Introduction

Invasive fungal infections (IFIs) have significant impact on leukemia patients’ survival. Although antifungal drugs are empirically given to most of the patients, breakthrough fungal infections are not uncommon.\(^1\)\(^5\)

Trichosporon infections are an increasingly common complication of neutropenia and other conditions associated with severe immunosuppression. The outcome of disseminated Trichosporon infection is most often poor, and the fatality rate is over 70%.\(^3\)\(^6\)\(^9\) Recently the genus Trichosporon has been taxonomically revised. Generally, two species have been associated
with IFIs in humans: *Trichosporon beigelii* and *Trichosporon capitatum*. *T. capitatum* has now been reclassified as *Geotrichum capitatum* or *Blastoschizomyces capitatus*. *T. beigelii* now corresponds to six different species. Invasive *Trichosporon* infections are due to *T. asahii* in most cases.\(^5\)\(^6\)

The increased use of echinocandins leads to significant selective pressure, which favors opportunistic fungi, that are resistant to these agents. Disseminated trichosporonosis has been reported in immunocompromised patients under echinocandin therapy.\(^3\)\(^4\)\(^7\)\(^-\)\(^14\) Breakthrough trichosporonosis and *G. capitatum* infections occurred in four children on empirical caspofungin therapy.

**Case reports**

**Case 1**

A 16-year-old girl with acquired very severe aplastic anemia (vSAA) received immunosuppressive therapy (IST) consisting of rabbit anti-thymocyte globulin (ATG), cyclosporine A, granulocyte colony stimulating factor (GCSF), and prednisolone after replacement of central venous catheter (CVC). She had no hematological response to IST. Six months after diagnosis of vSAA and 44 days after initiation of IST, the patient was still on regular platelet and erythrocyte transfusion, had very severe neutropenia, and developed febrile neutropenia (FN). On 6th day of FN caspofungin was initiated as empirical antifungal therapy. She developed maculopapular rash on 11th day of caspofungin treatment. Her clinical condition worsened. The patient developed hepatosplenomegaly (HSM) and severe respiratory distress. She was admitted to the pediatric intensive care unit (PICU), and required mechanical ventilation (MV). Blood cultures taken 15 days after initiation of caspofungin revealed yeast, later identified as *T. asahii*. Table 1 shows the minimal inhibitory concentration (MIC) of antifungals. Voriconazole (VCZ) was started. Although blood cultures were negative seven days after initiation of VCZ, the patient clinical condition did not improve. Fever, HSM, respiratory failure, and pancytopenia persisted. She developed renal failure and expired 13 days after clearing blood culture.

**Case 2**

A 5-year-old girl with pre-B cell acute lymphoblastic leukemia (ALL) was included in the standard risk (SR) arm of ALL IC-BFM 2002 treatment protocol. A CVC was inserted. On 42nd day of treatment (day 0), she developed FN (ANC was 12 mm\(^{-3}\)) and empirical caspofungin was started on day 5 thereafter. She presented diarrhea and feeding intolerance. Leukemia treatment was discontinued on day 21 (63rd day of induction therapy). Disseminated maculopapular lesions appeared and she developed sepsis. VCZ (4 mg/kg every 12 h) was added to treatment empirically on day 26 and three days later she developed severe respiratory distress. CVC was removed. The patient was transferred to PICU, requiring intubation and MV. Cultures of three blood samples obtained 19 days after initiation of caspofungin treatment and three days before starting VCZ yielded yeasts, later identified as *T. asahii*. The agent was sensitive to VCZ (Table 1). Although all blood cultures became negative after four days of VCZ therapy, she developed secondary hemophagocytosis (HLH) and was treated according to HLH 2004 protocol for two weeks. After resolution of clinical and laboratory findings related to secondary HLH, she continued to receive ALL IC-BFM 2002 chemotherapy protocol. Secondary antifungal prophylaxis was administered with VCZ for six months and she completed the chemotherapy protocol without reactivation of *T. asahii*.

**Case 3**

A 2.5-year-old boy with pre-B cell ALL was included in HR arm of ALL IC-BFM 2002 treatment protocol. A port catheter was inserted. On 22nd day of treatment (day 0), he developed FN (ANC was 12 mm\(^{-3}\)). Empirical caspofungin was started on day 4. He could not achieve hematologic remission by day 15 (33rd day of treatment protocol) and on day 17, VCZ was added as a second antifungal agent due to worsening clinical condition. Serum galactomannan test was found to be positive. Blood samples for culture were taken on day 18 (14th day of Caspofungin treatment and 1st day of voriconazole treatment) yielded yeasts, later identified as *G. capitatum*. On day 19, caspofungin was stopped and liposomal amphotericin B (LiAmB) was started at the dose of 5 mg/kg, then the dose was increased up to 10 mg/kg/day. Blood cultures were negative on day 23, eight days after VCZ initiation and four days of LiAmB. CVC was removed and culture of the catheter tip yielded the same fungi. Antifungal therapy was continued with combined antifungals for three months without reactivation of IFI.

