Breakthrough Trichosporonosis in Patients with Hematologic Malignancies Receiving Micafungin

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Background. Micafungin is a newly approved antifungal agent in the echinocandin class that is active against Candida species and Aspergillus species. However, this agent has limited activity against a number of fungi, including Trichosporon species. We describe 4 patients who developed disseminated trichosporonosis during the use of micafungin. No cases of trichosporonosis had been seen in the 2 years prior to January 2003, when micafungin became available in our hospital.

Methods. We reviewed microbiological records of patients at Kameda General Hospital (Kamogawa City, Chiba, Japan) from 1 January 2002 to 31 July 2005, and identified 4 patients whose blood culture results were positive for Trichosporon species.

Results. Since January 2003, four patients—3 with acute myelocytic leukemia and 1 with myelodysplastic syndrome—developed disseminated trichosporonosis while receiving treatment with micafungin with or without amphotericin B. The initial 2 isolates were identified as Trichosporon beigelii, and the later 2 isolates were identified as Trichosporon asahii. All 4 patients received micafungin, and 2 also received amphotericin B concomitantly. Minimal inhibitory concentrations of micafungin were ≥16 μg/mL for the 2 isolates available for susceptibility testing. One patient with hematologic recovery (neutrophils >500 cells/mm³) showed elimination of the fungus after receiving treatment with voriconazole. However, the 3 other patients without hematologic or immunological recovery died of disseminated infection.

Conclusions. The rarity of trichosporonosis in our hospital and its emergence after the introduction of micafungin therapy support the idea that micafungin may exert a significant, selective pressure toward resistant fungi, such as Trichosporon species. Therefore, care should be taken regarding the possibility of trichosporonosis in patients receiving micafungin with or without amphotericin B.

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Trichosporonosis is a relatively rare fungal infection associated with neutropenic patients, such as those with acute leukemia and other severely immunocompromised conditions [1–4]. Although the portal of entry is unclear, fungemia after persistent fever is the most common presentation of trichosporonosis, with common dissemination to the skin, kidneys, and other organs. Susceptibility to amphotericin B (AmB) is variable, and resistance to fluconazole (Flu), itraconazole (Itr), and echinocandins, has been reported, rendering treatment with these agents usually ineffective [5–7]. The outcome of disseminated disease is usually poor, with a mortality rate of >80% [8].

Micafungin is a newly developed antifungal agent that has recently been approved for clinical use in Japan. This agent is a glucan synthesis inhibitor of the echinocandin structure class, and it has been reported to be active against Candida species and Aspergillus species but to have limited activity against a number of fungi, including Trichosporon species [6]. Therefore, it is possible that use of micafungin may exert selective pressure for growth of resistant fungi, such as Trichosporon species. Indeed, breakthrough trichosporonosis in a patient receiving caspofungin acetate, a similar antifungal agent of the echinocandin class, has been reported [9]. Since 1 January 2003, when micafungin became available at our hospital, we have treated 4 patients with acute myelogenous leukemia (AML) who developed breakthrough trichosporonosis during treatment with micafungin.
PATIENTS AND METHODS

We reviewed microbiological records from the Department of Hematology and Oncology at Kameda General Hospital (Kamogawa City, Chiba, Japan) and identified patients with positive blood culture results for Trichosporon species from 1 January 2002 to 31 July 2005. During this period, a total of 915 patients with hematologic disorders were admitted to our department, and only 4 patients with positive blood culture results for Trichosporon species were identified.

Isolation and identification of yeasts. Blood cultures and clinical isolates were processed by the automated Bactec 9240 system (Becton Dickinson) in our hospital's microbiology laboratory. Yeasts were subcultured on Sabouraud dextrose agar. For identification of yeast, Microscan Rapid Yeast ID panel (Dade Behring) was used. Because this system permits identification of Trichosporon species at the species level, all clinical isolates of Trichosporon species had been reported as Trichosporon beigeli until June 2005 at our institution. Clinical isolates from case patients 3 and 4 were analyzed using API 20C AUX yeast assimilation system (bioMérieux) at the Special Reference Laboratory (Tokyo, Japan). The identification of Trichosporon asahii in patients 3 and 4 was further confirmed by PCR amplification of an rRNA gene fragment with specific primers conducted by Dr. Takashi Sugita of Meiji Pharmaceutical University (Tokyo, Japan), as described elsewhere [10].

