

A case of fusariosis in an immunocompromised patient successfully treated with liposomal amphotericin B

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Abstract. Although aspergillosis remains the most common mould infection in patients with haematologic malignancies, disseminated *Fusarium* infection is an emerging problem with a poor prognosis in this patient population. The treatment options are limited due to relative resistance of the fungus to standard antifungals. We present a patient with acute lymphoblastic leukaemia successfully treated with AmBisome® for a disseminated *Fusarium solani* infection that did not respond to first line treatment with voriconazole. Despite the fact that he received additional myelosuppressive chemotherapy and underwent two stem cell transplantations from HLA mismatched donors the *Fusarium* infection did not recur during the subsequent phases of neutropenia. The clinical presentation, diagnosis, prognosis and therapeutic options of fusariosis in immunocompromised patients are briefly discussed. (www.actabiomedica.it)

Key words: *Fusarium*, fungal infections, liposomal amphotericin B, acute leukaemia

Introduction

Although aspergillosis remains the most common mould infection in patients with haematologic malignancies, disseminated *Fusarium* infection is an emerging problem with a poor prognosis in this patient population. The treatment options are limited due to relative resistance of the fungus to standard antifungals. In the following case report we describe a severely immunocompromised patient with a typical presentation of fusariosis refractory to voriconazole but responding to Ambisome®. This case report also demonstrates that eradication of *Fusarium* makes further myelosuppressive and immunosuppressive treatment feasible eventually leading to cure of the patient.

Case Report

A 49 year old male presented in March 2002 with Philadelphia-positive acute lymphoblastic leukaemia.

The disease presentation was rather atypical with osteolytic lesions in the vertebral column and ribs and limited bone marrow infiltration. The blast cells expressed the fusion protein p190. He was treated with conventional induction and consolidation chemotherapy according to a German multicenter protocol for high risk ALL and achieved a bcr-abl negative status. During the consolidation course bcr-bl negative autologous stem cells were collected from the peripheral blood. In August 2002 and November 2002 he underwent a double autologous stem cell transplantation after conditioning with high dose melphalan and after conditioning with high dose cyclophosphamide and total body irradiation. The disease remained in a complete remission for 15 months but relapsed in February 2004. The leukaemia relapse was treated with imatinib and rituximab, but a second molecular remission was only achieved after additional intensive chemotherapy with teniposide and cytarabine.

In January 2005, during the third chemotherapy course, he presented with a nail plate infection (pa-



Figure 1. Paronychia caused by *Fusarium*

ronychia) of the right little toe (Figure 1). The cultures from the nail grew *Fusarium solani*, which was sensitive to amphotericin B and voriconazole but resistant to fluconazole and itraconazole. Osteomyelitis was ruled out by bone scintigraphy. In February 2005 after 6 weeks of continuous oral treatment with voriconazole 200 mg b.i.d. he developed intramuscular abscesses in the left quadriceps muscle and the right gastrocnemius muscle with a diameter of respectively 20 and 40 mm. Pus from these lesions was aspirated with an ultrasound guided fine needle, the cultures again grew *Fusarium solani*. No other foci of infection with *Fusarium* were found. The infection was treated with liposomal Amphotericin B (Ambisome®) 5 mg/kg IV daily or every two days as a two hour infusion on the day clinic for 4 weeks (21 doses of 300 mg, total dose: 6300 mg). The treatment was well tolerated, its only side effect was a mild renal dysfunction with a rise of serum creatinine to 1.9 mg/dl. The intramuscular abscesses completely disappeared. To consolidate the second complete remission a transplant with allogeneic peripheral stem cells from an unrelated English donor was performed in April 2005. The donor and the receptor had a major mismatch at the HLA-C and HLA-DP loci. The conditioning consisted of intravenous busulfan, melphalan and antithymusglobulins. During the period of bone marrow aplasia no signs of fusariosis were noticed (although the treatment with Ambisome® was discontinued). Because of late graft failure and persistent transfusion dependency the patient underwent a second allogeneic stem cell transplantation from his haploidentical daughter. The pre-

parative regimen consisted of fludarabine, cyclophosphamide and antithymusglobulin. The stem cells were T cell depleted with a Clinimacs CD34 selection column. The transplantation resulted in a good engraftment with normalisation of the peripheral blood counts. The patient is currently alive and well and in continuous complete remission with no signs of fusariosis.

Discussion

This case report describes a patient with acute lymphoblastic leukaemia successfully treated with Ambisome® for a disseminated *Fusarium solani* infection that did not respond to first line treatment with voriconazole. Despite the fact that he received additional myelosuppressive chemotherapy and underwent two stem cell transplantations from HLA mismatched donors the *Fusarium* infection did not recur during the subsequent phases of neutropenia.

