CASE REPORT

POST-OPERATIVE ENDOPHTHALMITIS DUE TO *FUSARIUM DIMERUM*

Sadia Khan[1], Gopal S Pillai[2], V Vivek[1], Kavitha Dinesh[1] and PM Shamsul Karim[1]

[1]Department of Microbiology, [2]Department of Ophthalmology,
Amrita Institute of Medical Sciences, Kochi, Kerala, India

Abstract. Fungal endophthalmitis is a destructive intraocular infection resulting in poor visual prognosis. Endophthalmitis due to *Fusarium* spp has the worst visual prognosis. We report a case of a 58-year-old female patient who underwent cataract extraction and intraocular lens implantation in the right eye and presented two months after the surgery with fungal endophthalmitis. The aqueous humor culture grew *Fusarium dimerum.* The patient was treated with intravitreal and oral voriconazole and topical prednisolone. The patient experienced one episode of recurrence following by remarkable improvement. To our knowledge, this is the first reported case of *Fusarium dimerum* endophthalmitis.

Keywords: *Fusarium dimerum,* fungal endophthalmitis, post-operative endophthalmitis, exogenous endophthalmitis

INTRODUCTION

Ocular infections due to fungi cause significant morbidity, particularly when the diagnosis and treatment are delayed. Fungal endophthalmitis is a destructive intraocular infection resulting in a poor visual prognosis. Endophthalmitis due to *Fusarium* spp has a poor visual prognosis (Dursun *et al,* 2003). Causes for this poor prognosis include a lack of adequate treatment for these species (Dursun *et al,* 2003), a delay in starting treatment (Garg *et al,* 2000) and the ability of *Fusarium* spp to produce extracellular proteases resulting in tissue matrix degradation (Gopinathan *et al,* 2001). *Fusarium dimerum* is a rare cause of ocular infections (Gabriele and Hutchins, 1996; Vismer *et al,* 2002). Two percent of ocular infections are caused by *F. dimerum* (Azor *et al*, 2009; Oechsler *et al*, 2009). We report a case of endophthalmitis due to *F. dimerum.*

Correspondence: Dr Sadia Khan, Department of Microbiology, Amrita Institute of Medical Sciences, Kochi, Kerala 682 04I, India.
E-mail: drsadiakhan83@gmail.com; sadiakhan @aims.amrita.edu

CASE REPORT

A 58-year-old female patient underwent cataract extraction and intraocular lens implantation of the right eye. Two months after surgery, she was referred to our hospital with complaints of discomfort of the right eye. The patient had been started on empirical fluconazole therapy before being referred to our hospital. Slit lamp examination showed right eye conjunctival hyperemia, hypopyon, cor-

neal edema and the intraocular lens was displaced to the nasal side. Intraocular pressure of the right eye was 18 mmHg. Examination of the fundus showed vitreous haze and mild cystoid macular edema. Ultrasonography of the eye did not reveal any choroidal thickening. An anterior chamber tap was done and an aqueous humor sample was obtained and sent for microscopy and culture. The patient was given an intravitreal injection of voriconazole and vancomycin after the sample was collected. A fluffy mass was noticed; probably dislodged from the pars plana following intravitreal injection.

The aqueous humor was sent for standard microbiological tests. Initial microscopic examination of the sample was inconclusive. The sample was plated on Sabouraud's Dextrose Agar (SDA) and incubated at 25ºC and 37ºC. The sample was also inoculated into 5% sheep blood agar and the needle used for aspirating the aqueous humor was placed in Brain Heart Infusion (BHI) broth for further incubation. An organism grew out on the third day of incubation with the SDA, blood agar and BHI. Two to 3 milimeter white, round, flat cotonies with a smooth, velvety surface were seen. The colonies subsequently developed a feathery margin. On microscopic examination 2-4 m sized, slender sickle shaped conidia were seen. Further incubation of the colony revealed a pale orange color seen on the reverse side of the media. A microscopic examination at this stage revealed thin, hyaline, septate hyphae and numerous small curved macroconidia. The organism was presumptively identified as *Fusarium* spp.

Definitive identification was done based on morphological observations made on colonies which developed after subculture on potato dextrose agar and SDA, incubated at 25ºC for 14 days. The colonies were 2-3 cm in diameter with a pale orange on the reverse. Microscopic examination of the slide culture showed hyaline, septate hyphae with monophialides arising from short conidiophores. The phialides showed numerous curved hyaline macroconidia (2-4 m) with a single septum and a pointed apex. Microconidia were not visualized. Intercalate smooth walled chlamydospores were also seen. Based on these findings, the organism was identified as *F. dimerum.*

The patient was started on oral voriconazole 300 mg twice daily with topical prednisolone for 3 weeks; the treatment resulted in considerable improvement. One month later the patient again developed redness and pain of the right eye. She was diagnosed with recurrent exogenous fungal endophthalmitis. An anterior chamber wash with voriconazole (200 g/0.1 ml) was performed under local anesthesia. Post-voriconazole wash, small fungal elements near the suture site were removed. At follow-up 2 months later the fungal infection appeared to have subsided. The best corrected visual acquity was 6/36 at the 2 month follow-up appointment.

