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Paecilomyces variotii Fungemia in a Patient with Lymphoma Needing Liver Transplant

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Abstract *Paecilomyces* sp. are emerging pathogens in immunocompromised patients. We report here a case of *Paecilomyces variotii* fungemia, cured with amphotericin and anidulafungin, illustrating difficulties of early diagnosis and therapeutic choice in such rare fungal infection.

Keywords *Paecilomyces variotii* · Mold · Fungemia · Antifungal treatment · Anidulafungin

Introduction

Paecilomyces infection is an uncommon infection that is emerging among immunocompromised patients. The two main species most involved in human infections are *Paecilomyces lilacinus* (current name *Purpureocillium lilacinum*) and *Paecilomyces variotii* [1–3]. Among the clinical cases reported in the scientific literature, infections due to *P. lilacinum* [2–9] are largely predominant compared to infections due to *P. variotii* [10–15]. The susceptibilities of these two fungal species to antifungals are very different [2, 12, 16], thus identifying rapidly at the species level the fungi is of great importance for patient's management, especially implementation of an effective antifungal therapy. We report a case of *P. variotii* fungemia in a patient treated for diffuse large cells-B lymphoma and viral hepatitis B but cured using liposomal amphotericin B and anidulafungin.

Case Report

A 55-year-old male patient was diagnosed in March 2012 with Richter syndrome (diffuse large cells-B lymphoma). The treatment consisted of successive

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chemotherapy R-CHOP cycles (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone). After the third cycle of R-CHOP, the patient developed fulminant viral hepatitis B with high alanine aminotransferase levels (ALAT, 1770 U/L), and high hepatitis B virus (HBV) replication ($>10^9$ UI/ml, positive HBe antigen, negative IgM anti HBc). Antiviral treatment with entecavir (0.5 mg/day) was implemented immediately. However, the hepatic function worsened with progressive coagulopathy and stage II to III hepatic encephalopathy requiring intubation and transfer from the Hematology Department toward the Hepatology Unit. The patient was immediately listed for high urgency liver transplantation. He developed acute renal failure and hepatorenal syndrome, leading to anuria too. After 11 h, an appropriate deceased donor graft was identified and the patient underwent liver transplantation. The patient was transferred to Surgical Intensive Unit Care and steadily improved with progressive recovery of digestive, renal, pulmonary and hemodynamic functions. However, a single blood culture bottle, sampled few hours before the liver transplantation, revealed positive for *Paecilomyces* sp. The preliminary identification at the genus level was based on microscopic features. An antifungal therapy was initiated at D1 post-graft with liposomal amphotericin B (L-AmB, 5 mg/kg) and voriconazole (200 mg × 2 per day) based on patterns of susceptibility of *Paecilomyces* spp. and the large predominance of *P. lilacinum* in human infections reported in the scientific literature [2–9]. Four days later, subcultures on mycological culture media, mycological microscopic and macroscopic features [17], and result of molecular identification (using internal transcribed spacer (ITS) sequencing (using ITS5 and ITS2 primers as described previously [18]), revealed that the filamentous fungus was in fact *P. variotii* (Fig. 1). Result of *E* test MIC testing for voriconazole, posaconazole, amphotericin B, caspofungin and anidulafungin showed a peculiar sensitivity profile of the strain which was resistant to voriconazole (MIC 2 µg/ml) and caspofungin (MIC 2 µg/ml) while being sensitive to posaconazole (MIC 0.016 µg/ml), 5-fluorocytosine (MIC 0.06 µg/ml), AmB (MIC 0.032 µg/ml) and even anidulafungin (MIC $<$ 0.002 µg/ml). The strain was sent to the National Reference Center for Invasive Fungal Infections and Antifungals (CNRMA), based at the Pasteur Institute in Paris (France), for confirmation of the species identification and of MIC testing using EUCAST standard. The CNRMA confirmed our species identification of *P. variotii* and EUCAST MIC values were in accordance with the *E* test MIC results: resistance to voriconazole (EUCAST MIC 8 µg/ml) and caspofungin (EUCAST MIC 2 µg/ml) and susceptibility to posaconazole (EUCAST MIC 0.03 µg/ml) and AmB (EUCAST MIC 0.125 µg/ml). According to the antifungal susceptibility data and the context of liver transplantation, the antifungal therapy was switched to anidulafungin (100 mg per day) in association with L-AmB at D9 post-graft. This antifungal treatment was well tolerated, maintained 3 weeks and completed by the removal of material (including central line) that could have been a portal of entry for the fungus. Thereafter, a relay with oral posaconazole suspension (200 mg × 4 per day) was given to the patient during 10 weeks. After 10 days of treatment, the posaconazole plasma concentration reached the target threshold of 0.7 µg/ml, recommended by several authors for clinical efficacy [19, 20]. This treatment was well tolerated. Regular sampling of blood cultures was done for this patient but all of them were sterile. No sign of endocarditis was detected. The HBV infection was treated postoperatively with entecavir and anti-HBV gammaglobulins. The immunosuppression regimen consisted of mycophenolate mofetil (500 mg × 2 per day) and prednisolone (20 g per day initially with a decrease of 1 mg every 5 days, for a total treatment of 3 months). The patient was discharged home on postoperative day 43. The outcome was favorable.

