Successful Treatment of Systemic Geotrichum capitatum Infection by Liposomal Amphotericin-B, Itraconazole, and Voriconazole in a Japanese Man

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Abstract

Severe systemic Geotrichum capitatum (G. capitatum) infection is rare, especially in Japan. G. capitatum infection has been reported mainly in immunocompromised patients and the prognosis is poor with a mortality rate of approximately 50-75%. Here, we report a Japanese case of systemic G. capitatum infection in a severe neutropenic patient who was receiving chemotherapy for acute myelogeneous leukemia with multilineage dysplasia. G. capitatum was isolated from blood cultures, and also formed multiple nodular lesions in lung fields. The infection was successfully cured with a combination of amphotericin B, itraconazole, and voriconazole.

Key words: Geotrichum capitatum, acute myelogeneous leukemia (AML), amphotericin B, itraconazole, voriconazole


Introduction

Patients who receive intensive chemotherapy especially for hematological malignancies such as acute leukemia experience neutropenic periods that entail a high risk of fungal infections. Those fungal infections are usually caused by Candida and Aspergillus species, although many other molds and yeasts have emerged as causes of invasive infections and the prevalence of infectious fungi has been increasing in recent years.

Invasive systemic Geotrichum capitatum (G. capitatum) infection is rare, and has been reported exclusively in immunocompromised patients, particularly those receiving intensive chemotherapy for hematological malignancies such as acute leukemia (1-4). G. capitatum, formerly known as Trichosporon capitatum or Brastochizomyces capitatus, is an anamorph of Dipodascus capitatus, so that Dipodascus capitatus is a teleomorphic species of G. capitatum (5). Despite intensive antifungal therapy, the mortality rate is approximately 50-75% (1, 2). The emergence of G. capitatum has been noted predominantly in European countries, particularly in Mediterranean areas (1). Here, we report a Japanese case of systemic G. capitatum infection in a severely neutropenic patient with acute myelogeneous leukemia with multilineage dysplasias. He was cured of that infection with a combination of liposomal-amphotericin-B (L-AMPH-B), itraconazole (ITCZ) and voriconazole (VRCZ).

Case Report

A 64-year-old Japanese man who had consulted a physician because of liver dysfunction was referred to our department because of anemia and thrombocytopenia in September 2006. Bone marrow aspiration was performed, and he was given a diagnosis of myelodysplastic syndrome (MDS) (refractory anemia with excess blasts (RAEB) -2). He was admitted to our hospital because of leukemic evolution of MDS. The laboratory data on admission showed that his WBC was 13.17×10⁹/L, with a differential of 24% neutro-

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Figure 1. Computed tomography showed many nodular shadows of approximately 10 mm in size in the lung field.

Table 1. The Results of the Susceptibility Testing

<table>
<thead>
<tr>
<th>Antifungal agents</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPH-B</td>
<td>0.25</td>
</tr>
<tr>
<td>5-FC</td>
<td>0.12</td>
</tr>
<tr>
<td>FLCZ</td>
<td>8</td>
</tr>
<tr>
<td>ITCZ</td>
<td>0.01</td>
</tr>
<tr>
<td>MCZ</td>
<td>0.5</td>
</tr>
<tr>
<td>MCFG</td>
<td>1</td>
</tr>
<tr>
<td>VRCZ</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Minimum inhibitory concentrations (MIC) for AMPH-B, 5-FC, ITCZ, VRCZ were low, but the MICs for FLCZ, MCFG were high.

The abbreviations used are: AMPH-B, amphotericin B; 5-FC, 5-fluorouracil; FLCZ, fluconazole; ITCZ, itraconazole; MCZ, miconazole; MCFG, micafungin; and VRCZ, voriconazole.

phils, 10% lymphocytes, 3% monocytes, 0% eosinophils, 1% basophils, and 61% blasts. The hemoglobin concentration was 99 g/L with a mean corpuscular volume of 106.6 fL indicating mild macrocytosis. The platelet count was 48×10^9/L and revealed thrombocytopenia. Biochemical data included an elevated AST of 93 IU/L, ALT of 109 IU/L, γ-GTP of 147 IU/L (normal range: 4-67 IU/L), lactate dehydrogenase (LDH) of 402 IU/L (105-210 IU/L), CRP of 0.44 mg/dL (<0.3 mg/dL), and serum ferritin of 1,300 ng/mL. β-D-glucan was <0.5 pg/mL, within the normal range.

