SHORT REPORT

Systemic Fungemia and Hepatic Localizations of *Fusarium Solani* in a Liver Transplanted Patient: an Emerging Fungal Agent

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The incidence of invasive fungal infection is increasing especially in the field of transplantation, affecting as many as 50% of bone marrow transplant (BMT) patients with neutropenia and 5-20% of solid-organ transplant (SOT) recipients. *Fusarium* species are soil saprophytes and plant pathogens. They may cause superficial mycoses or important opportunistic infections in patients with bone marrow suppression and neutropenia, they have been rarely described in solid organ recipients, and up to now there have been no reports of such infection in isolated liver transplanted patients. We describe a case of disseminated *Fusarium solani* infection with hepatic localization in a liver transplanted patient that resolved with the administration of amphotericin B. Our observation confirms that *Fusarium* spp. are emerging pathogens that may most frequently affect not only BMT patients and patients with hematological malignancies, but also SOT patients. They may cause both localized and disseminated infection. In conclusion, *Fusarium* spp. etiology should be considered in the context of infectious diseases following liver transplantation. ***Liver Transpl 12:1711-1714, 2006.*** © **2006 AASLD.**

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Fungal infections after organ transplantation are a major problem affecting 5-20% of solid organ-transplanted patients.[1] *Fusarium* species are soil saprophytes and plant pathogens recognized to cause superficial mycoses such as keratitis or onychomycosis[2] and important opportunistic infections in patients with bone marrow suppression and neutropenia.[3] They rarely have been described in solid organ recipients, and up to now, there are no reports of such infection in recipients of isolated liver.

Herein we describe a case of disseminated *Fusarium solani* infection with hepatic localization, in a liver transplanted patient.

CASE REPORT

A 31-year-old male patient was transplanted in June 2000 because of Caroli's disease. The donor was blood-group compatible, but in May 2001 the patient was retransplanted for the occurrence of intractable chronic rejection while on cyclosporine and steroids (within the expected serum levels). After the second liver transplant immunosuppressive regimen consisted of steroids and FK506. According to the transplantation unit immunosuppression schedule, steroids were slowly tapered and then stopped 1 year after liver transplantation. No significant events occurred until June 2003 when the patient developed hepatic artery thrombosis and graft ischemia with preserved arterial inflow from collateral vessels recruited from the jejunal arcade of the Roux limb.[4] The patient was found to be positive for lupus anticoagulant antibodies; therefore, oral anticoagulant therapy and low-dose steroids (deltacortene, 5 mg/day) were started in December 2003. Later he also developed a mild chronic renal impairment due to calcineurin inhibitors. In August 2005 he presented to our department for the fever (high of 39°C) that was unre-

Abbreviation: BMT, bone marrow transplant.

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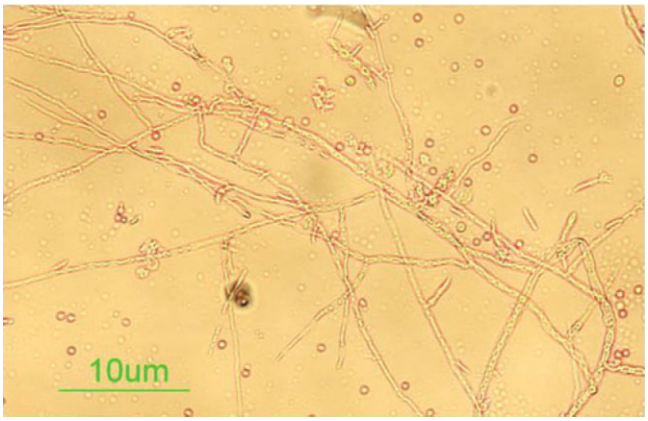

Figure 1. Hyaline hyphae of *Fusarium solani* observed under direct light microscopy in blood culture after 4 days of incubation. Original magnification ×100.

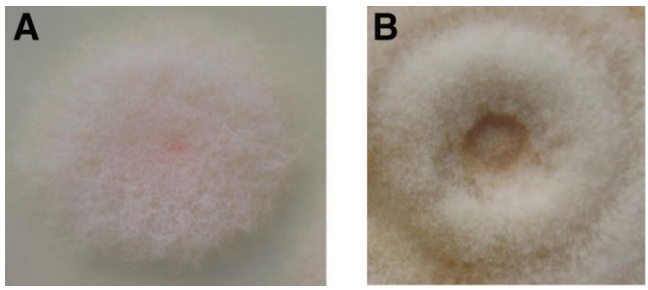

Figure 2. (A)White woolly aerial mycelium of *Fusarium solani* after 4 day of growth on Czapek agar medium (25°C). (B) Larger and creamy aerial mycelium after 7 days of growth on Czapek agar medium (25°C).

