Fatal disseminated *Trichosporon asahii* infection in a child with acute lymphoblastic leukemia

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Few cases of *Trichosporon* species infection have been reported in children. The present report describes a case of fatal disseminated *Trichosporon asahii* infection in a child treated for relapsed leukemia. Voriconazole has previously shown promising activity in vitro, and has been used successfully in the treatment of *T. asahii* infections. The patient died five days after voriconazole treatment was started, and the autopsy revealed widespread systemic dissemination to all organs.

Key Words: Children; *Trichosporon asahii*; Voriconazole

Trichosporon species are known to cause white piedra and hypersensitivity pneumonitis, and are also an emerging cause of systemic fungal infection in immunocompromised hosts (1). *Trichosporonosis* has been reported mainly in neutropenic adults (2) but remains uncommon in children. With amphotericin B antifungal treatment, the mortality rate remains high (80%), and prompt initial therapy with new antifungal drugs may potentially increase the survival of these critically ill patients. The case of a leukemic child with fatal *trichosporonosis* is described in the present report. Voriconazole introduced after five days of ineffective therapy with amphotericin B did not improve the outcome.

CASE PRESENTATION

An 11-year-old boy was treated with intensive chemotherapy for acute lymphoblastic leukemia, which initially presented as profound anemia. A medullary relapse was diagnosed on week 28 of therapy. Reinduction therapy (vincristine, doxorubicin, prednisone, L-asparaginase and methotrexate) was performed, with the aim of undertaking a hematopoietic stem cell transplant in remission. On April 20, 2005, 12 days after the last chemotherapy treatment, he became febrile (temperature of 39°C).

His physical examination revealed severe mucositis and mild respiratory distress. The chest radiograph was normal, while the chest computed tomography scan showed mild atelectasia of the left lower lobe. Treatment was immediately

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Peu de cas d'infections à *Trichosporon* ont été signalés chez les enfants. Le présent rapport fait état d'un cas fatal d'infection disséminée à *Trichosporon asahii* chez un enfant traité pour une rechute de leucémie. Le voriconazole avait manifesté une activité prometteuse *in vitro* et a été utilisé avec succès pour le traitement des infections à *T. asahii*. Le patient est décédé cinq jours après le début du traitement par voriconazole et l'autopsie a révélé une dissémination systémique de l'agent infectieux à tous les organes.

started with ticarcillin-clavulanate (300 mg/kg/day divided in four doses), tobramycin (7.5 mg/kg/day divided in three doses) and vancomycin (40 mg/kg/day divided in four doses). His condition improved rapidly, and a blood culture yielded *Streptococcus oralis*. On May 1, after 10 days of continuous antibiotic therapy, the fever recurred (temperature of 39°C) and was sustained for the remainder of the clinical course. No other symptom or physical sign occurred. Laboratory tests disclosed a total leukocyte count of $0.06 \times 10^9/L$, a hemoglobin level of 88 g/L and a platelet count of $5 \times 10^9/L$. Aspartate aminotransferase and alanine aminotransferase levels were 22 U/L and 31 U/L, respectively. On May 2 and 3, four blood cultures, all drawn from a central venous catheter, yielded yeast. Treatment with intravenous liposomal amphotericin B (Ambisome [Astellas Pharma US Inc] 5 mg/kg/day) and granulocyte-colony stimulating factor was started. The central venous catheter was removed and its culture was negative. Despite these interventions, the patient's condition deteriorated, and he developed respiratory distress with hypoxemia and hepatosplenomegaly with rapidly increasing transaminase levels (aspartate aminotransferase level of 1364 IU/L and alanine aminotransferase level of 1018 IU/L). Thus, on May 5, liposomal amphotericin B was discontinued and replaced with voriconazole (4 mg/kg every 12 h intravenously) to obtain broader coverage for yeasts. On May 6, hypoxemia progressed rapidly with radiographic bilateral diffuse infiltrates requiring

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Figure 1) The patient's autopsy revealed a disseminated fungal infection with multiple renal (A–C) and splenic (D–F) abscesses of disseminated trichosporonosis. Tissue sections were stained by the Gomori-Grocott procedure. Original magnifications $\times 200$ (B), $\times 400$ (C) and $\times 50$ (F)

mechanical ventilation. Blood cultures remained positive, and fungal identification revealed *T. asahii*. An ultrasound-guided liver biopsy was performed and yielded *T. asahii* on culture. This yeast was also cultured from urine.

