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Use of combination therapy to successfully treat breakthrough *Trichosporon asahii infection* in an acute leukemia patient receiving voriconazole

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ABSTRACT

Trichosporon species is an important life-threatening opportunistic systemic pathogen, especially in leukemia patients. Voriconazole is proved to be a promising agent in past decade. However, recently we observed a case of breakthrough *Trichosporon asahii* infection while receiving voriconazole, which calls for an alternative treatment strategy. A combination therapy of liposomal amphotericin B (AmB) plus caspofungin – in which liposomal AmB dose was reduced due to renal toxicity – was administered to successfully treat this patient.

1. Introduction

Trichosporon species is now emerging as an important life-threatening opportunistic systemic pathogen, especially in leukemia patients. The approximate morality rate of *Trichosporonosis* was 77–80% [1–4]. *Trichosporon asahii* is the most common cause of disseminated infection in *Trichosporon* species [5]. Although the optimal antifungal therapy for treatment has yet to be established, voriconazole seems to be preferred as first-line antifungal agent in past decade, according to the promising effect both in clinic and in pre-clinical studies [6]. However, recently we observed a case of breakthrough *T. asahii* infection while receiving voriconazole, which calls for an alternative treatment strategy.

2. Case

An adult with acute erythroleukemia (AML-M6) was admitted for induction chemotherapy including decitabine, idarubicin and cytarabine. During the treatment, a suspected catheter-associated infection and mucositis occurred consecutively which resulted in the administration of teicoplanin, tinidazole and fluconazole (400 mg/d) sequentially for about 2 weeks. At the first day after chemotherapy (day+1), the fever developed up to 38.2 °C when teicoplanin and fluconazole were still administered. Neither CT scan nor blood culture has positive finding. Concerning the risk of serious infection during the immunosuppression period, the antibiotic strategy was empirically modified to piperacillin-tazobactam, vancomycin combined with voriconazole (6 mg/kg/12 h for the first day, followed by 4 mg/kg/12 h), and the temperature gradually returned to normal within 3 days. The granulocyte counts fell to lower than 0.5×10^9/L at day +4. At day +12, the temperature rose again up to 39.2 °C, while the chest CT scan revealed diffused nodular infiltrates in both of the lungs. Blood culture was performed in both peripheral and central venous catheter samples, and as a pre-emptive treatment, anti-infection regimen was switched to imipenem-cilastatin, linezolid, and liposomal amphotericin B (liposomal AmB) at a target dose of 3 mg/kg everyday. Blood culture yielded *T. asahii* in both samples 3 days later (identification was taken by Vitek 2 Compact, 94% reliability index). During the first 3 days of liposomal AmB administration, daily peak temperature remained around 39.0 °C, whereas serum creatinine rose from 60.4 μmol/L to 199.8 μmol/L. Due to the progressive renal dysfunction, the dose of liposomal Amb was reduced to 2 mg/kg at day +15. Instead, caspofungin 50 mg every day (70 mg for the first dose) was combined. Meanwhile, G-CSF was administered at a dose of 300 μg/d to accelerate the hematopoietic recovery. Hyperpyrexia was controlled at day +17, and finally

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returned to normal at day +19 when the neutropenia period ended. Complete remission was achieved as confirmed by bone marrow examination, and renal dysfunction was also gradually recovered later. The combination anti-fungal therapy continued for 3 weeks, until the previous nodules in chest CT completely disappeared. Blood culture was repeated for several times before the discontinuation of anti-fungal therapy, and all the results were negative. With voriconazole as secondary prophylaxis, the patient then received subsequent consolidation chemotherapy and an identical-sibling bone marrow transplant in 3 months without any manifestation of invasive fungal infection, which hinted the clearance of *T. asahii*.

3. Discussion

Reported risk factors of disseminated *T. asahii* infection include malignancies, neutropenia, chronic active hepatitis, cystic fibrosis, administration of immunosuppressive agents, use of broad-spectrum antibiotics, and disruption of the skin–mucosa barrier. The route of invasion includes respiratory tract, gastrointestinal tract, central venous catheter or percutaneous interventional treatment [7–9]. In this case, previous infections, neutropenia after chemotherapy, and combined antibiotics might jointly result in subsequent *T. asahii* invasion, even if antifungal agent had been used.