sponsive to broad-spectrum antibiotics. His white blood cell count was normal (8.47 × 10^3/uL), and his neutrophils were 75%. Anemia (hemoglobin 8.4 g/dL), increase of erythrocytes sedimentation rate (26 mm/hour), and C reactive protein (2.07 mg/dL) were also present. His creatinine level was 1.46 mg/dL, and liver function tests showed increased alkaline phosphatase (691 U/L) and gamma-glutamyltransferase (337 U/L) levels, with normal bilirubin and minor increase in alanine aminotransferase levels (49 U/L). HAV and hepatitis B virus antibodies tested negative, as well as antibodies against cytomegalovirus, Epstein-Barr virus, and parvovirus B19. Liver ultrasonography showed the presence of the previously observed ischemic areas related to hepatic artery thrombosis and new small hypoechoic nodules with a peripheral ring suggestive for microabscesses. The same pattern was then confirmed by spiral computed tomography. Chest x-ray, thorax spiral computed tomography, and heart ultrasonography were negative. The patient was treated with teicoplanin 200 mg intravenously twice daily, with piperacillin plus tazobactam 2.25 mg intravenously 3 times a day, and fluconazole 100 mg intravenously once daily. We did not perform the lesions biopsy, because the patient was on oral anticoagulant therapy. The clinical picture did not improve despite the broad-spectrum antibiotic therapy, and the patient continued to have persistent shaking and fever. Four days after hospitalization, the patient's blood culture tested positive for *F. solani*. The blood culture was performed with an automated system (BacTAlert, BioMeriuex). The positive sample was checked under light microscopy at ×400, and hyaline hyphaes were observed (Fig. 1). Consequently, the original blood culture was subcultured in malt extract agar and Czapek agar media to allow for the development of colonies. The typical morphology of the *F. solani* colony (woolly with white-cream aerial mycelium and a cream reverse) was visible after 4 (Fig. 2A) and 7 (Fig. 2B) days of incubation at 25°C. The microscopic examination of cotton blue stained preparation from colonies grown on malt extract agar showed the typical macroconidia of *Fusarium* spp. (3- to 5-septate, fusiform, cylindrical).

The patient was given amphotericin B lipid complex (Abelcet) 3 mg/kg intravenously once daily. The treatment was well tolerated, and beside the mild preexisting impaired renal function, there were no further increases in creatinine levels. The outcome was satisfactory with rapid disappearance of fever and liver abscesses within 1 month. The treatment was then continued for another month to ensure a complete recovery.

DISCUSSION

The incidence of invasive fungal infection and sepsis is increasing in the setting of transplantation (up to 50% in neutropenic bone marrow transplant (BMT) patients and 5-20% in solid-organ transplant).[1,5] Nowadays, invasive fungal infections are a major cause of mortality related to posttransplantation infectious diseases.[6] A wider use of antifungal agent prophylaxis has led to a decline in the incidence of *Candida* spp. infections and the emergence of other less susceptible agents.[7,8]

Fusarium species are a common soil mold causing localized infection both in immunocompetent and immunocompromised patients. The *Fusarium* spp. most frequently involved in human infections are *F. solani, F. oxysporum,* and *F. moniliforme*.[2] Disease may ensue from either *Fusarium* spp. toxins or tissue invasion. Disseminated infection usually occurs in patients suffering from hematological malignancies or severe immunodeficiency, as well as in BMT recipients.[3,9] Neutropenia and impaired macrophage function are important risk factors[9] for the emergence of these mycoses. Skin lesions are present in 85% of patients with disseminated infection and are usually an early finding,[3,10,11] while blood cultures test positive in 50-70% of cases.[3] Prognosis of *Fusarium* spp. infection is usually poor, with a mortality rate between 70% and 100% in patients with hematological malignancies,[3] and clinical remission is associated with the resolution of neutropenia.[12,13] These fungi are usually resistant to most of the standard antifungal agents. In vitro studies showed that amphotericin B is the most active agent, while fluconazole, itraconazole, and flucytosine have no activity. Terbinafine, ketoconazole, and miconazole

show limited activity.[14,15] New triazoles, voriconazole and posaconazole, have been recently described to be active against these pathogens. Voriconazole has some in vitro activity[16] and has been used in clinical practice in some cases.[17-21] Posaconazole seems to be highly effective in vitro,[22] and a recent retrospective study documented a good efficacy in vivo.[21] In 2 reports, combination therapy of amphotericin B and voriconazole was successfully used in 2 patients with hematological malignancies not responding to amphotericin B alone.[23,24] Until the pharmacological activities are extensively investigated, the use of these new agents, alone or in combination with amphotericin B, should be limited to infections refractory to standard treatment or in patients intolerant to amphotericin B.

Fusarium species infections have been rarely reported after solid-organ transplantation,[18,25-31] apparently with a better outcome with respect to BMT recipients (7 of 8 cases described in the scientific literature eradicated the infection, and only 1 patient died).

Previously reported infections occurred in kidney (n = 5) and lung (n = 2) transplantation, and in a combined heart-liver transplantation. To our knowledge, no cases have been reported following isolated liver transplantation. Five cases of localized skin lesions, 1 case of peritonitis, 1 case of lung abscess and 1 case of disseminated infection with endocarditis have been described. There is no report on liver involvement by *Fusarium* spp.

Our case occurred in a liver transplanted patient who developed hepatic artery thrombosis with residual necrotic areas of the liver. These could have represented an anatomically susceptible background for the development of liver fungal localizations. The patient had no skin lesions, but diagnosis was suggested by blood culture positive for *F. solani.* and the appearance of liver abscesses, indicating a disseminated disease. He responded to antifungal therapy promptly with remission of clinical symptoms and disappearance of liver abscesses.

In summary, *Fusarium* spp. are emerging pathogens that most frequently affect not only BMT patients and those with hematological malignancies, but also solid-organ transplant patients. These opportunistic agents may cause both localized and disseminated infections with possible involvement of different organs (lung, heart, liver). A previous report described *F. solani* infection after combined heart-liver transplantation. The case described in this paper is the first report of *F. solani* infection following liver transplantation, and it provides the first evidence of liver abscesses due to this fungal agent. In conclusion, *Fusarium* spp. etiology should be considered in the context of infectious diseases following liver transplantation.

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