



# Trichosporon faecale invasive infection in a patient with severe aplastic anemia: Efficacy of voriconazole and liposomal amphotericin B before neutrophil recovery



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## ABSTRACT

We report a case of a 51-year old man with a severe aplastic anemia who developed an invasive trichosporonosis to *Trichosporon faecale* with fungemia and skin lesions during severe neutropenia. The treatment was successful before neutrophil recovery with a combination of voriconazole and liposomal amphotericin B.

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## 1. Introduction

Invasive trichosporonosis is a life-threatening fungal infection mostly reported in patients with hematologic malignancies and sometimes in patients with peritoneal dialysis or solid tumors [1]. Despite its rarity, *Trichosporon spp.* has been reported as the second most common yeast after *Candida* in patients with hematologic malignancies [2]. The most frequent underlying hematologic malignancies are acute leukemias in 60 to 86% of cases with infections occurring during neutropenia following chemotherapy [1,3,4]. The infections are commonly associated with mortality rates of 50 to 80%, even if mortality might be lower in the absence of underlying malignancy [1,3–5]. The most frequent form of invasive infection is fungemia in 74.7% of cases with 2/3 of fungemia associated with clinically or microbiologically documented tissue infection, mostly lung (16.2%) and skin (9.1%).<sup>1</sup> Most cases of invasive infections are reported with *Trichosporon asahii* while other species are more rarely identified [1,4,5]. Several risk factors for invasive trichosporonosis have been identified, namely hematological disease with prolonged neutropenia, presence of central venous catheter, male sex and steroid use [6].

Originalities of the present case report of invasive trichosporonosis to *Trichosporon faecale* in a patient with severe neutropenia

and aplastic anemia are resolution of the infection before neutrophil recovery with a combination of voriconazole and liposomal amphotericin B together with rarity of the *Trichosporon* specie. Indeed, most reports indicate that a successful outcome seems to rely more on neutrophil recovery than on antifungal treatment [3,7]. As a consequence, a successful outcome exclusively due to antifungal agents as reported here is a valuable information. *Trichosporon faecale* is rarely reported in humans and almost always in localized infections [1,5,8] like tinea pedis [9,10]. Our case identified *Trichosporon faecale* as the causative agent of an invasive trichosporonosis with fungemia and skin lesions in a patient with an hematological disease, clearly indicating that *Trichosporon faecale* can be a human pathogen in immunocompromised patients.

## 2. Case

A 51-year old man was diagnosed in our unit with severe aplastic anemia (neutrophil cell count:  $0.01 \times 10^9$ /liter, hemoglobin level: 7.3 gr/dl, platelet count:  $5 \times 10^9$ /liter). Day 1 was defined as the first day of treatment of aplastic anemia. He was treated with an immunosuppressive regimen consisting of horse antithymocyte globulin (ATG; ATGAM, Pfizer) at 40 mg/kg/day from day 1 to day 4 and cyclosporine at 5 mg/kg/day given in divided doses every 12 hours from day 1 together with G-CSF at 5 µg/kg/day. To

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prevent serum sickness, oral prednisone was given before each daily dose of horse ATG at 1 mg/kg/day, reducing the dose by half every 5 days.