Antifungal susceptibility. The in vitro antifungal susceptibilities of the T. asahii isolates from patients 3 and 4 to AmB, Flu, Itr, and micafungin were determined using the Clinical and Laboratory Standards Institute (NCCLS) M-27 microdilution method [11]. The MICs were defined as the lowest drug concentrations that resulted in complete inhibition of visible growth. The MIC of voriconazole could not be determined because of lack of availability of the drug.

CASE REPORTS

Patient 1. A 60-year-old man was referred to Kameda General Hospital for treatment of fever, liver abscess, and pulmonary infiltrates on 26 September 2003. He received a diagnosis for myelodysplastic syndrome on the basis of findings of a complete blood cell count, peripheral blood smear, and bone marrow morphological examination. Cytogenetic examination of the bone marrow also revealed multiple complex abnormalities. X-ray and CT scan of the chest revealed diffuse pulmonary infiltrates corresponding to bronchiolitis obliterans with organizing pneumonia, which was treated with high-dose therapy with steroids and cyclosporine with minimal effect. Despite use of various antibiotics, including ampicillin-sulbactam, meropenem, vancomycin, amikacin, Flu, and AmB, the patient still had intermittent fever with a temperature up to 39.0°C. Micafungin (150 mg per day) was substituted for AmB because of renal insufficiency on 3 November 2003. In addition to intermittent fever, generalized edema and pleural effusion developed on 12 November. However, blood culture results remained sterile (the results were negative for Trichosporon species also for other bacteria), and clinical isolates from sputum and urine samples did not yield the fungus. On 4 December 2003, blood culture yielded Trichosporon species, and micafungin was switched to Flu (400 mg per day). The patient's central venous catheter was removed. Although results of blood culture were sterile again 2 days after commencement of treatment with Flu, the patient's clinical condition deteriorated rapidly, and he died on 24 December 2003. Autopsy was not permitted.

Patient 2. A 56-year-old man was admitted to Kameda General Hospital for a relapse of AML after undergoing an unrelated bone marrow transplantation 2 years previously. High-dose reinduction chemotherapy with cytarabine and idarubicin was unsuccessful, and leukemic cells persisted in both peripheral blood and bone marrow. During the patient's neutropenic period after chemotherapy, he developed polymicrobial septicemia due to Streptococcus viridans, Escherichia coli, and Klebsiella oxytoca, which was treated successfully with a combination of cefepime, amikacin, and Flu. Because the patient's renal function was impaired as a result of previous use of aminoglycosides and AmB, micafungin (150 mg per day) was substituted for Flu on 12 November. He remained febrile, and his clinical condition did not improve because of persistent pancytopenia secondary to refractory leukemia. Therefore, we decided to perform an allogeneic stem cell transplantation with 2-HLA antigen–mismatched cord blood. The patient was conditioned with a regimen of busulfan, and he received 2 x 10^6 kg cord blood on 25 November. The patient developed antibiotic-resistant fever at the beginning of the conditioning regimen, but results of blood culture remained sterile, and cultures of sputum and urine samples were negative for fungus. On post-transplant day 1 (26 November), Trichosporon species was simultaneously observed in cultures of blood and urine samples. Treatment with micafungin was discontinued, and treatment with Flu (200 mg per day) was restarted. Despite the change in antifungal agent, repeated blood cultures remained positive for Trichosporon species. The patient's clinical condition deteriorated rapidly, and he died of multiple-organ failure on post-transplant day 8. Autopsy was not permitted.