**Case 4**

A 2.5-year-old girl with pre-B cell ALL was included in HR arm of ALL IC-BFM 2002 treatment protocol after insertion of CVC. She had central nervous system involvement. On the 4th day (day 0) of treatment, she developed FN (ANC was 104 mm\(^{-3}\)). Empirical caspofungin was started on day 8. Fever disappeared 12 days thereafter. A port catheter was inserted on day 15. While she was still on caspofungin treatment she again developed febrile neutropenia on day 17. On day 21, abdominal computerized tomography showed multiple spleen and kidney hypodense nodular lesions with less than 1 cm diameter. On day 25 she developed severe agitation, and cranial magnetic resonance imaging (MRI) showed multiple diffuse cortical and subcortical lesions. On day 29 (33rd day of treatment), bone marrow aspiration revealed hematological remission, and intrathecal treatment was given after cerebrospinal fluid (CSF) sample was taken according to the protocol. Two days later, on day 31, she developed status epilepticus. She was then transferred to PICU and required MV. Serum galactomannan antigen test was found to be weak positive. Empirical VCZ (8 mg/kg/day) was added. On day 32, CSF culture yielded yeasts, later identified as *G. capitatum*. Antifungal susceptibility is shown in Table 1. Caspofungin was stopped and LiAmB was started at the dose of 5 mg/kg/day. Catheter tip, peripheral blood, and urine cultures yielded *G. capitatum*. Port catheter was removed. After four days of LiAmB and five days of VCZ all blood cultures were negative. However, cranial MRI showed progressive encephalitis on day 40. CSF reservoir was inserted and CSF samples from
the reservoir yielded *G. capitatum*. Intrathecal amphotericin B at the dose of 0.25 mg/day was given. The first sterile CSF culture was achieved after 16 days of intravenous VOR, 15 days of LIAMB, and four days of intrathecal amphotericin B. Despite antibiotic and antifungal therapies, fever persisted. Cranial MRI showed progressive encephalitis, external ventricular drainage was inserted and intrathecal AmB was given for 21 days. She weaned from MV 78 days thereafter. She continued to receive combined antifungal therapy for 267 days but developed severe neurological sequelae.

**Discussion**

IFI is a significant cause of morbidity and mortality among patients with hematologic malignancies. Empirical antifungal therapy is highly recommended after four days of FN in this population. Caspofungin and amphotericin B are the suggested antifungal agents for empirical therapy.15

Invasive infections caused by *Trichosporon* species are rare but potentially fatal complications of the immunosuppression associated with treatment of cancer.3,7 Among *Trichosporon* species, *G. capitatum* has emerged as a rare fungal pathogen in recent years, particularly in severely immunocompromised hosts. IFI caused by this agent is often characterized by a multiorgan involvement with a fatal course despite antifungal therapy.16–19 The incidence of *G. capitatum* infection among patients with leukemia was found to be 0.5% with a crude mortality rate of 55%. Several studies collecting cases of *G. capitatum* infections in hematological patients have showed a 30-day attributable mortality ranging from 40% to 75%.

Caspofungin has a good fungistatic and fungicidal activity against a variety of yeasts, but does not show activity against *G. capitatum* and the other fungi of Trichosporon species.3,5,17

The presented four patients with hematologic malignant disease developed severe fungal breakthrough infections with rare causative agents. All of the patients had a CVC, very severe neutropenia, and were initially treated with broad-spectrum antibiotics. Since fever and severe neutropenia persisted in all patients, empirical changes in antibiotic combinations were implemented despite no agent being isolated in the cultures. At a median of five days (range 4–8 days) of FN, caspofungin was started in all these patients, who had fever and hepatosplenomegaly. Cutaneous maculopapular rash was seen in two patients. One had status epilepticus and multiple cerebral abscesses at presentation of mycotic infection. Three of these patients required intubation and MV, and were admitted at the PICU.

Because the patients’ clinical situation worsened, in two patients VOR was added to antifungal therapy empirically one and three days before the agent was detected.

Echinocandins alone have little to no activity against *Trichosporon* spp. and are not recommended for trichosporonosis treatment.3,5 In the literature almost all IFIs caused by *T. asahii* or *G. capitatum* occurred as breakthrough infection in patients who received antifungal therapy, especially echinocandins for at least five to seven days.6–10

Fluconazole was used as the initial therapy in 85% of 19 patients with invasive trichosporonosis documented in a single medical center in Taiwan, and the mortality rate was 42%.9 Suzuki et al.10 recently evaluated the clinical and therapeutic aspects of 33 cases of *Trichosporon* fungemia documented in patients with hematological malignancies. The authors clearly demonstrated that survival was longer for patients treated with an azole than for those treated with other drugs. Triazoles seem to have better in vitro and in vivo antifungal activity against *Trichosporon* spp. than amphotericin B. VOR also has excellent in vitro activity against *Trichosporon* strains and may be useful for treating patients with trichosporonosis.6,16

In conclusion, disseminated trichosporonosis and *G. capitatum* infections have been increasingly reported worldwide. Treatment with echinocandins should be accepted as a risk factor in immunosuppressed patients, especially in institutions where the infection had been detected before. Prophylaxis is limited, and antifungal regimens containing triazoles appear to be the best therapeutic approach.

**Conflicts of interest**

The authors declare no conflicts of interest.

**REFERENCES**

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