

Fatal Invasive Trichosporonosis Caused by *Trichosporon inkin* after Allogeneic Stem Cell Transplant for very Severe Idiopathic Aplastic Anem

Daphné Krzisch¹, Vincent Camus¹, Marion David², Gilles Gargala³, Stéphane Lepretre

¹ Department of Haematology, Centre Henri Becquerel, Rouen, France;

² Laboratory of Microbiology, Centre Henri Becquerel, Rouen, France;

³ Laboratory of Parasitology-Mycolology, CHU de Rouen, Charles Nicolle Hospital, Rouen, France

Abstract

Invasive *Trichosporon inkin* fungal infections are rare and unusual, occurring nearly exclusively in immunocompromised patients experiencing prolonged neutropenia during treatment of malignant hemopathies or other immunodeficiency conditions. We report a case of a 27-year-old patient with severe aplastic anemia who developed *Trichosporon inkin* sepsis with skin lesions during aplasia after myeloablative allogeneic stem cell transplant. He was treated with liposomal amphotericin B but died from multiple organ failure. We then discuss the epidemiological, clinical and therapeutic features of these serious fungal infections compared to the published data

Keywords: *Trichosporon inkin*; Aplastic anemia; Invasive fungal infection; *Trichosporonosis*; Hemopathy; Immunodeficiency; Antifungal therapy basidiomycete

INTRODUCTION

Fungal infections are an important cause of death in immunocompromised patients, and particularly with hematologic disease. The most common fungal infections are invasive aspergillosis and invasive candidiasis [1,2] but mucormycosis are one of the most dreaded disease. Here, we want to approach about *Trichosporon* spp, least well-known, but which have devastating effects. Currently, no standard recommendations for *Trichosporon* spp antifungal prophylaxis and treatment exist

CLINICAL EVOLUTION:

We report medical history of a 27 years old man of Turkish origin with no relevant medical history, who has been admitted to our haematology unit for a severe idiopathic aplastic anemia, according to standard diagnostic and severity criteria [3-5], (Thrombopenia 6 Giga/L; Hb 12 g/dL, Reticulocyte 12 G/L–bone marrow hypocellularity<15%, absolute neutrophil count 1.3 G/L

. An induction by cyclosporine 2 mg/kg twice daily associated with daily granulocyte colony-stimulating factors (lenograstim, G-CSF) is started, but the course has been unfavourable, with a persistence of medullary depression and quick appearance of very severe aplastic anemia criteria: Hb 8 g/dL, reticulocytes 3 G/L, platelets 20 G/L, absolute neutrophil count 0 G/L) on October 2012 . The patient presented with fever and

development of herpetic gingivostomatitis. The patient's room was located in the leukaemia unit and was a positive pressure ventilation clean room. The explorations fund no documentation. The patient was treated with broad spectrum antibiotherapy (piperacillin/tazobactam) with absence of bacteriological documentation. At day 14, an anal cellulitis appeared with perineal pains and persistence of fever. The evolution is complicated with several bacteraemia documented with *Stenotrophomonas maltophilia* and *Staphylococcus epidermidis* Meticilline-resistant. Unfortunately, there was no possibility of surgical management of this perineal cellulitis, no surgical indication, because of the thrombocytopenia and uncollected skin damage. The patient received different anti-infectious therapies (Figure 1). At day 18, the patient presented a pneumonitis characterised by an interstitial syndrome. Because of a suspicious positive aspergillosis antigenemia we treated the patient by VORICONAZOLE 4 mg/kg twice a day switched for CASPOFUNGINE 50 mg per day (hepatitis toxicity), No broncho-alveolar lavage was performed at this time. The evolution was favourable under this treatment. Because of persistent medullary abnormalities and multiple infectious complications, an pheno-identical 10/10 allogeneic stem cell transplant was performed 20 days after the initial ciclosporin-based therapy; the conditioning was non-myeloablative, with Cyclophosphamide 300 mg/m² /d and horse anti-thymocyte globulin 40 mg per kg per day. At day 20, the patient has presented a new infectious pneumonitis, characterized by bilateral interstitial and micro nodular infiltrates and an apical predominance. The broncho-alveolar lavage revealed a small lymphocytosis, and the bacteriological and mycological cultures remained negative. The CASPOFUNGINE was switched to VORICONAZOLE 4 mg/kg twice a day (after loading dose 6 mg/kg twice a day once) in ad of the antibiotics. Then, at day 43, the patients developed skin nodules on the left foot, then an extension until the left thigh. At this time, the patient benefited from a large anti-infectious therapy (Figure 1). The multiple positivity of samples proved the disseminated *Trichosporin* spp: The skin biopsy fund a fibrinous necrosis associated with histiocytes and septate and budding fungal structures, arguments for alternariose or trichosporinose. One blood culture (at day 66) was positive to *Trichosporon inkin*, which was identified by mass spectrometry (MALDI-TOF), as well as an anal sample. The transthoracic echography did not find argument for endocarditis or myocarditis. We added AMBISOME 3 mg/kg/day to VORICONAZOLE at day 52 to broaden the spectrum

and used in dual therapy. Alternatively, the patient developed a CMV viremia, probably due to a reactivation (positive CMV serologic status of the recipient). It was treated in the first place by GANCICLOVIR 10 mg/kg twice a day, switched by Foscavir because of the persistence of the significant viral load. Before the transplant, the initial CMV serologic status for CMV the recipient was positive, which allowed a negotiation of the viremia. At the day 80, the patient was transferred in medical reanimation for an acute respiratory distress syndrome, in relation with an acute cardiac deficiency due to a myocarditis. The viral aetiology was excluded because of the decrease of the CMV viral load. The privileged hypothesis was fungal, and potentially due to Trichosporon, because of the disseminated character, the cardiac tropism and the slowly good evolution under treatment. The patient went out of aplasia at day 110. In front of the favourable evolution and because of persistent fever, the antibiotic and antifungal drugs, except FOSCAVIR (decreased viral load) were stopped in order to make new infectious samples. Unfortunately, the patient developed a febrile pancytopenia, without argument for a macrophage activation syndrome, and a skin rash. No microbiological documentation was found. Antibiotics PIPERACILLINE-TAZOBACTAM 4 g four times a day VANCOMYCINE 30 mg/kg in continuous and AMIKACINE are reintroduced. The new skin biopsy was in favour of a drug eruption. The VANCOMYCINE is switched by DAPTOMYCINE 4 mg/kg once a day, without improvement of the skin. The thoracic tomography showed an aggravation of pulmonary lesions, with an excavation. The patient died for a new acute respiratory distress due to an acute cardiac insufficiency, and multivisceral organ failure.

CONCLUSION:

In conclusion, to our knowledge this is the first published case of fatal invasive fungal infection with Trichosporon inkin in an allogeneic stem cell transplant recipient that was not successfully controlled with liposomal amphotericin B and voriconazole. Trichosporon spp. seems to be an emerging, opportunistic agent in immunocompromised patients with malignant haematological disease. Further research is needed to determine the best antifungal strategy, the optimal time and posology of treatment, and to identify the mode of dissemination of this fungal agent, the incubation period and mode of transmission in immunocompromised patients, and risk factors.