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Case report

Rare severe mycotic infections in children receiving empirical caspofungin treatment for febrile neutropenia

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ABSTRACT

Empirical antifungal therapy is most often given to patients with leukemia. However breakthrough fungal infections under antifungal therapy are not uncommon. Four children, with hematologic malignant disease developed mycotic breakthrough infections while on empirical caspofungin treatment for a median of 14 (range 11–19) days. *Trichosporon asahii* was detected in the blood culture of two patients and *Geotrichum capitatum* in the other two (one patient also had positive cerebrospinal fluid culture). Because the patients' clinical situation worsened, voriconazole was empirically added for two patients three and five days before the agent was detected. The first sterile blood culture was obtained 3–7 days of voriconazole treatment. All patients reached clear cultures but one patient died. One patient with central nervous system infection with *G. capitatum* had severe neurological sequelae. Very severe fungal infections can occur during empirical caspofungin therapy. Therefore, patients should be followed closely.

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 immuncompromise. 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

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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.[6,7]

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 globuline (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