Discussion

Patients with advanced or acute liver disease have an increased susceptibility to bacterial and fungal infections, in relation to a significant impairment of neutrophil immune mechanism, increased intestinal permeability, frequent use of corticosteroids or malnutrition and depression of both humoral and cell-mediated immunity [21, 22].

Paecilomyces spp. are ubiquitous hyaline filamentous fungi, usually found in nature as saprophytes and considered as emerging human pathogens in heavily immunocompromised patients. In contrast to *Aspergillus* species, growth of *Paecilomyces*-like species is relatively frequently reported in blood cultures, similarly as

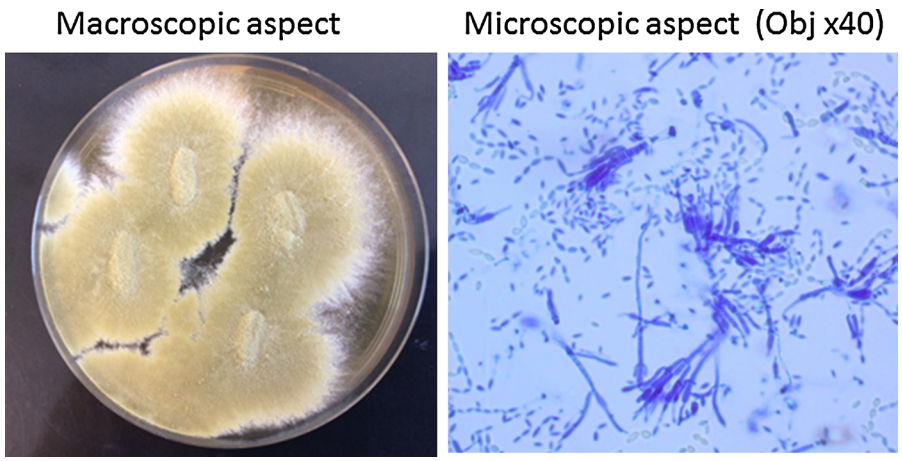

Fig. 1 Macroscopic aspect after 2 days of culture on Sabouraud agar of our *P. variotii* strain and microscopy, showing typical cylindrical or ellipsoidal phialides, tapering abruptly into a long, thin beak and ellipsoidial condia, arising in long chains

