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Case Report

Fusarium Endophthalmitis: About a Case of Enucleation

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Abstract
Fungal eye damages are rare but severe diseases that cause corneal opacity and blindness. The most common pathogens of such damages are *Fusarium* and *Aspergillus*. *Fusarium* is ubiquitous mold found commonly in soil and organic debris. The risk factors for fungal eye damages are trauma (plants, soil, metallic or foreign bodies), corneal surgery (keratoplasty), disruption of corneal epithelium, contact lens wear, and immunosuppressed patients. Clinical suspicion of fungal keratitis is helpful because the diagnosis is difficult to reach based on a laboratory verification, with corneal scraping in adequate culture medium and PCR. *Fusarium* sp are generally resistant to most antifungal drugs. Despite medical therapy with topical natamycin and voriconazole, surgery is often required with antifungal intracorneal injection, corneal transplantation, and enucleation. A 37-year-old patient presented with a trauma of cornea with a metallic piece was examined in this study. Nine months after local treatment, he complained of painful ocular lesion with a hypopyon. He was treated by intravitreal injection of vancomycin. A corneal scrapping showed hyphae of *Fusarium proliferatum*. He was treated with amphotericin B and voriconazole; however, no convincing efficacy was achieved and the unbearable eye pain persisted and, unfortunately, he was diagnosed with hepatic cytolysis. Due to the treatment failure, therefore, the enucleation was required and the pathological examination of the eye was found negative.
Keywords: *Fusarium*, Endophthalmitis, Keratitis, Cornea Ulcer, Voriconazole, Keratectomy, Enucleation

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Introduction

The eye can be affected by various infectious agents, including fungi. Ocular mycological lesions are rare (< 5% of infectious keratitis) (1), but known to cause long-term and more serious complications than bacterial lesions. Such mycologic infection of the eye may result in enucleation, as was the case investigated in the present study.

Case Presentation

A patient aged 37, with no particular history, consulted the doctor about a wound in the cornea of the right eye, that caused by direct trauma of a rusty cable used for holding trees. After cleaning the wound and suturing, the patient was sent home with local treatments by anti-inflammatory eye drops and antibiotics. Nine months later, signs of eye inflammation appeared and, therefore, his eye was treated with another anti-inflammatory eye drops. Due to the unfavorable development of inflammation and the appearance of a hypopyon (Figure 1A) associated with post-traumatic cataract and hyalitis, his eye was washed and the puncture of the anterior chamber was performed, for direct examination and a microbial culture. The patient is then treated with phacovitrectomy and intravitreal injection of vancomycin and ceftazidime. However, his vision continued to decline, leading to blindness in the right eye.

A brain scan detected no foreign body. Due to the persistence of significant local pain associated with hypopyon and the growing concern about endophthalmitis, a new sample was taken by scraping and puncture of the anterior chamber, which revealed a *Fusarium* proliferation. The patient was treated with intravenous voriconazole (200 mg × 2/day) and intravitreal voriconazole, then with drops in the eye and *per os*. Despite the good clinical tolerance of the treatment, no objective efficacy of the antifungal drugs was achieved and, especially, no relief in insomnia eye pain was observed. In addition, hepatic cytolysis appeared but the rest of the biological assessment was found normal. The oral voriconazole was discontinued and replaced by weekly intravitreal injections of voriconazole and amphotericin B. Treatment with posaconazole was discussed, but it was not retained due to hepatic cytolysis. Finally, an enucleation was performed. Direct examination of the surgical specimen revealed the presence of some hyphae

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which, however, did not grow in culture (persistent elements but rendered inactive by antifungal drugs?) and the PCR analysis remained negative. (Table 1)

Discussion

An Expanding Filamentous Fungus

Fusarium, including many species, are cosmopolitan filamentous fungi. They are widespread in the environment but have long been considered to be simple contaminants (2). However, skin and eye lesions (onychomycosis, keratitis) caused by these fungi have already been recognized for many years (3). During some diseases and treatments that suppress the immune system, sometimes serious lesions are also observed with these fungi.