On day 3, empirical broad spectrum antibacterial anti-biotherapy with cefepim (4 gr/day) and amikacin (loading dose 25 mg/kg, then 15 mg/kg/day) was started for febrile neutropenia. The fever disappeared in 24 h without bacterial identification but reappeared on day 6. A chest CT Scan was normal. Vancomycin (2 gr/day) and caspofungin (loading dose 70 mg, then 50 mg/day) were empirically started without efficacy. A peripheral blood culture performed on day 10 returned positive for yeasts on day 12. On day 16, subcultures on Sabouraud-Chloramphenicol-Gentamicin (Becton-Dickinson) and CHROMagar (Becton-Dickinson) of the blood culture revealed white colonies with rough and dry appearance that were identified as *Trichosporon* spp. using the matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry BioTyper system (Bruker Daltonics). Identification at the species level was subsequently performed by sequencing the intergenic spacer 1 (IGS1) region using IGS\_26S\_F (5'-ATCCTTTGCAGACGACTTGA-3') and IGS\_5S\_R (5'-AGCTTGACTTCGACATCGG-3') primers. Sequence data were compared by individual BLASTn (Basic Local Alignment Search Tool) searches using NCBI (National Center for Biotechnology Information) BLAST database. A 100% sequence similarity with *Trichosporon faecale* L8331-EB087B (GenBank accession number KM488281) and *Trichosporon faecale* L8333-EB108A (GenBank accession number KM488280) was obtained. Antifungal susceptibility was investigated using E-test<sup>®</sup> (bioMérieux). The minimal inhibitory concentrations (MICs) were 1 µg/ml for amphotericin B, 32 µg/ml for 5-fluorocytosine, 2 µg/ml for fluconazole, 0.32 µg/ml for voriconazole and > 32 µg/ml for micafungin.

On day 12, the fever persisted with poor performance status (ECOG 3: capable of only limited selfcare; confined to bed or chair more than 50% of waking hours) [11], jaundice and inflammatory nodular skin lesions on both legs whose biopsy revealed the presence of *Trichosporon faecale*. The yeast was not present in stools or oral cavity. The central venous catheter was removed (culture was negative), caspofungin was discontinued and replaced by intravenous voriconazole (loading dose 6 mg/kg × 2/day, then 4 mg/kg × 2/day). Prednisone was discontinued on the same day. Voriconazole blood levels were subsequently checked at least once a week to target 1 to 5 µg/ml [12]. Plasma levels averaged 2014 µg/mL (0.4–7.4 µg/mL).

Because the performans status of our patient was poor, liposomal amphotericin B (3 mg/kg/day) was added on day 13 and subsequently continued with results of in vitro susceptibility tests. The liver function tests revealed cholestasis (bilirubine, 129 µmol/liter; γ-glutamyltransferase, 387 U/liter, alkaline phosphatase, 248 U/liter). Liver ultrasound was normal and no virus or hepatotoxic agent was identified. The patient remained profoundly neutropenic (< 0.1 × 10<sup>9</sup>/liter). On day 16, because of lethargy and cerebellar symptoms, a lumbar puncture, a cerebral CT scan and a cerebral magnetic resonance imaging were performed. The results of these tests were normal and the neurologic symptoms improved and disappeared in less than 1 week without therapeutic intervention. Afterwards, the performance status improved but the fever persisted. Nodular lesions were identified at ultrasound of the spleen but no biopsy could be performed. From Day 10 to Day 61, 54 standard blood cultures and 16 mycologic specific blood cultures were performed. All returned negative. The fever persisted until day 62 without any further documented infection. The skin lesions progressively healed and disappeared on day 62. The neutrophil count reached 0.5 × 10<sup>9</sup>/liter on day 91 and the patient left the unit a few days later with a good performans status (ECOG 1). Liposomal amphotericin B was discontinued on day 89 and voriconazole on day 148. Neither fever nor skin lesions recurred

after day 62. After a 7-month follow-up, the patient remains under immunosuppressive therapy with cyclosporine, still dependent on transfusions but with neutrophils > 1 × 10<sup>9</sup>/liter and no recurrence of trichosporonosis.

### 3. Discussion

The optimal therapy of invasive trichosporonosis has yet to be established and remains a challenge. Flucytosine and echinocandins are not recommended because of lack of in vitro activity [4–6]. Moreover, some breakthrough infections have been reported in patients treated with echinocandins [7,13]. In contrast, azoles and especially voriconazole are suitable antifungal agents because of better in vitro and in vivo activities [4,5,14]. Interestingly, a recent study by Suzuki et al. reported a better survival with azoles as compared to other antifungal agents in 33 patients with hematologic malignancies and invasive trichosporonosis [3]. Concerning amphotericin B, the available data suggest a limited activity both in vitro and in vivo [1]. It is less potent than azoles but more potent than echinocandins [5]. In a report by Girmenia et al., a clinical response to amphotericin B was observed in 24% of patients with hematologic malignancies [1]. Moreover, in a study reporting on 22 *Trichosporon asahii* isolates, MIC50 and MIC90 were 0.25 and 1 µg/ml, respectively [15]. As a consequence, antifungal regimens containing azoles, especially voriconazole by rank order of activity appear to be the best therapeutic option [14]. There is no convincing data in the literature to recommend a combination of antifungal agents. In our case report, we empirically chose to add liposomal amphotericin B to voriconazole because the performance status of the patient was poor and because of the results of in vitro susceptibility tests. Interestingly, in contrast to our case, most reported isolates of *Trichosporon faecale* seem to be resistant to amphotericin B [8].