Fusarium, Scedosporium and *Acremonium* spp., probably due to its ability to sporulate during tissue invasion [17]. The significance of a single positive blood culture for an emerging saprophytic mold in the context of a patient with multiple risk factors of IFI cannot be questioned and should always be considered as definite fungemia due to the mortality risk if antifungal treatment is delayed [23]. In the present case, no infection source could be identified and no other proof than the positive blood culture was obtained to support the presence of the fungus (negative galactomanann, no histology data, no complementary biomarkers such as beta-D-glucan for example). However, all material that could have been a portal of entry for the fungus was removed during the early stage of antifungal therapy. In addition to our case, there are two other reports describing *P. variotii* fungemia in immunocompromised patients without infection localization [11, 13]. Pneumonia and peritonitis are the most frequent type of infections due to *P. variotii* that are regularly reported in the literature either in immunocompromised patients [14, 15, 23, 24], in patients with diabetes mellitus [25, 26], or in patients undergoing chronic peritoneal dialysis [27–29]. More rarely, cases of sternotomy wound infection [30] and osteomyelitis [31] due to *P. variotii* were reported in immunocompromised patients. In immunocompetent patients, *P. variotii* is mostly reported in endophthalmitis [32, 33] and sinusitis [34, 35] cases.

Choice of an effective first-line antifungal therapy is the main concern for management of rare fungal infection [36]. A rapid and effective identification of the involved fungus is a key point. Distinction between *P. variotii* and *P. lilacinum* is clinically highly relevant, as *P. variotii* is in vitro susceptible to azoles but highly resistant to voriconazole, whereas *P. lilacinum* is susceptible to voriconazole in vitro [37]. In our case, standard morphological examination and ITS sequencing allowed rapid identification of *P. variotii*. Matrix-assisted laser desorption ionization–time-of-flight mass (MALDI-TOF) spectrometry identification of isolates belonging to *Paecilomyces-/Purpureocillium*-like fungi could also be an attractive, approach, but misidentification of several *P. variotii*-like fungus was reported by MALDI-TOF compared to molecular methods [38]. The MALDI-TOF strategy for filamentous fungi identification was not available in our center when this case occurred.

In our case, antifungal susceptibility testing led clinicians to switch from voriconazole to anidulafungin, in combination with L-AmB. Recently, L-AmB was recommended for the first-line therapy of *P. variotii* infection [37]. A recent study showed that a MIC for AmB $\leq$ 0.5 µg/ml was associated with better 6-week outcome in non-*Aspergillus* invasive mold infections in immunocompromised patient, as in our patient [36]. Notably, the voriconazole-L-AmB combination was required to cure *P. variotii* peritonitis in a liver transplant patient, which was unresponsive to the initial L-AmB treatment (MIC 1 µg/ml for both L-AmB and voriconazole) [14].

Treatment of IFI is also challenging in patient with severe liver disease. The drug of choice is voriconazole, but this drug is potentially hepatotoxic and is metabolized by cytochrome P-450 isoenzymes causing

important drug interactions. Thus, it should be used with caution in patients with severe hepatic failure. The alternative options are represented by lipid formulation of AmB, which are less nephrotoxic than AmB desoxycholate. Patients with advanced cirrhosis and ascites frequently suffer from additional renal failure or even a condition called hepatorenal syndrome that could potentially preclude use of L-AmB. More recent options are antifungal agents of echinocandin class, including caspofungin, anidulafungin and micafungin, although clinical data on their use in such case are scarce. The main advantage of this option is the particularly favorable pharmacokinetic properties of these molecules as they are not metabolized through the cytochrome P-450 enzyme system. Candins can thus be administered safely to patients with moderate to severe liver failure. Among this class, anidulafungin is excreted via the bile and not degraded by hepatic enzymes and has the advantage to not interfere with the cytochrome P450 pathway, limiting interactions with blood levels of immunosuppressants [39].

This case report illustrates the difficulty to start rapidly an appropriate antifungal therapy in critically ill patients while in vitro susceptibility results are often delayed of several days, and drugs of limited toxicity are scarce.

Conclusion

In conclusion, IFI are potentially fatal complications in severe liver disease. Rapid appropriate antifungal therapy is needed. Thus, management is based on both rapid mold identification and in vitro susceptibility results, while taking into account drugs interactions and toxicity. Recent publication of ESCMI-ECMM joint guidelines on diagnosis and management of hyalohyphomycosis is highly helpful for clinicians in such cases [37].

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Compliance with Ethical Standards

Conflict of interest The authors report no conflicts of interest.

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