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Endophthalmitis as the initial manifestation of invasive fusariosis in an allogeneic stem cell transplant patient: A case report*

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ABSTRACT

Fusarium species manifests as an opportunistic infection with intrinsic resistance to most antifungals. We present a case of a 63-year-old male with myelodysplasia who received allogeneic stem cell transplantation and presented with endophthalmitis as the initial manifestation of invasive fusariosis that progressed to a fatal outcome despite combined intravitreal and systemic antifungal therapies. We urge clinicians to consider this complication of fusarium infection especially with the widespread use of antifungal prophylaxis that may incur selection of more resistant, invasive fungal species.

1. Introduction

Fusarium species is a widely distributed plant organism transmitted by airborne inhalation or direct inoculation through skin sites [1]. Its pathogenicity ranges from locally invasive superficial keratitis, onychomycosis, sinusitis, mycotoxicosis to disseminated, opportunistic infection primarily in those with neutropenia, T cell immunodeficiency, hematopoietic stem cell transplants, and hematological malignancies [2]. Mortality rate is 60–80% in disseminated infection; 50% and 21% in 30 and 90 days survival rate among those with hematologic malignancies [3]. Prognosis is favorable for hosts with normal absolute neutrophil counts and poor with use of chronic steroids therapy.

Histopathologically, *Fusarium* species exhibit septate, and hyphae branched at 45° angle similarly seen in *Aspergillus*. A differentiating characteristic of *Aspergillus* is dichotomous branching, whereas *Fusarium* displays random branching [4]. Prompt aggressive antifungal therapy is clinically imperative. The literature has further shown that *Fusarium* exhibits higher antifungal sensitivity to Amphotericin B in comparison with azoles, making Amphotericin B a favorable initial therapy [3,5]. This is because *Fusarium* species exhibit intrinsic resistance to widely used azoles, largely due to its robust efflux mechanism to remove xenobiotics and improper use of azoles in agriculture both contributing to the increasing resistance [6,7]. Susceptibility testing is crucial to initiate antifungal therapy, particularly in those with refractory keratitis, breakthrough disease, and immunocompromising conditions.

2. Case

We present a case of a 63-year-old male with myelodysplasia who received allogeneic stem cell transplantation on + Day 0. He received posaconazole prophylaxis during a two-week period of severe neutropenia. No further neutropenia was seen. He continued tacrolimus and mycophenolate mofetil for graft vs host disease prophylaxis. +Day 24, he reported visual changes in his right eye. Fundoscopy of the right eye showed corneal edema in anterior segment and 2–3 disk diameter white lesion nasal to optic disc (Fig. 1). Left eye was clear. On + day 30, he was initiated with intravitreal injection of 100mcg per 0.1mL Voriconazole every 2–4 days. On + day 40, he developed fever and hypoxia. A thoracic CT showed pulmonary nodules with cavitation (Fig. 2). Bronchoscopy with BAL and sputum cultures were done. Respiratory culture only grew *Fusarium* sp. Serum 1,3 Beta-D-Glucan (BD) was elevated above 500 pg/mL (reference 0–59 pg/mL). C-reactive protein was elevated with highest level of 79.4 mg/L (normal high <5.0 mg/L). Fungal blood cultures remained negative, and no skin lesions were identified. Using broth microdilution, the *Fusarium* sp. was most susceptible to Amphotericin B of MIC >8 relative to other -azole agents of MIC >16. On + day 40 he was treated with liposomal Amphotericin 5mg/kg and Voriconazole 200mg BID. On + day 49, the vitreal culture