Originalities of our case are resolution of infection before neutrophil recovery and rarity of *Trichosporon* specie. In a report by Matsue et al. on 4 patients with hematologic malignancies and invasive trichosporonosis, 1 patient with neutrophil recovery survived while others died with persistent neutropenia [7]. These results led the authors to conclude that outcome of invasive trichosporonosis seems to rely more on neutrophil recovery than on antifungal agents [7]. In addition, Suzuki K et al. reported on 33 patients with *Trichosporon* spp. fungemia and observed that only 1 patient without neutrophil recovery survived [3]. In that study, resolution of infection was significantly associated with neutrophil recovery [3]. Hosokawa K et al. reported in 2011 on a patient recovering from *Trichosporon asahii* fungemia before neutrophil recovery after a combination therapy with voriconazole and liposomal amphotericin B, as in our case [16]. The patient eventually died of acute myeloid leukemia but the combination therapy was effective enough to allow subsequent chemotherapies and allogeneic stem cell transplantations [16]. *Trichosporon faecale* is rarely reported in humans and almost always in localized infections [1,5,8–10]. Two case reports of tinea pedis caused by *Trichosporon faecale* have recently been reported [9,10]. A *Trichosporon faecale* was isolated and reported in 2009 in a 6-year old female patient with fungemia successfully treated with liposomal amphotericin B [17]. Unfortunately, the clinical condition of the patient was not detailed [17]. Our case identified *Trichosporon faecale* as the causative agent of an invasive infection with fungemia and skin lesions in a patient with an hematological disease.

In conclusion, we report a case of an invasive trichosporonosis to *Trichosporon faecale* in a patient with severe aplastic anemia, successfully treated before neutrophil recovery with a combination of voriconazole and liposomal amphotericin B. Our case clearly indicates that *Trichosporon faecale* are potential human

pathogens of invasive infections in immunocompromised patients.

### Conflict of interest

None.

### Ethical Form

There is no source of funding or potential conflict of interest to disclose.

We have obtained a written and signed consent to publish the case report from the patient.