Several studies have demonstrated low sensitivity *in vitro* of *T. asahii* to common antifungal agents [6], and breakthrough *trichosporonosis* has been reported during the administration of various antifungal agents [10–13]. The susceptibility to AmB is varied, and echinocandins display low activity against *Trichosporon* species [1,6]. Voriconazole is probably the most sensitive drug against *T. asahii in vitro*, which has also succeeded in a number of cases, including breakthrough infections [4,14–17]. However, it has been reported that the correlation between clinical and mycological resistance is poor [1], and cases of successful treatment with AmB or echinocandins alone can be found in literatures when used alone or in combination [1,3,14].

A joint clinical guideline for the diagnosis and management of rare invasive yeast infections was recently published by ESCMID/ECMM, in which the optimal option to treat *Trichosporon* species has yet been established [6]. Voriconazole, which is the preferred antifungal agent, is recommended in Grade B strength, with level III evidence. However, this case developed *trichosponosis* during the treatment of voriconazole, which led physicians into a dilemma. AmB is supposed to be an alternative option but toxicities frequently limit their dose as well as efficacy. With more acquaintance of *T. asahii* and the development of antifungal agents, combined administration of antifungal agents attracts more attention for obtaining better clinical results and for reducing the antifungal doses. *In vivo* and *in vitro* studies have demonstrated a better synergic effect between AmB and echinocandin (either caspofungin or micafungin) not only in *Trichosporon* species, but also in *Candida* species, *Aspergillus* species, *Fusarium* species and *Cryptococcus neoformans* [3,18]. The probable mechanism of synergy is that echinocandins could enhance the penetration of AmB into the cell membrane, causing an increase in the antifungal activity of AmB. Basetti et al. firstly used liposomal AmB and caspofungin to successfully treat an acute leukemia patient with *T. asahii* fungaemia [3]. De Vasconcelos and his colleagues cured an invasive *T. asahii* infection in an acute myeloid patient by AmB with caspofungin [14]. Our observation suggested that even with a lower dose, the combination therapy of liposomal AmB and caspofungin may synergistically improve the antifungal activity with better tolerance. In patients with voriconazole-breakthrough *trichosporonosis* who cannot tolerate standard-dose AmB, this combined regimen seems to be the best choice.

Renal dysfunction is a frequently observed feature of Amb, which may limit the dose of the drug. However, our observation suggested that even if the dose of liposomal AmB is reduced, the combination therapy of liposomal AmB and caspofungin may synergistically improve the antifungal activity with minimum toxicity. Despite a successful treatment against disseminated *T. asahii* infection, subsequent chemotherapy or hematopoietic stem cell transplantation is still challenging. However, recrudescence of *Trichosporonosis* did not occur in this case, which hinted the clearance of *T. asahii*. Unfortunately, the lack of susceptibility test and other post-mortem examinations did not allow us to identify this isolate further.

Although the combined regimen is effective, the clinical outcome seems to also depend on the patient's hematologic recovery of the underlying disease. The mortality of disseminated Trichosponosis may reach approximately 100% in patients with persistent neutropenia [3]. Thus, to improve the immunosuppressive status is obligatory in the treatment strategy, and an appropriate antifungal therapy allows the patient to live through this period post-chemotherapy, which usually lasts for 2 weeks or longer.

Because of the excellent activity against a broad spectrum of fungi as well as the convenience of maintenance treatment with oral products, voriconazole is widely used as empirical or pre-emptive treatment for fungal infection. To our knowledge, breakthrough disseminated infection of *T. Asahii* during voriconazole administration has not been reported previously. Our observations in this case provide an encouraging treatment option in this special clinical setting. We concluded that liposomal AmB combined with caspofungin may potentially eradicate *T. asahii*, and clinical experience of this combination regimen is worth to be more accumulated.