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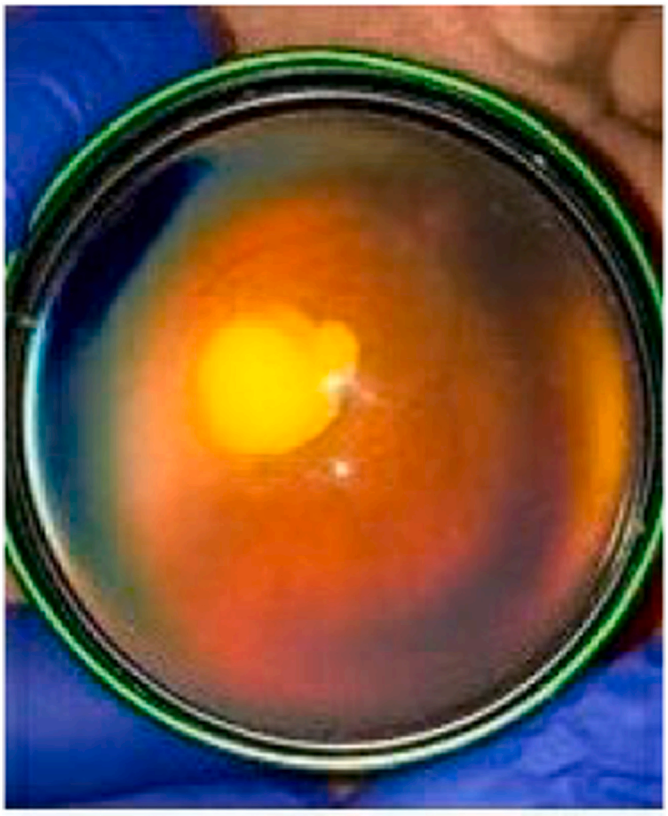

Fig. 1. Fundoscopy of the right eye on Day +24. Corneal edema in anterior segment and 2–3 disk diameter white lesion nasal to optic disc.

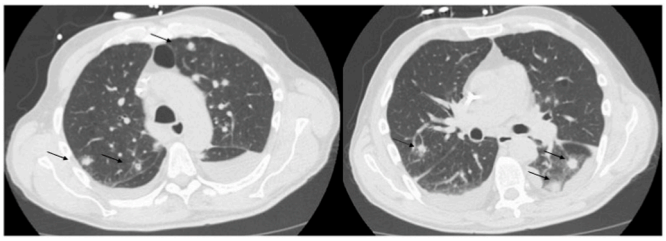

Fig. 2. Thoracic CT on Day +40. Multiple pulmonary nodules few with cavitation and small bilateral pleural effusion.

still grew *Fusarium* sp. Intravitreal injection of 5mcg per 0.1mL of Amphotericin B every 5 days was added to voriconazole. Two vitrectomies were performed. Intravitreal injections were discontinued on + day 74 when the lesion in right eye showed improvement on subsequent fundoscopy. +Day 57, serum BD remained elevated above 500 pg/mL, thus Terbinafine 250mg BID was added. He continued this regimen with improving BD levels until + day 109 when he was noted to be acutely delirious. Voriconazole level was 5.5 μg/mL, which was within normal limits of reversible neurotoxicity. A lumbar puncture revealed findings suspicious for meningitis: protein 114 mg/dL (reference 15–45 mg/dL), glucose 17 mg/dL (reference 40–70 mg/dL) and lactic acid 5.0 mMol/L (reference 1.1–2.4 mMol/L). The CSF culture remained negative. He was treated with vancomycin, ampicillin, cefepime and acyclovir along with his antifungal therapy. On + day 116, the patient decompensated with worsening mentation and hypoxia requiring intubation, progressing to septic shock. He passed away + day 121. From the autopsy, *Fusarium* sp. was cultured from a 2cm × 2cm green abscess in the sphenoidal bone. Both lungs were pale with greenish tinge. Serial sectioning of the lungs revealed green froth. No apparent masses identified. Fungal staining (GMS, PAS) of brain and lungs sections were unremarkable.