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### References

- [1] C. Girmenia, L. Pagano, B. Martino, D. D'Antonio, R. Fanci, G. Specchia, et al., GIMEMA Infection Program. Invasive infections caused by *Trichosporon* species and *Geotrichum capitatum* in patients with hematological malignancies: a retrospective multicenter study from Italy and review of the literature, *J. Clin. Microbiol.* 43 (4) (2005) 1818–1828, Apr.
- [2] A.L. Colombo, A.C. Padovan, G.M. Chaves, Current knowledge of *Trichosporon* spp. and Trichosporonosis, *Clin. Microbiol. Rev.* 24 (4) (2011) 682–700, Oct.
- [3] K. Suzuki, K. Nakase, T. Kyo, T. Kohara, Y. Sugawara, T. Shibasaki, et al., Fatal *Trichosporon* fungemia in patients with hematologic malignancies, *Eur. J. Haematol.* 84 (5) (2010) 441–447, May.
- [4] D.P. Kontoyiannis, H.A. Torres, M. Chagua, R. Hachem, J.J. Tarrand, G.P. Bodey, et al., Trichosporonosis in a tertiary care cancer center: risk factors, changing spectrum and determinants of outcome, *Scand. J. Infect. Dis.* 36 (8) (2004) 564–569.
- [5] S.Y. Ruan, J.Y. Chien, P.R. Hsueh, Invasive trichosporonosis caused by *Trichosporon asahii* and other unusual *Trichosporon* species at a medical center in Taiwan, *Clin. Infect. Dis.* 49 (1) (2009) e11–e17, Jul 1.
- [6] M.C. Arendrup, T. Boekhout, M. Akova, J.F. Meis, O.A. Cornely, O. Lortholary, European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group; European Confederation of Medical Mycology. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast infections, *Clin. Microbiol. Infect.* 20 (Suppl 3) (2014) S76–S98, Apr.
- [7] K. Matsue, H. Uryu, M. Koseki, N. Asada, M. Takeuchi, Breakthrough trichosporonosis in patients with hematologic malignancies receiving micafungin, *Clin. Infect. Dis.* 42 (6) (2006) 753–757, Mar 15.
- [8] J.L. Rodriguez-Tudela, T.M. Diaz-Guerra, E. Mellado, V. Cano, C. Tapia, A. Perkins, et al., Susceptibility patterns and molecular identification of *Trichosporon* species, *Antimicrob. Agents Chemother.* 49 (10) (2005) 4026–4034, Oct.
- [9] D. Hahner, R. Kirschner, M. Piepenbring, H. Schöfer, First isolation of the anamorphic basidiomycetous yeast *Trichosporon faecale* in Germany, from the skin of a patient with tinea pedis, *Mycopathologia* 165 (3) (2008) 149–153, Mar.
- [10] A.A. Fallahi, M. Moazeni, F. Noorbakhsh, P. Kordbacheh, F. Zaini, H. Mirhendi, et al., A case report of tinea pedis caused by *Trichosporon faecale* in Iran, *Med. Mycol. Case Rep.* 1 (1) (2012) 49–51, Jul 20.
- [11] M. Oken, R. Creech, D. Tormey, et al., Toxicity and response criteria of the Eastern Cooperative Oncology Group, *Am. J. Clin. Oncol.* 5 (1982) 649–655.
- [12] A. Hulin, E. Dailly, C. Le Guellec, [Level of evidence for therapeutic drug monitoring of voriconazole]. Groupe Suivi Therapeutique Pharmacologique de la Societe Francaise de Pharmacologie et de Therapeutique, *Therapie* 66 (2) (2011) 109–114, Mar–Apr.
- [13] T. Akagi, K. Yamaguti, T. Kawamura, T. Nakamura, K. Kubo, H. Takemori, Breakthrough trichosporonosis in patients with acute myeloid leukemia receiving micafungin, *Leuk. Lymphoma.* 47 (6) (2006) 1182–1183, Jun.
- [14] G. Hazirolan, E. Canton, S. Sahin, S. Arkan-Akdagli, Head-to-head comparison of inhibitory and fungicidal activities of fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole against clinical isolates of *Trichosporon asahii*, *Antimicrob. Agents Chemother.* 57 (10) (2013) 4841–4847, Oct.
- [15] M.S. Tsai, Y.L. Yang, A.H. Wang, L.S. Wang, D.C. Lu, C.H. Liou, et al., Susceptibilities to amphotericin B, fluconazole and voriconazole of *Trichosporon* clinical isolates, *Mycopathologia* 174 (2) (2012) 121–130, Aug.
- [16] K. Hosokawa, H. Yamazaki, K. Mochizuki, K. Ohata, K. Ishiyama, T. Hayashi, et al., Successful treatment of *Trichosporon* fungemia in a patient with refractory acute myeloid leukemia using voriconazole combined with liposomal amphotericin B, *Transpl. Infect. Dis.* 14 (2) (2012) 184–187, Apr.
- [17] S.J. Taj-Aldeen, N. Al-Ansari, S. El Shafei, J.F. Meis, I. Curfs-Breuker, B. Theelen, et al., Molecular identification and susceptibility of *Trichosporon* species isolated from clinical specimens in Qatar: isolation of *Trichosporon dohaense* Taj-Aldeen, Meis & Boekhout sp., *J. Clin. Microbiol.* 47 (6) (2009) 1791–1799, Jun.