)	Contaminated corneal graft	-	PK performed. Final BCVA 20/30
Locher [3]	50/M	Necrotizing scleritis with adjacent keratitis caused by *Rhizopus* species	4 weeks after uncomplicated cataract surgery	Diabetes	Enucleation
Marshall [6••]	37/M	Keratitis caused by *Absidia corymbifera*	Scratching of the cornea with a galvanized nail	-	PK performed. Final BCVA 20/400
Varona [7•]	55/M	Keratitis caused by *Absidia corymbifera*	Unknown	Use of topical steroids	Successful treatment with topical amphotericin B and oral posaconazole. Final BCVA 4/10
Maria [10]	30/M	Keratitis	Entry of dust particles into the eye	-	Treatment with topical and systemic antifungal therapy. Outcome was dense opacification of site of ulcer
Schwartz [11]	26/M	Keratitis with anterior segment involvement caused by *Rhizopus* species	Corneal laceration with a soil-contaminated screw	Von-Willebrand's disease	PK performed. Outcome was graft that was moderately edematous and vascularized

M male, *F* female, *ROCM* rhino-orbital-cerebral mucormycosis, *BCVA* best-corrected visual acuity, *DALK* deep anterior lamellar keratoplasty, *PK* penetrating keratoplasty

Acknowledgments The authors wish to thank Mr. H. Argasi at the Research Consultation Center (RCC) of Shiraz University of Medical Sciences for his invaluable assistance in editing this manuscript.

Compliance with Ethical Standards

Conflict of Interest Mohammad Reza Khalili, Seyed Mohammad Bagher Abtahi, Mehrnaz Atighehchian, Shahla Hosseini, Mohammad shirvani, Elham Sadeghi, Meysam Ghanbari, and Masoomeh Eghtedari declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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