Conflict of interest

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References

[1] Girmenia C, Pagano L, Martino B, D'Antonio D, Fanci R, Specchia G, et al. Invasive infections caused by *Trichosporon* Species and *Geotrichum capitatum* in patients with hematological malignancies: a retrospective multicenter study from Italy and review of literature. J Clin Microbiol 2005;43:1818–28.
[2] Thibeault R, Champagne M, de Repentigny L, Fournet JC, Tapiero B, Moghrabi A, et al. Fatal disseminated *Trichosporon asahii* infection in a child with acute lymphoblastic leukemia. Can J Dis Med Microbiol 2008;19:203–5.
[3] Bassetti M, Bisio F, Di Biagio A, Pierri I, Balocco M, Soro O, et al. *Trichosporon asahii* infection treated with caspofungin combined with liposomal amphotericin B. J Antimicrob Chemother 2004;54:575–7.
[4] Kudo K, Terui K, Sasaki T, Kamio T, Sato T, Ito E. Voriconazole for both successful treatment of disseminated *Trichosporon asahii* infection and subsequent cord blood transplantation in an infant with acute myelogenous leukemia. Bone Marrow Transplant 2011;46:310–1.
[5] Sugita T, Ichikawa T, Matsukura M, Sueda M, Takashima M, Ikeda R, et al. Genetic diversity and biochemical characteristics of *Trichosporon asahii* isolated from clinical specimens, houses of patients with summer-typer-hypersensitivity pneumonitis, and environmental materials. J Clin Microbiol 2001;39:2405–11.
[6] Arendrup MC, Boekhout T, Akova M, Meis JF, Cornely OA, Lortholary O. ESCMID/ECMM joint clinical guideline for the diagnosis and management of rare invasive yeast infections. Clin Microbiol Infect 2014;Suppl. 3:S76–98.

[7] Biasoli MS, Carlson D, Chiganer GJ, Parodi R, Greca A, Tosello ME, et al. Systemic infection caused by *Trichosporon asahii* in a patient with liver transplant. Med Mycol 2008;46:719–23.
[8] Vazquez JA. Trichosporon infection. Curr Fungal Infect Rep 2010;4:52–8.
[9] Wolf DG, Falk R, Hacham M, Theelen B, Boekhout T, Scorzetti G, et al. Multidrug-resistant *Trichosporon asahii* infection of nongranulocytopenic patients in three intensive care units. J Clin Microbiol 2001;39:4420–5.
[10] Groll AH, Walsh TJ. Uncommon opportunistic fungi: new nosocomial threats. Clin Microbiol Infect 2001;7(Suppl. 2):S8–24.
[11] Antachopoulos C, Papakonstantinou E, Dotis J, Bibashi E, Tamiolaki M, Koliouskas D, et al. Fungemia due to *Trichosporon asahii* in a neutropenic child refractory to amphotericin B: clearance with voriconazole. J Pediatr Hematol Oncol 2005;27:283–5.
[12] Gueho E, Smith MT, de Hoog GS, Billon-Grand G, Christen R, Batenburg-van der Vegte WH. Contributions to a revision of the genus Trichosporon. Antonie Leeuwenhoek 1992;61:289–316.
[13] Lo Passo C, Pernice I, Celeste A, Perdichizzi G, Todaro-Luck F. Transmission of *Trichosporon asahii* oesophagitis by a contaminated endoscope. Mycoses 2001;44:13–21.
[14] Menezes EA, Marinho JAS, Angelo MR, Cunha Mda C, Cunha FA, Vansconcelos Junior AA. Isolation and antifungal susceptibility testing of *Trichosporon asahii* in Ceara, Brazil. Rev Inst Med Trop Sao Paulo 2012;54:1–3.
[15] Matsue K, Uryu H, Koseki M, Asada N, Takeuchi M. Breakthrough Trichosporonosis in patients with hematologic malignancies receiving micafungin. Clin Infect Dis 2006;42:753–7.
[16] Shang ST, Yang YS, Peng MY. Nosocomial *Trichosporon asahii* fungemia in a patient with secondary hemochromatosis: a rare case report. J Microbiol Immunol Infect 2010;43:77–80.
[17] Asada N, Uryu H, Koseki M, Takeuchi M, Komatsu M, Matsue K. Successful treatment of breakthrough *Trichosporon asahii* fungemia with voriconazole in a patient with acute myeloid leukemia. Clin Infect Dis 2006;43:e39–41.
[18] Serena C, Pastor FJ, Gilgado F, Mayayo E, Guarro J. Efficacy of micafungin in combination with other drugs in a murine model of disseminated trichoporonosis. Antimicrob Agents Chemother 2005;49:497–502.