Fusarium are pathogens for many plants (e.g., corn) (Figure 1B) and animals. They are found in soil, plants, as well as water, and are disseminated by wind and runoff. The *Fusarium proliferatum species*, isolated from our patient, has already been recognized as a pathogen responsible for rare ocular (4), pulmonary (5), and even diffuse damage in humans.

Eye Damage Due to Fusarium

The epithelium of the cornea constitutes a barrier in the eye; if it is altered, however, the fungus can penetrate into the cornea where treatments are ineffective due to the lack of vascularization of this organ.

Various factors that cause ocular involvement (keratitis and more rarely endophthalmitis) (Table 2) (6,7,8) include improper use of antibiotic or corticosteroid eye drops, wearing contact lens (9,10), contaminated cleaning or storage liquid, eye surgery or even corneal kissing, and contact with, in particular, plant elements (e.g., tree branch, sugar cane, corn stalk, palm leaf), minerals (e.g., sand) (11), or animals (e.g., cow's tail, cat's claw, bird feather).

In industrialized countries, fungal keratitis is quite rare, occurring especially among high-risk patients (cornea transplant, topical corticosteroids) with *Fusarium, Candida,* and *Aspergillus* (Table 3). In China, fungal keratitis caused by *Fusarium* is more common among farmers, whereas *Candida* infections are rare among them (<1%).

Fungal keratitis is characterized by ulceration of the cornea, and is associated with one or more of corneal stromal infiltrates, suppuration eye pain, a feeling of foreign body, and a reduced visual acuity. Local examination has shown that keratitis with feather or ring infiltrates, visible with an ophthalmoscope. A hypopyon is frequently found in 30% of cases (6). *In vivo* confocal microscopy examination facilitates direct visualization of fungal hyphae on the cornea (12).

Endophthalmitis, rarer and more serious, occurs several weeks or months after keratitis (44%), eye surgery (32%), and penetrating intraocular trauma (24%), as in our case report. Due to *Fusarium oxysporum* and to *Fusarium solani*, 18 keratitis out of 41 ones are progressed to endophthalmitis, 10 of which require enucleation, the

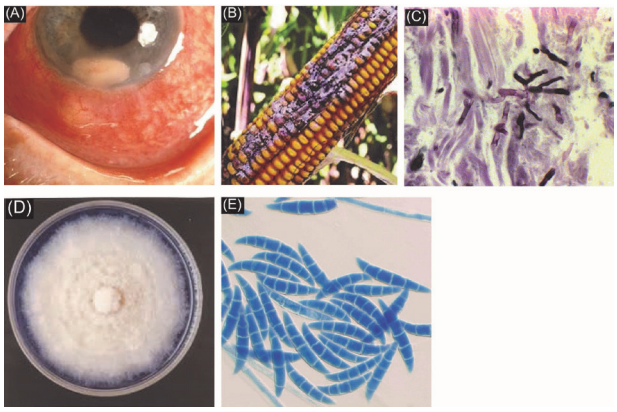

Figure 1. (A) Hypopion. (B) Corn Infected by *Fusarium*. (C). Biopsy: Septate *Filaments*. (D). Cottony Colony of *Fusarium*. (E). Spindle Multiseptate Macroconidia of *Fusarium*.

Table 1. Evolution of the Hepatic Enzymes of the Patient Treated With Voriconazole (in June and July 2020)

Liver Enzymes	25/06	01/07	07/07	13/07	17/07
ASAT (UI/L)*	57	150	156	152	46
ALAT (UI/L)**	171	378	507	545	93
ɣGT (UI/L)***	43	50	70	43	40

*Aspartate Amino Transferase, ** Alanine Amino Transferase; *** Gamma-Glutamyl Transferase.