Minimal inhibitory concentrations were determined using the National Committee on Clinical Laboratory Standards M27-A microdilution broth-based method (3), and were 8 mg/L, 0.03 mg/L, 1 mg/L and greater than 8 mg/L for amphotericin B, voriconazole, fluconazole and caspofungin, respectively. Plasma concentrations of voriconazole determined by high-performance liquid chromatography assay were 8.3 mg/L and 6.9 mg/L for the peak (2 h after infusion) and trough, respectively.

Two days after starting voriconazole, on May 7, blood cultures became negative; however, the patient remained febrile and neutropenic, developed multiple organ failure and died on May 10, after five days of treatment with voriconazole. His autopsy revealed disseminated fungal infection with multiple fungal abscesses in the kidneys, spleen (Figure 1), liver and gastrointestinal tract (not shown). Examination of the lungs showed diffuse alveolar damage, hemorrhages and multiple fungal abscesses.

DISCUSSION

Trichosporon species is an emerging pathogen in immunocompromised hosts, and *T. asahii* is the species most frequently involved in disseminated infections (1,2). Most of the cases have been reported in neutropenic adults with hematological malignancies, although trichosporonosis has also been recently reported after solid organ transplantation (4). Disseminated *T. asahii* infection remains uncommon in childhood, and has been mainly reported in immunocompromised children with hematological malignancies (5,6) and more rarely in preterm newborns (7). The present case of disseminated *T. asahii* infection occurred in a boy with severe neutropenia following

chemotherapy for relapsed acute lymphoblastic leukemia, and its clinical course shared similarities with those previously reported, particularly the poor outcome. As described in adults, systemic infections with *T. asahii* are associated with a poor prognosis (2), and the mortality rate is estimated to be approximately 80% with amphotericin B therapy.

Cutaneous involvement with papulonodular or pustular lesions that are sometimes necrotic is frequently observed and is suggestive of trichosporonosis. Biopsies of these skin lesions reveal *Trichosporon* species in more than 75% of cases, and are helpful to promptly confirm the etiology and initiate appropriate treatment (2). Pulmonary involvement, with respiratory symptoms and radiological features of alveolar or interstitial infiltrates, is also frequently observed (30% of cases). Although, *Trichosporon* species are isolated on culture of the sputum in some cases (2), in our patient, the culture was negative despite widespread invasion of the lungs. Our patient did not have skin lesions and the diagnosis was obtained by repeated positive blood cultures, liver biopsy and urine culture. Although liver and splenic abscesses have been less frequently reported (2), the pathological findings in our patient revealed extensive involvement of the liver, spleen, kidneys, stomach and lungs that likely resulted from sustained fungemia. In our case, identification of *Trichosporon* species required five days after the collection of blood cultures. Development and clinical application of a panfungal polymerase chain reaction assay could be a very useful tool for rapid detection and identification of fungal pathogens including *Trichosporon* species, allowing earlier intervention with specific treatment leading to improve patient outcomes (8).

Susceptibilities of *Trichosporon* species to antifungal agents are variable in the literature; in vitro activity does not always correlate with efficacy in vivo. Recently, new azoles have appeared as promising therapies for this infection. In vitro

studies have shown that azoles, particularly voriconazole, were more potent than amphotericin B (9). In the present case, voriconazole exhibited a low minimum inhibitory concentration value against the *T asahii* isolate. However, pharmacokinetic data indicate that children two years of age or older require a larger dosage per kg of body weight than adults to achieve similar peak concentrations at the same dosing interval (10). Thus, voriconazole assays were performed for our patient and showed plasma concentrations above the minimum inhibitory concentration, similar to those observed in adults. Recently, a relationship between fungal infection progression and voriconazole concentrations has been suggested. Favourable responses are observed in patients with concentrations above 2.1 mg/L (11). However, voriconazole plasma concentrations are clearly not the sole predictor of outcome, because the patient died despite achieving concentrations well beyond this threshold value. To date, no comparison of amphotericin B and azoles

has been performed in the treatment of trichosporonosis, and the most efficacious regimen has not been defined. However, some reported cases suggest clinical efficacy for voriconazole in these infections, in monotherapy (2) or in combination therapy with amphotericin B (5). In another patient with acute myeloid leukemia, monotherapy with amphotericin B and subsequently voriconazole failed to cure disseminated *T asahii* infection, but combined treatment with amphotericin B and caspofungin produced a clinical and microbiological response (6).

The death of our patient highlights the critical requirement for early diagnosis and rapid appropriate therapy of trichosporonosis to obtain a favourable outcome.

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