Patient 3. A 56-year-old man was referred to Kameda General Hospital for evaluation of leukocytosis and anemia on 12 February 2004. A diagnosis of AML with minimal differentiation was made on the basis of the results of hematologic and immunophenotypic examination. He was treated with induction chemotherapy consisting of idarubicin and cytarabine. Antifungal prophylaxis was performed with Flu (100 mg per day orally), which was then substituted with Itr (200 mg per day orally). His clinical course was complicated by the persistence
of blast cells and the development of pulmonary infiltrates with effusion. The patient became febrile on day 7 of induction therapy and developed nodular infiltrates in the left lower lobe of the lung. He was treated with a number of antibiotics, including ciprofloxacin, meropenem, vancomycin, and amikacin, with marginal effect. On 4 April, the patient had a persistent fever, and a CT scan of the chest showed nodular infiltrates with halo signs in the left lower lung, and the optical density index (ODI) of his serum galactomannan became positive (>3.0) in 2 consecutive samples. He was suspected of having pulmonary aspergillosis and was treated with a combination of AmB (1 mg/kg per day) and micafungin (300 mg/kg per day), which resulted in the disappearance of pleural effusion and partial improvement of the pulmonary infiltrates. Fever also subsided. Because cytopenia due to refractory leukemia persisted, the patient received low-dose reinduction chemotherapy consisting of cytarabine, aclacinomycin, and granulocyte CSF from 13 April 2004. He became febrile again, and pulmonary infiltrates increased on 7 May 2003. In addition to antifungal therapy with AmB and micafungin, broad-spectrum antibiotics, including ciprofloxacin, vancomycin, and tobramycin, were re instituted. Treatment with AmB was discontinued on 20 May because of the elevation of the patient’s serum creatinine level.

On 19 May 2005, x-ray and CT scan of the chest revealed a mass-like infiltrate in the middle lobe of the right lung. Bronchoscopy was performed to evaluate the pulmonary infiltrate. Microbiological examination of the patient’s bronchoalveolar lavage fluid specimen revealed Trichosporon species that was further identified as T. asahii, and antifungal therapy with micafungin was switched to high-dose treatment with Flu (800 mg per day), which was later reduced to 400 mg per day. Despite high-dose Flu therapy, blood culture revealed T. asahii on 11 and 13 June. On 17 June, voriconazole became available in our hospital, and Flu was switched to voriconazole (400 mg per day). Because T. asahii infection would not resolve without hematologic recovery, we decided to perform bone marrow transplantation with an unrelated, HLA-matched donor. The patient was conditioned with fludarabine, busulfan, and low-dose total body irradiation (4 Gy), and bone marrow transplantation was performed on 23 June 2004. After transplantation, the patient’s condition deteriorated progressively, and he died on 11 July (post-transplant day 18) without hematologic recovery. Permission was not given to perform an autopsy.

On 11 July (post-transplant day 18) without hematologic recovery. Permission was not given to perform an autopsy.

DISCUSSION

Invasive trichosporonosis is a rare, emerging, life-threatening fungal infection caused by Trichosporon species. The incidence of Trichosporon infection in patients with acute leukemia was 0.4% in a previous multicenter study performed in Italy [12]. Using modern molecular biological techniques, Trichosporon species associated with human infection have been further classified into at least 8 species: T. asahii, Trichosporon asteroides, Trichosporon cutaneum, Trichosporon inkin, Trichosporon mucoides, Trichosporon ovoides, Trichosporon pullulans, and Trichosporon loubieri [12, 13]. The T. asahii strain is thought to be the most common cause of trichosporonosis. In the present series, 2 isolates were identified as T. asahii, but 2 other isolates were not classified further because of a lack of available isolates. Most disseminated Trichosporon infections have been reported in immunocompromised patients with severe neutropenia, usually in patients with hematologic malignancy [1, 2, 12, 14]. The infection progresses rapidly and results in multiple-organ failure involving the lungs and kidneys, as well circulatory collapse. Because of the rarity of this condition, the optimal an-
tifungal agent for treatment of and duration of therapy for disseminated trichosporonosis have yet to be established. In addition, Trichosporon species are relatively resistant to most antifungal agents, including AmB, Flu, Itr, and flucytosine [5]. Although combinations of AmB with flucytosine or high-dose fluconazole have been used in isolated cases [15, 16], the outcome of therapy seems to depend not only on effective antifungal therapy, but also on the patient’s hematologic recovery of the underlying disease.