Table 2. Factors That Favored Eye Infection With *Fusarium*

Context	Taiwan (6) (N = 65)	Australia (7) (N = 51)	Paris (8) (N = 19)
Eye trauma (%)	46.4	34	31.6
Eye pathology (%)	27.7	13	-
Systemic disease (%)	15.4	-	-
Wearing lenses (%)	10.8	38	5.3
Topical corticosteroid (%)	10.8	47	42.1
Eye surgery (%)	1.5	9	15.8
Transfixing keratoplasty (%)	-	9 %	31.6
History of keratitis (%)	-	6 %	10.5

Table 3. Main Fungi Responsible for Eye Mycosis

Country	*Fusarium*	*Aspergillus*	*Candida*
Australia	22	10	15
Brazil	67	10.5	10
China	54.1	14.8	1.6
France	21.1	21	21.1
India	10.8	55.4	18.9
India *	52.5	14.3	0.1
Mexico	37	11	7.3
Taiwan	44	9.2	6.2
Tunisia	49	22	17

Data are expressed as percent.
According to 6, 7, 8, 10, * on 500 cornea samples.

other patients with defective visual acuity of 20/80 seen in 18 patients and with defective visual acuity of 20/400 seen in 22 patients (13). In another study in Florida, 10 cases out of 159 patients with *Fusarium oxysporum* keratitis progressed to endophthalmitis, 2 of which resulted in enucleation (14). In addition, fungemia can lead to vascular invasion of ocular tissues with the risk of local necrosis (15).

Difficult Treatment

It is difficult to confirm the diagnosis of keratitis stage, but it is a necessary step to prevent the development of keratitis and its transformation into endophthalmitis (16). Direct examination of the corneal sample revealed septate hyaline filaments (Figure 1C) which became more visible by adopting a Grocott-Gomori stain. The culture on specialized media for 48 to 72 hours developed white and cottony colony (Figure 1D). The microscopic analysis suggested the presence of phialides which produced spindle multiseptate macroconidia (Figure 1E), a characteristic of *Fusarium*. Even though the sample was negative, the PCR analysis facilitated the identification of the fungus. No specific serology was performed.

In a study carried out in China on 877 *Fusarium* keratitis, it was found that 17.7% of their keratitis is due to Fusarium proliferatum, the patients presented a corneal ulcer greater than 7 mm (18%) and a hypopyon (13%). The hyphae were found by scraping the cornea (97%). Since this fungus was resistant to many antifungal drugs, a combination of amphotericin B (1%) and ketoconazole (3%) eye drops was applied to treat 51 patients for a period of 5 weeks to five months. Improvement was observed in 45% of the cases, but 54% ones underwent surgery (keratoplasty), including two enucleation surgeries. Another group including 22 patients received 0,5% natamycin and 0.5% voriconazole eye drops for a period of 4 weeks to five months. In this group, 59% of the cases recovered, 9 patients had keratoplasty, and 2 patients underwent enucleation (17).

The treatment of mycosis is difficult, because *Fusarium* immediately develop resistance to flucytosine (the first azole derivatives) and echinocandins (18) and drug resistance in fungi is an inherent property of them (19). Posaconazole is effective in dealing with ocular (20) and deep damage as well as the combination of terbinafine and voriconazole. In the case of ocular involvement, few treatments are effective, With the exception of amphotericin B or voriconazole, which are used topically and have good effects, other treatments such as intra-vitreous therapy (21) and systemic therapy with topical natamycin have been associated with approximately 60% success (22-24). Natamycin and amphotericin B, bind to ergosterol, stabilize fungal cell membrane and contribute to inhibition of amino-acid and glucose membrane transport proteins. Voriconazole is used to block the cytochrome p450, which results in a reduction of the ergosterol concentration in the membrane and its destabilization (25). In the case of endophthalmitis, surgery is a basic requirement, with which surgery is performed for keratectomy and corneal transplantation or even enucleation of the eye (26).

Conclusion

Fungal eye damage (keratitis and endophthalmitis) was concluded to be a relatively rare health problem which, however, caused serious issues. Establishing an early diagnosis of fungal keratitis was determined to be critical when dealing with a corneal wound complicated by infection. Moreover, combining the bacteriological and mycological samples was also detected to be a vital necessity to treat it. Mycological ocular damage was discovered to be difficult to treat since the fungi were found responsible for developing resistance to the main antifungal drugs.

Conflict of Interests

The authors declare that they have no conflict of interests.

Ethical Issues

Written informed consent was obtained from the patient for publication of this report.

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