Successful Treatment of Breakthrough Trichosporon asahii Fungemia with Voriconazole in a Patient with Acute Myeloid Leukemia

Noboru Asada,1 Hidetaka Uryu,1 Mihoko Koseki,1 Masami Takeuchi,1 Masaru Komatsu,2 and Kosei Matsue1

1Division of Hematology/Oncology, Department of Medicine, Kameda General Hospital, Chiba, and 2Division of Clinical Microbiology, Department of Clinical Pathology, Tenri Hospital, Nara, Japan

We describe a 55-year-old man with acute myelogenous leukemia who developed breakthrough Trichosporon asahii fungemia during 5 days of micafungin treatment. Although the patient’s clinical condition improved considerably after the start of voriconazole treatment, blood culture results remained positive for T. asahii for 3 days, and fever persisted for 7 days thereafter. The patient achieved complete hematological remission, and he received successful consolidation chemotherapy without developing Trichosporon infection with the prophylactic use of voriconazole therapy. This case report illustrates that voriconazole may be useful in the treatment of disseminated T. asahii infection in neutropenic patients.

A 55-year-old man was admitted to Kameda General Hospital (Chiba, Japan) on 7 June 2005 and received a diagnosis of acute myelogenous leukemia. He received induction chemotherapy consisting of idarubicin and cytosine arabinoside, beginning 9 June. Cefepime and amikacin were administered to treat a high fever, and oral itraconazole (200 mg/day) was prescribed as prophylactic use of voriconazole therapy. This case report illustrates that voriconazole may be useful in the treatment of disseminated T. asahii infection in neutropenic patients.

Received 11 January 2006; accepted 10 May 2006; electronically published 28 June 2006. Reprints or correspondence: Dr. Kosei Matsue, Div. of Hematology/Oncology, Dept. of Medicine, Kameda General Hospital, 929 Higashi-Chou, Kamogawa-shi, Chiba, 296-8602, Japan (koseim@dc4.so-net.ne.jp).

Clinical Infectious Diseases 2006;43:e39–41
© 2006 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2006/4304-00E2$15.00

BRIEF REPORT
CID 2006:43 (15 August) • e39

face, trunk, and upper extremities (figure 1). A chest CT revealed nodules with halo sign in the bilateral regions of the lungs (figure 2). Bronchoalveolar lavage was not performed because of neutropenic fever and signs of respiratory failure with hypoxia and tachypnea. On 28 June, Trichosporon asahii was cultured from blood samples and identified using the API 20C AUX yeast assimilation system (bioMérieux). In vitro susceptibility of the isolated strain of T. asahii was determined by the broth microdilution method, according to National Committee for Clinical Laboratory Standards (NCCLS) [1]. The MICs of voriconazole (VCZ), amphotericin B, flucytosine, micafungin, fluconazole, itraconazole, and micafungin against the T. asahii isolate were 0.5 μg/mL, 1 μg/mL, 16 μg/mL, 2 μg/mL, 32 μg/mL, 1 μg/mL, and >16 μg/mL, respectively.

Micafungin therapy was discontinued, and treatment with intravenous VCZ was instituted at 300 mg twice daily on 29 June, followed by 200 mg twice daily thereafter. After initiation of VCZ therapy, the patient’s respiratory condition began to improve gradually, although T. asahii was cultured repeatedly from blood specimens for the 3 days after starting VCZ (until 1 July), and the patient’s fever persisted over the next 7 days. On day 4 of VCZ therapy, the patient noted blurred vision, visual hallucinations, and leg weakness. Using high-performance liquid chromatography, plasma VCZ trough levels measured 7.2 μg/mL on day 7 of therapy and 2.8 μg/mL on day 12 of therapy. The VCZ dosage was reduced, and treatment was discontinued on day 13 and restarted on day 17 with an oral formulation (400 mg/day). The patient’s VCZ toxicity diminished after the drug dose was reduced. The patient attained complete hematological remission on day 28 of chemotherapy (6 July). The optical density index of serum galactomannan decreased to 0.4 by day 30 of chemotherapy, and the appearance of pulmonary nodules was markedly improved. The patient received successful consolidation chemotherapy with high-dose cytosine arabinoside and prophylactic VCZ from day 56 of induction chemotherapy, without developing trichosporonosis.

