Case Report

Trichosporon: another yeast-like organism responsible for immune reconstitution inflammatory syndrome in patients with hematological malignancy

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Abstract

Trichosporon has recently emerged as a life-threatening opportunistic fungal pathogen, notably in patients with hematological malignancy. Fungemia, sometimes associated with cutaneous lesions and/or pneumonitis, is the major clinical form. Here, we report two cases of patients suffering from acute leukaemia who developed hepatic and/or splenic lesions apart from *Trichosporon* positive blood cultures. The appearance of hepatic and splenic lesions following the recovery from neutropenia is highly suggestive of a chronic disseminated infection, now considered as an immune reconstitution inflammatory syndrome. Treatment with corticosteroid therapy led to clinical improvement in both cases. Copyright © 2016 John Wiley & Sons, Ltd.

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Introduction

Fungal infections are frequent and severe complications in patients with hematologic malignancy. Recently, non-*Aspergillus* and non-*Candida* fungal pathogens have emerged as life-threatening opportunist microorganisms [1]. *Trichosporon*, one of these emerging pathogens, is mostly responsible for fungemia, sometimes associated with cutaneous lesions and/or pneumonitis, while involvement of other organs is rare [2]. *Trichosporon* infections are particularly difficult to manage due to a natural resistance to echinocandins and, to a lesser extent, to polyenes [3].

Here, we report two cases of *Trichosporon* fungemia, complicated with the occurrence, in the following weeks, of hepatic and/or splenic abscesses, highly suggestive of chronic disseminated infections. Such clinical forms due to *Candida* are well known and are considered as immune reconstitution inflammatory syndromes and as such can benefit from corticosteroid therapy [4].

Case 1 (Figure 1)

A 65-year-old man was referred to our institution for peripheral blood blastosis. Bone marrow biopsy confirmed the diagnosis of acute myeloid leukaemia. Cytotoxic chemotherapy with cytarabine plus idarubicin (day 0) was initiated, combined with posaconazole prophylaxis (200 mg/day). On day 21, while still neutropenic and treated with cefepime Bristol-Myers Squibb, Reuil-Malmaison, France, the patient became febrile without any other clinical symptoms. Liposomal amphotericin B was introduced at 3 mg/kg/day, but the patient remained febrile. On day 24, two flasks of blood cultures returned positive for a yeast-like organism, further identified as *Trichosporon asahii*, using a home-made database for MALDI-TOF identification [5]. A β -D-glucan assay returned positive at 115 pg/ml ($N < 80$ pg/ml; Fungitell, CapeCod East Falmouth, MA, USA) while a galactomanan antigen assay was negative. At the same time, there was a dramatic increase of the serum level of C-reactive protein and a significant increase of hepatic enzymes. After fungal identification, liposomal amphotericin B was replaced with

Figure 1. Case 1: (A) Patient's clinical course; (B) Abdominal CT-scan showing the evolution of splenic nodules surrounded with peripheral hyposignal lesions

voriconazole Pfizer, Paris, France (400 mg i.v. bid for 24 h then 200 mg bid). While clinical breakpoints have not yet been determined for *Trichosporon*, minimal inhibitory concentrations (MIC) determined using the E-test method (BioMérieux, Marcy l'Etoile, France) were indicative of susceptibility to amphotericin B, fluconazole and voriconazole. After a couple of days of improvement and despite an increasing number of neutrophils, fever reappeared and the patient's clinical condition worsened. A very large panel of microbiological and serological tests only revealed few colonies of *C. glabrata* and coagulase-negative *Staphylococcus*

in a BAL specimen. On day 30, β -D-glucan remained positive at 212 pg/ml. The abdominal CT-scan was considered normal. Because of difficulties in drug monitoring, voriconazole was replaced by i.v. fluconazole Pfizer, Paris, France (400 mg/day) after a 6-day course. At the same time, bone marrow examination revealed a hemophagocytic syndrome treated with corticosteroids (1 mg/kg/d) for a 6-day course. This allowed control of the fever and a decrease in the C-reactive protein. Nineteen days after the fungemia episode, positron emission tomography (PET)/CT revealed multiple splenic nodules, further confirmed by a CT-scan,