3. Discussion

We present an unusual case of endophthalmitis as the initial manifestation of disseminated fusariosis that progressed despite aggressive intravitreal and systemic antifungal therapy to encephalopathy with green abscess in the sphenoidal bone growing *Fusarium* mold. *Fusarium* endophthalmitis is an unusual occurrence with two possible ports of entry. Exogenous spread from initial keratitis followed by eye trauma or surgery is well described, as *Fusarium* species is the second most observed fungal isolate from infectious keratitis after *Candida* species [12]. Another route is endogenous dissemination due to transient or persistent fungemia associated with immunosuppression, as demonstrated in our case [13]. Endophthalmitis is usually a late clinical presentation of disseminated fusariosis with major complications of retinal detachment, vitreous prolapse, and vision loss [14]. Resolution of endophthalmitis has been reported with aggressive multimodal regimen of immediate vitrectomies followed by intraocular and systemic antifungal therapy [15,16]. Intravitreal amphotericin B deoxycholate of 5–10 mcg in 0.1 mL sterile water and intravitreal voriconazole of 100 mcg in 0.1 mL sterile water can achieve rapid therapeutic level of antifungals in the eye; this regimen has high safety profile and may be given repeatedly with short dose interval of days until resolution of fungal endophthalmitis [17].

Concomitant fungal osteomyelitis of the sphenoidal bone is likely due to a direct, local spread through nasal sinus from the endophthalmitis. Hematogenous dissemination was less likely as repeated blood culture with fungal stain did not reveal organism growth. From the literature, bone involvement is an atypical manifestation of disseminated disease with higher incidence among cases of diabetes mellitus and immunocompromised conditions [18]. The optimal treatment remains under investigation as simple debridement is unsuccessful. Systemic antifungal therapy and surgical resection or amputation of affected site have led to successful resolution among immunocompetent and several immunocompromised hosts [18].

Most *Fusarium* osteomyelitis documented in the literature involved the extremities. In our case, the fungal abscess was found invading the sphenoidal bone. The presence of abscess provided a nidus of persistent infection despite vitrectomy and intravitreal antifungal injections. The abscess was a potential source of acute encephalopathy with lumbar puncture findings supportive of meningitis. Central nervous system involvement of fusariosis tends to manifest as endophthalmitis or chorioretinitis, rarely meningoencephalitis and brain abscesses [10,11]. A recent epidemiology study showed that allogeneic stem cell transplant is the highest risk factor for this complication followed by acute myeloid leukemia and autologous stem cell transplant [9]. Given the wide resistance pattern, we opted for the upfront use of synergistic antifungal therapy of systemic liposomal amphotericin B and voriconazole with the later addition of terbinafine. Current indications of early synergistic antifungal therapy are still under investigation, as prognosis is generally poor due to the host's advanced underlying disease. Multiple case reports delineated successful outcomes with combination therapy of Amphotericin B in addition to another agent. However, large group analysis of invasive fusariosis has yet to show a superiority of combination in comparison to monotherapy [19,20].

This case highlights that fungal endophthalmitis as the initial presentation of a refractory complication of disseminated fusariosis. As *Fusarium* is an uncommon opportunistic infection that exhibits increasing resistance, clinicians should maintain a high index of suspicion among immunocompromised patients with severe neutropenia, hematologic malignancies, or prior history of transplant [2,3,8,9]. Due to a lack of standardized treatment and poor prognosis, signs of disseminated infection should prompt confirmatory diagnostic testing with appropriate cultures or biopsies. Antifungal susceptibility testing should be performed immediately to initiate early aggressive

multimodal therapy with antifungal agents and when appropriate resection of disseminated sites.

Ethical Form

Please note that this journal requires full disclosure of all sources of funding and potential conflicts of interest. The journal also requires a declaration that the author(s) have obtained written and signed consent to publish the case report from the patient or legal guardian(s).

The statements on funding, conflict of interest and consent need to be submitted via our Ethical Form that can be downloaded from the submission site www.ees.elsevier.com/mmcr. **Please note that your manuscript will not be considered for publication until the signed Ethical Form has been received.**

Declaration of competing interest

The authors declare no conflict of interest. No other disclosures are reported.

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