DISCUSSION

Fusarium spp are common filamentous fungi found as soil saprophytes and plant pathogens. The *Fusarium* species frequently involved in human infections include *F. solani*, *F. moniliforme* and *F. oxysporum* (Guarro and Gene, 1995). *F. dimerum* has been reported to cause superficial ocular infections and rarely invasive infections (Zapater and Arrechea, 1975; Camin *et al,* 1999; Sallaber *et al,* 1999). Fungal endophthalmitis due to *F. dimerum* has not been reported to the best of our knowledge.

F. dimerum can be differentiated from other members of the genus by its characteristic morphological features. The colonies develop on solid media at a relatively slow rate forming white colonies initially, later producing an orange-apricot pigmentation due to conidial slime production. Under the microscope the fungus presents with hyaline, septate hyphae, loosely branched conidiophores, and strongly curved short sparsely septate macroconidia with pointed apices, borne on swollen phialids (deHoog *et al*, 2000; Azor *et al*, 2009). In contrast to macroconidia of other *Fusarium* spp, which measure 30-50 m in length, the macroconidia of *F. dimerum* are short and measure only around 5-20 m. *F. dimerum* characteristically lacks microconidia (de Hoog *et al*, 2000). Resistance among *Fusarium* spp toward most antifungal drugs make species level identification an exercise of only epidemiological interest. However, of clinical significance is the identification of species, such as *F. verticillioides*, which are susceptible to posaconazole (Marangon *et al*, 2004). When species differentiation based on morphology becomes difficult molecular techniques may be employed. In the case of *F. dimerum* the striking morphological features help in quick identification.

Our patient developed late post-operative endophthalmitis due to *F. dimerum*. Empiric fluconazole therapy was started prior to sending a sample for mycological examination. This led to an altered morphology on culture, mimicking yeast like organisms and slow development of the hyphae in culture. The initial microscopic examination of the culture was misleading. Mycologists should keep the possibility of altered morphology due to antifungal therapy in mind when dealing with conflicting macroscopic and microscopic findings.

In immunocompetent individuals, *Fusarium* endophthalmitis can occur as a result of penetrating trauma, keratitis and intraocular surgery (Pflugfelder *et al*, 1988; Ferrer *et al*, 2005; Azor *et al*, 2009). Eradicating *Fusarium* endophthalmitis can be extremely difficult since *Fusarium* spp are often resistant to antifungal medication. Optimal treatment of *Fusarium* spp has not yet been established. *Fusarium* strains yield high MICs for ketoconazole, fluconazole, itraconazole, miconazole, posaconazole and flucytosine (Ferrer *et al*, 2005). The antifungal drugs with relatively lower MICs against *Fusarium* spp include amphotericin B, voriconazole and natamycin (Rotowa *et al*, 1990; Clancy and Nguyen, 1998). Intravenous amphotericin B is one of the most commonly used treatment regimens for fungal endophthalmitis. While it is effective in treating disseminated infection, it has poor intraocular penetration (O'Day *et al*, 1985). Therefore, intravitreal amphotericin B with vitrectomy is advocated for fungal endophthalmitis (O'Day *et al*, 1985). However, there are concerns about the toxicity of intravitreal administration to the retina in the event of incorrect dilution or injection into an air-filled eye (Hariprasad *et al*, 2004). Posaconazole is available in oral formulation only; hence, it is not usually relied on for acute treatment in severe infections since 3-5 days may be required to achieve therapeutic drug levels. As clinical experience is limited, posaconazole is considered for treatment in refractory cases only.

Voriconazole is a broad-spectrum antifungal with high oral bioavailability and rapid systemic absorption. Ocular *Fusarium* isolates have shown an MIC of voriconazole of 2-8 g/ml with rare cases of resistance (Marangon *et al*, 2004).

Voriconazole has time dependent activity, which implies enhancing the duration of exposure enhances the fungistatic action (Comer *et al*, 2012).Oral voriconazole along with intraocular voriconazole can maximize the intraocular concentration of the drug and achieve clearance of the infection (Comer *et al*, 2012). Therefore, our patient was started on intravitreal and oral voriconazole.

In ocular fungal infections, early identification of the species is vital. Response rates to amphotericin B, voriconazole and posaconazole have ranged from 45% to 48% (Perfect *et al*, 2003; Perfect, 2005; Cuenca-Estrella *et al*, 2006). Voriconazole has shown a global response rate of 45.5% in fusariosis refractory to treatment; posaconazole has shown a response rate of 48% in invasive fusariosis (Perfect, 2005; Hachem *et al*, 2008). Response rates to amphotericin B in *Fusarium* infections have varied from 32% to 66%; with higher failure rates in immunosuppressed individuals (Nucci and Anaissie, 2007; Rao *et al*, 2007). Fungal endophthalmitis is notoriously difficult to diagnose and treat, and generally results in protracted therapy with poor final outcomes. *Fusarium* ocular infections are visually destructive due to their high rates of antifungal resistance, the ability to infiltrate ocular tissue and cause intravascular occlusion (Comer *et al*, 2012). Keratitis due to *Fusarium* spp causes infiltrative endophthalmitis in 6% of the cases, which leaves 60% of these eyes with visual acquity of finger counting or worse, and 30% of the eyes with phthisis or requiring enucleation (Pflugfelder *et al*, 1988; Dursun *et al*, 2003). Even though current treatment options are far from optimal, early initiation of therapy can go a long way toward preserving the patients' vision (Hariprasad *et al*, 2008). The duration of therapy varies based on the virulence of the organism, the extent of intraocular involvement and the timing of intervention. The role of aggressive surgical and medical intervention in treating fungal endophthalmitis cannot be over-emphasized.

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