suggestive of a fungal dissemination (Figure 1). Blood cultures were negative, but β -D-glucan remained high at 251 pg/ml. Fluconazole was replaced by voriconazole again (280 mg every 12 h), and the fever stopped after a few days. The general status of the patient improved progressively, and, 1 month later, the patient was afebrile, the biological markers of inflammation and hepatic enzymes had returned to normal and the β -D-glucan level decreased to 149 pg/ml. Three months later, abdominal CT-scan and positron emission tomography/CT showed stability of the splenic lesions. Voriconazole was maintained for several months because of future predictable neutropenia episodes. Unfortunately,

allogenic bone marrow transplantation was excluded leading to the prescription of palliative monthly cytarabine courses. Relapse of the hematological disease occurred 9 months later, and the patient eventually died.

Case 2 (Figure 2)

A 17-month-old boy was initially referred to our emergency department with a 10-day history of fever with deterioration of his general status (day 0). Clinical examination showed peripheral lymphadenopathies associated with

Figure 2. Case 2: (A) Patient's clinical course; (B) Abdominal ultrasound showing hepatic (left) (diameter around 15 mm) and splenic (right) (diameter <10 mm) abscesses

liver and spleen enlargement. Temperature was at 38.7 °C. The child was neutropenic (neutrophil counts at $0.3 \times 10^9/l$) with circulating blasts at $14 \times 10^9/l$. Respiratory failure led to admission in intensive care unit, where empirical antibiotic therapy combining piperacilline-tazobactam and vancomycin was initiated. On day 2, bone marrow examination confirmed the diagnosis of acute lymphoblastic leukaemia. On day 3, while the child was still febrile, clinical exam revealed an ano-rectal abscess. Piperacillin-tazobactam was switched for imipenem, ciprofloxacin, ornidazole and liposomal amphotericin B was started at 3 mg/kg/day. On day 10, the ano-rectal abscess turned into a cellulitis, requiring a colostomy in order to allow the abscess to heal. Five days later, the patient became afebrile and induction chemotherapy with prednisone, vincristine and L-Asparaginase was then started. At this time, because of digestive colonization by *Candida lusitanae*, liposomal amphotericin B was replaced by caspofungin (70 mg/m² the first day and then 50 mg/m²/day). Three days later, a white necrotic lesion appeared on the colostomy mucosa. Caspofungin was then switched back to liposomal amphotericin B, which resulted in rapid apyrexia. However, a blood culture and the colostomy lesion grew positive for a yeast-like organism further identified as *T. asahii* [5]. Liposomal amphotericin B was then changed for voriconazole (14 mg/kg/day i.v.) for 2 days, then fluconazole (10 mg/kg/day i.v.). This treatment led to rapid improvement of the clinical condition. MIC of antifungals showed a decrease in susceptibility to amphotericin B, but susceptibility to fluconazole, voriconazole and posaconazole. However, 20 days after the positive *Trichosporon* bloodculture, and while still treated with fluconazole, the child became febrile again. Bacterial and fungal bloodcultures remained negative. An abdominal ultrasound revealed two hepatic and multiple splenic nodules, suggestive of fungal abscesses (Figure 2). Dexamethasone treatment (1 mg/12 h) resulted in an immediate apyrexia and was maintained for 15 days. An attempt to stop steroids led to the reappearance of fever. Therefore, dexamethasone (0.5 mg/12 h) was maintained for another 2 weeks, followed by a prolonged treatment with hydrocortisone. Afterwards, a chemotherapy protocol was pursued leading to complete cytological and molecular remission. Fluconazole treatment was stopped after 4 months, based on the recovery of a normal abdominal ultrasound. Six months after fluconazole discontinuation, no sign of relapse of the fungal infection has appeared.