Micafungin is newly approved for use in Japan. Similar to other antifungals of the echinocandin class, micafungin inhibits the synthesis of 1,3-β-D-glucan, which is an essential component of the fungal cell wall. The susceptibility pattern of micafungin is similar to that of caspofungin acetate [6]. Although it has excellent activity against a broad spectrum of fungi, such as Candida species and Aspergillus species, it is not active against other fungi, including Trichosporon species. Because micafungin has been shown to be active against Aspergillus fumigatus with minimal toxicity, it has become an attractive alternative to AmB treatment for patients with fungal infection who have multiple comorbidities. We have encountered 4 patients with disseminated trichosporonosis over the past 2.5 years, all of whom received micafungin for treatment of high fever complicated with prolonged neutropenia (table 1). Three patients received aggressive antileukemic treatment, including a preparative regimen of allogeneic stem cell transplantation or induction chemotherapy for AML, and 1 patient received prolonged, high-dose immunosuppressive therapy with steroids and cyclosporin. Micafungin was used to empirically treat 3 patients for pulmonary infiltrates or suspected pulmonary aspergillosis, although AmB was used simultaneously in 2 patients, with the expectation that there would be a synergistic antifungal effect [17]. The time that the breakthrough appearance of Trichosporon fungemia occurred and the duration of micafungin exposure were variable in our series. Patient 4 developed Trichosporon fungemia after 5 days of micafungin therapy and was treated successfully with voriconazole; Trichosporon fungemia developed in patient 3 after 65 days of exposure to micafungin, and treatment with voriconazole was unsuccessful. In addition, positive culture results for T. asahii from bronchoalveolar lavage fluid specimens preceded positive culture results from blood samples for this patient. Because Aspergillus galactomannan assay and CT scan of the lung suggested the presence of pulmonary aspergillosis, and bronchoalveolar lavage fluid specimen cultures positive for T. asahii also indicated the presence of T. asahii pneumonia, we speculated that this patient developed mixed mycoses of aspergillosis and trichosporonosis.

Breakthrough trichosporonosis has been reported during the administration of various antifungal agents, including AmB and azoles [8, 18]. Goodman et al. [9] recently reported a breakthrough infection in a patient who underwent bone marrow transplantation and was receiving caspofungin acetate, an echinocandin class antifungal, which was treated successfully with a combination of AmB lipid complex and Flu. However, van Burik et al. [19] reported the prophylactic use of micafungin during the neutropenic period among 425 patients undergoing hematopoietic stem cell transplantation. Although breakthrough infection was observed in 7 (1.6%) of these 425 patients—4 had candidiasis, 1 had aspergillosis, 1 had fusariosis, and 1 had zygomycosis—no breakthrough trichosporonosis was observed in their series. In our hospital, over the past 2.5 years, we have encountered 4 patients who developed Trichosporon fungemia after receiving micafungin, whereas no cases occurred during the 2 years prior to the introduction of this agent. Our experience is in contrast to the observations of van Burik et al. [19]. Because T. asahii is the causative agent of summer-type hypersensitivity pneumonitis, which has been reported exclusively in Japan [20], the geographic distribution of this fungus or factors such as climate may explain the difference.