Disseminated Trichosporon infections in immunocompromised or granulocytopenic patients are frequently fatal, despite treatment with various antifungal agents [2–4]. Although amphotericin B and triazoles show activity against Trichosporon species in vitro [5], clinical failure and microbiologic resistance to amphotericin B have been documented in vivo [6–8]. Trichosporon species are resistant to the fungicidal effects of amphotericin B [8]. In addition, T. asahii, the most common of the Trichosporon species in systemic Trichosporon infection, seems less susceptible to amphotericin B [9]. In animal models,
antifungal triazoles have been shown to be more active than amphotericin B against *T. asahii* [7, 8]. Several reports of treatment of a number of cases of *Trichosporon* infections with various antifungal regimens, or with amphotericin B alone or in combination with other antifungal agents, did not allow conclusions to be drawn regarding effective regimens for disseminated *Trichosporon* infection [6, 10–12]. New extended-spectrum triazoles, especially VCZ, posaconazole, and ravuconazole, have been shown to have good activity against *Trichosporon* species in vitro [9, 13]. Thus, these antifungals are attractive choices for treatment strategies for this infection. However, there have been a few reports regarding the clinical efficacy of these new triazoles for disseminated trichosporonosis: to our knowledge, there have been only 2 previous case reports of successful treatment of disseminated trichosporonosis with VCZ [14, 15], whereas the failure of VCZ therapy to ameliorate disseminated trichosporonosis was reported in another patient with acute myelogenous leukemia [16]. Unfortunately, because antifungal susceptibility studies were performed in only 1 case, and because the serum concentration of VCZ was not measured in any of the cases, a correlation of in vitro susceptibility of *T. asahii* isolates to VCZ and clinical outcome could not be assessed from these cases.

Our patient developed fever, cough, hemoptysis, pulmonary nodules with halo sign, and elevation of optical density index of serum galactomannan after completion of induction chemotherapy, which were strongly suspected to be due to pulmonary aspergillosis. Micafungin was substituted for itraconazole as empirical therapy, and breakthrough *T. asahii* fungemia developed after 5 days of exposure to micafungin therapy. In agreement with an earlier report [9, 13], the antifungal profile of the *T. asahii* isolate exhibited reduced susceptibility to amphotericin B, miconazole, flucytosine, fluconazole, itraconazole, and micafungin. VCZ therapy exhibited potent antifungal activity. In spite of the clinical improvement of the patient’s respiratory condition, fungemia and fever persisted 3 and 7 days after the start of VCZ therapy, respectively. The trough level of VCZ was higher than the MIC of VCZ against *T. asahii* isolated from cultures of samples obtained from our patient. The correlation between the results of in vitro susceptibility tests and clinical response is not well established; however, the delayed clinical response to VCZ observed in our patient suggests that an improvement of underlying disease also seems important for eradication of the pathogen.

Breakthrough trichosporonosis occurred in our patient during 5 days micafungin therapy. Goodman et al. [17] also reported breakthrough trichosporonosis in a bone marrow transplant recipient receiving caspofungin acetate therapy, an echinocandin-class antifungal agent. However, van Burik et al. [18] did not recognize breakthrough trichosporonosis during micafungin administration as prophylaxis against invasive fungal infection in 426 patients undergoing hematopoietic stem cell transplantation.

We recently experienced 4 cases of disseminated trichosporonosis (including this case) in micafungin recipients [19]; increased use of this class of agent may exert a selective pressure on the development of fungi resistant to the agent.

In conclusion, because of the increased use of cytotoxic drugs and the increased use of antifungal agents (including echinocandins), breakthrough trichosporonosis may be encountered with prolonged neutropenia, especially in patients with leukemia. Although an optimal therapy for trichosporonosis has yet to be identified, our observations in this case provide en-
Courageous evidence of the utility of VCZ for treatment of disseminated trichosporonosis.

Acknowledgments

We are indebted to Dr. David Gremillion (Department of Postgraduate Education, Kameda Medical Center) for his careful reading and suggestions in this manuscript. We also thank Yohko Nagasaka (Department of Clinical Pathology, Tenri Hospital) for her technical assistance in this study.

Potential conflicts of interest. All authors: no conflicts.

References