Fusarium belongs to the group of non pigmented (hyaline) septate filamentous fungi and is widely distributed in soil, plants, air and water. Most frequently pathogenic in man is *Fusarium solani*, followed by *Fusarium oxysporum*. In immunocompetent patients the main risk factor for infection with *Fusarium* is tissue breakdown as a result from a direct trauma or the presence of a foreign body. Localized infections occurring in immunocompetent patients include keratitis in contact lens wearers, endophthalmitis, onychomycosis, cutaneous infections, and peritonitis following continuous peritoneal dialysis (1, 2). *Fusarium* is also increasingly recognized as a cause of invasive fungal infections in neutropenic patients and in those undergoing stem cell transplantation. While the incidence of fusariosis in Europe has remained stable over the past twenty years, it is increasing in certain haematopoietic stem cell transplantation units in the United States where it occurs in up to 0.5 % of HLA matched related and in up to 2% of HLA mismatched allogeneic stem cell transplantations (3). In the immunocompromised patient population *Fusarium* can involve almost every organ, most frequently affected are the skin, the lungs and the sinuses. Entry is either airborne or through a breakdown in the skin barrier. The cli-

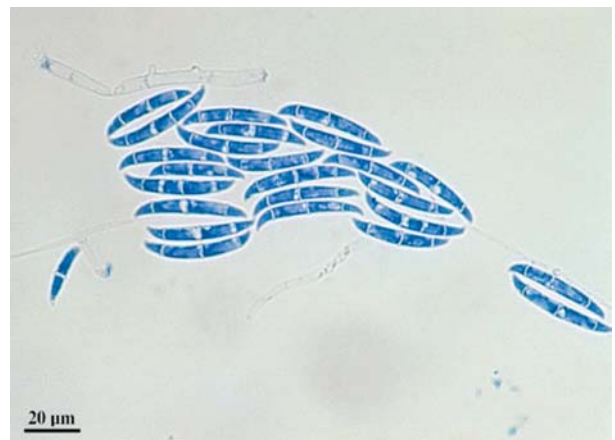
Table 1. Comparison of clinicopathological features of aspergillosis and fusariosis

Similarities	Differences associated with <i>Fusarium</i>
1. Sinopulmonary portal of entry	1. Skin frequent portal of entry
2. Nodular or cavitary lung lesions	2. Metastatic (sub)cutaneous lesions in 70%
3. Histopathology: vascular invasion and acute branching septate hyphae	3. Positive blood cultures in 50%
4. High mortality	4. More resistant to antifungals (azoles, amphotericin B, echinocandins)
5. Risk factors: neutropenia and steroids	

nical features of disseminated fusariosis are similar in many respects to those of aspergillosis (Table 1). Unlike aspergillosis infection with *Fusarium* is associated with a high incidence of cutaneous (nodular or ecthyma-like) and subcutaneous lesions (70-90 % of patients) and positive blood cultures (40-60 % of patients). A typical clinical presentation of fusariosis observed in neutropenic patients is paronychia of the toe or finger spreading by local invasion and causing extensive cellulitis of the extremities or disseminating to distant organs or tissues (Figure 1) (1, 2, 4).

The diagnosis of *Fusarium* is based on a high index of suspicion in immunocompromised patients with skin lesions and nail infections. The skin is a very important source for the diagnosis, skin lesions were reported to be the single source of diagnosis of fusariosis in 55% of the patients (5). Blood cultures are positive in about 40% of patients (4). Histopathology of invasive fusariosis is difficult to distinguish from aspergillosis and shows septate hyphae branching at acute or right angles and invading blood vessels causing thrombosis and tissue infarction. The definitive diagnosis relies on isolation of *Fusarium* in cultures from clinical specimens. The banana-shaped macroconidia in culture are typical for the genus *Fusarium* (Figure 2) (1, 2).

Prompt therapy of localized disease is critical to prevent progression to disseminated infection and includes surgical debridement. Surgery is, however, rarely feasible in immunocompromised patients with thrombocytopenia. The optimal treatment for disseminated fusariosis remains unclear. It is a life-threatening disease and the outcome is very much influenced by the host immune status. The overall mortality of fusariosis in immunocompromised patients ranges from 50 % to 80 %. Persistent neutropenia and therapy with corticosteroids is associated with a very poor out-

**Figure 2.** Banana-shaped macroconidia of *Fusarium solani*

come. In severely neutropenic patients treatment with G-CSF or granulocyte transfusions should be considered. Fusariosis is commonly resistant to Amphotericin B, but successful responses have been reported with higher doses of Amphotericin B (1-1.5 mg/kg/day) or lipid formulations of Amphotericin B using a dose of at least 3 mg/kg (6-10). Fluconazole, itraconazole and the echinocandins are not active against *Fusarium*. In vitro activity of the newer triazoles against *Fusarium* is variable and dependent on the method used for susceptibility testing. It remains unclear if in vitro activity of antifungal drugs is predictive of clinical outcome. Nevertheless, in vivo antifungal activity against fusariosis has been reported with the newer triazoles voriconazole and posaconazole. *Fusarium solani* (which was also isolated in our patient) seems somewhat more susceptible to Amphotericin B but less susceptible to voriconazole than *Fusarium oxysporum*, which may explain the response pattern seen in our patient (1, 2, 11, 12). In a paper describing the efficacy of voriconazole in uncommon fungal infec-

tions 45% of *Fusarium* infections responded to voriconazole (13). In another paper 82% of *Fusarium* infections responded to Amphotericin B Lipid Complex, suggesting a superior activity of the lipid formulations of Amphotericin B in comparison to voriconazole (7). A recent paper reported a successful outcome of disseminated fusariosis after combination therapy with Ambisome® and voriconazole (14).

The current recommendations for the management of fusariosis propose a first line treatment with a lipid formulation of Amphotericin B or voriconazole while attempts should be made to minimize the immune deficit with the use of G-CSF as well as reducing immunosuppressive therapy when possible (1, 2).

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