Table 1. Clinical characteristics of patients with breakthrough trichosporonosis who received micafungin.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex, age</th>
<th>Underlying disease or condition</th>
<th>Predisposing conditions for trichosporonosis</th>
<th>Site of infection</th>
<th>Previous antifungal treatment, dose size</th>
<th>Duration of MCF exposure, days</th>
<th>Treatment for Trichosporon species infection</th>
<th>Hematologic recovery achieved</th>
<th>Clinical response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male, 60 years</td>
<td>RAEB</td>
<td>Low-dose treatment with AraC, steroids, and CSP</td>
<td>Lung, skin, blood</td>
<td>AmB, 0.5 mg/kg; MCF, 150 mg</td>
<td>32</td>
<td>Flu</td>
<td>No</td>
<td>Died</td>
</tr>
<tr>
<td>2</td>
<td>Male, 55 years</td>
<td>Leukemia relapse after U-BMT</td>
<td>Treatment with Flu, BU, and CY; cord blood BMT</td>
<td>Blood</td>
<td>MCF, 150 mg</td>
<td>14</td>
<td>Flu</td>
<td>No</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>Male, 58 years</td>
<td>Primary refractory AML</td>
<td>Treatment with Flu, BU, and L-TBI; U-BMT</td>
<td>Lung, blood</td>
<td>AmB, 0.5 mg/kg; MCF, 150 mg</td>
<td>65</td>
<td>High-dose Flu, then VCZ</td>
<td>No</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>Male, 54 years</td>
<td>AML</td>
<td>Treatment with Ida and AraC</td>
<td>Lung, skin, blood</td>
<td>MCF, 150 mg</td>
<td>5</td>
<td>VCZ</td>
<td>Yes</td>
<td>Lived</td>
</tr>
</tbody>
</table>

NOTE. AmB, amphotericin B; AML, acute myelogenous leukemia; AraC, cytosine arabinoside; BMT, bone marrow transplantation; BU, busulfan; CSP, cyclosporine; CY, cytoxan; Flu, fluconazole; Flud, fludarabine; Ida, idarubicin; L-TBI, low-dose total body irradiation; MCF, micafungin; RAEB, refractory anemia with excess of blast cells; U-BMT, bone marrow transplantation with an unrelated, HLA-matched donor; VCZ, voriconazole.

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Actually, Fukuda et al. [21] more recently described 5 patients who developed disseminated trichosporonosis after undergoing hematopoietic stem cell transplantation, 3 of whom developed the disease while receiving micafungin. Micafungin invariably shows high MICs for T. asahii [5, 22, 23], and it is strongly anticipated that the increase in use of micafungin and/or AmB will exert significant, selective pressure toward opportunistic fungi resistant to these antifungal agents.

Efficacious therapeutic regimens for trichosporonosis have yet to be established, because of the rarity of the infection and the severity of the underlying diseases. In vitro susceptibility findings may be a useful guide in selecting antifungal drugs for trichosporonosis. In our series, T. asahii isolated from patients 3 and 4 showed extremely high MICs for micafungin. MICs for AmB, Flu, and Itr were also moderately elevated. Papavitou et al. [23] reported that the azoles appeared to be more potent than AmB. The new triazoles—voriconazole, posaconazole, and ravuconazole—showed excellent fungicidal activity in vitro and are promising agents for the treatment of trichosporonosis. Fournier et al. [24] reported a case of disseminated trichosporonosis treated successfully with voriconazole. We successfully treated 1 patient (patient 4) who showed hematologic recovery with voriconazole, although another patient (patient 3) without hematologic recovery did not respond to this agent. Although voriconazole showed excellent antifungal activity against Trichosporon species in vitro, the outcome of disseminated trichosporonosis seems to rely more on hematologic and immunologic recovery rather than on the in vitro efficacy of the antifungal agent.

Because the use of micafungin is anticipated to increase because of its minimal toxicity and excellent activity against a broad spectrum of fungi, such as Aspergillus species and Candida species, the possibility of trichosporonosis should be considered in patients treated with micafungin with or without amphotericin B who develop signs and symptoms of septicaemia.

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