Discussion

Trichosporon belongs to the long list of emerging fungal pathogens that complicate the course of hematological malignancies [6,7]. One peculiarity of *Trichosporon* is that it belongs to the basidiomycete phylum [7], and as such, it

is naturally resistant to echinocandins. In addition, and to a variable extent according to species, susceptibility to amphotericin B may be decreased [3], making therapeutic management challenging. Thereby, as seen in patient 2, *Trichosporon* infections commonly occur as a breakthrough infection in patients receiving either amphotericin B or echinocandin therapy [8]. Most of those infections emerge during an episode of neutropenia in patients with hematological malignancy [6]. Disseminated infection with positive blood culture(s), sometimes associated with cutaneous and/or pulmonary involvement, is the predominant clinical picture of invasive *Trichosporon* infection [2].

Immune reconstitution inflammatory syndrome (IRIS), initially reported in the context of AIDS-related opportunistic infections [9], has been described in other settings, notably in neutropenic patients [10]. The rapid relief of an effective immune response, combined with immunomodulatory effects linked to some pathogens' antigens, and to antimicrobials by themselves may lead to severe clinical pictures [9]. While mimicking treatment failure, the chronology of the symptoms, the persistently negative cultures and the potential benefit of limiting the immune response, either by delaying the ARV therapy or even adding corticosteroid therapy, support this difficult-to-prove diagnosis [4]. While the effect of corticosteroids is doubtful in patient 1, it seems truly efficient in case 2, where the discontinuation led to the recurrence of the fever.

Fungal pathogens seem particularly prone to induce such phenomena. Indeed, *Cryptococcus neoformans*, *Pneumocystis jiroveci*, *Aspergillus fumigatus* and *Histoplasma capsulatum* have been associated with IRIS too [11–13]. Recently, some reports suggest that chronic disseminated candidiasis, so-called hepato-splenic candidiasis, because of the organs usually involved, should be considered as an IRIS [4]. Indeed, concomitantly with the recovery of neutrophils, some patients, previously neutropenic and having undergone a *Candida* bloodstream disseminated infection, documented or not with positive blood cultures, develop abscesses in the liver, the spleen or more rarely the kidneys [4,14]. Our observations are highly suggestive of such a phenomenon induced by *Trichosporon* infection. In both cases, haematogenous dissemination of *Trichosporon* was documented during the neutropenic phase. Hepatic and/or splenic lesions were diagnosed 34 and 19 days later, respectively, while neutrophil count had returned to normal. Although there was no confirmation of the fungal nature of these lesions, imaging features were highly suggestive of fungal abscesses. The role of amphotericin B, received by our two patients, in the development of such lesions can be postulated. Indeed, this drug exhibits only limited activity against *Trichosporon* and has a well-known pro-inflammatory activity notably through

the release of inflammatory cytokines [15]. A similar case of a chronic disseminated *T. asahii* infection in a leukemic child has been previously reported [16]. The patient was treated with liposomal amphotericin B, then with an amphotericin B lipid complex when an abdominal ultrasound and CT-scan revealed multiple hepatic abscesses and splenomegaly. A favourable outcome was obtained when itraconazole therapy was initiated. No corticosteroid therapy was associated.

In vitro susceptibility testing and case reports suggest that voriconazole could be the best therapeutic alternative for such infections ([3] and personal data). Indeed, MICs of voriconazole against *Trichosporon* spp, including *T. asahii*, are usually the lowest as compared with the other antifungal drugs [3]. Nevertheless, in the context of cytotoxic chemotherapy, caution must be taken in the case of concomitant treatment with vincristine because of possible drug–drug interaction [17].

In conclusion, *Trichosporon*, a recently emerged fungal pathogen, may be responsible for chronic disseminated infection following fungemia. As shown for chronic disseminated candidiasis, corticosteroid therapy may be a valuable adjunctive therapy in such cases.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest

Ethics statement

According to the French legislation, patients or their representatives were informed that the clinical details of their history could be published, and none expressed opposition.

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