Bone marrow aspiration showed a marked increase of blasts, 51% of all nucleated cells. Blasts were slightly positive for peroxidase and had nucleoli. Many blasts had vacuoles in their cytoplasm. He was diagnosed as having acute myelogenous leukemia with multilineage dysplasia with prior MDS RAEB-2.

Induction therapy consisting of idarubicin (12 mg/m²/day on days 1-3) and cytarabine (100 mg/m²/day c.i.v. on days 1-5) was administered via central venous catheter. Antifungal prophylaxis was performed by administration of 200 mg/day of fluconazole (FLCZ) from the time of admission. Unfortunately, remission was not achieved by the first induction therapy.

A second induction therapy was then performed using mitoxantrone 7 mg/m²/day on days 1-3 and cytarabine 200 mg/m²/day c.i.v. on day 1-5 via the same central venous catheter. FLCZ had been administered for 41 days, but then it was changed to 150 mg/day of micafungin (MCFG) from day 2 of second induction therapy because β-D-glucan was slightly increased to 15.5 pg/mL. His WBC decreased to 0.1×10^9/L on day 16, and a fever exceeding 38°C developed during the neutropenic phase despite prophylaxis with MCFG. β-D-glucan increased to 78 pg/mL. Computed tomography (CT) showed many nodular shadows approximately 10 mm in size in both lungs (Fig. 1). No obvious abscess was detected in the liver or spleen by abdominal CT scan. The possibility of fungal infection was confirmed by blood culture taken on day 18 grown on potato dextrose and CHROM agar. White-pink and wrinkled colonies were observed on CHROM agar. Yeast-like fungi multiplying mainly by arthroconidia and partly by ameloconidia were observed, but blastoconidia was not observed. The fungi were then cultured on Sabouraud dextrose agar and identified using the commercially available fungus identification system ATB API ID 32 C (SYSMEX bioMérieux Co., Ltd., Tokyo, Japan). The sugar requirements led to the final diagnosis of *G. capitatum*.

Susceptibility testing using yeast-like fungi FP Eiken trays (Eiken Chemical Company, Ltd., Tokyo, Japan) showed low minimum inhibitory concentrations (MIC) for
amphotericin B (AMPH-B), 5 fluorouracil, ITCZ, and VRCZ, but the MIC for fluconazole and MCFG, both of which had been used for prophylaxis purpose, were high (Table 1).

Neutropenia was recovered on day 27, and MCFG was replaced by 215 mg/day of liposomal AMPH-B (L-AMPH-B) on day 28 because of the MIC information. (The period of MCFG administration was 27 days.) Although the central venous catheter could not be removed or substituted with a new catheter due to the risk of bleeding, his fever decreased in accompanied by a decrease in β-D-glucan. However, his fever rose after the second consolidation therapy was initiated; therefore ITCZ was added to the regimen on day 35. ITCZ appeared to be effective, but was accompanied by severe diarrhea so it was discontinued. The total period of ITCZ administration was 13 days. Fever declined again after stopping ITCZ administration, but mild renal dysfunction, indicated by a serum creatinine of 1.6 mg/dL, developed. L-AMPH-B was therefore discontinued, and 2.5 mg/kg of intravenous VRCZ was substituted. The total period of administration of L-AMPH-B was 50 days. Nodular shadows in lung fields disappeared by CT, and G. capitatum was no longer detected in blood culture after this change in therapy.

After remission was achieved several courses of chemotherapy should have been administered because his disease activity had not been controlled well and he often experienced high fever, therefore, oral administration of VRCZ was continued and no evidence of recurrence of G. capitatum infection was observed until he succumbed to leukemia about one year later.

Discussion

G. capitatum infection is an uncommon fungal infection, especially in Japan. This filamentous fungus is found in soil, and frequently isolated from human skin, respiratory and digestive tracts (1). Colonization in those sites sometimes leads to secondary localizations via hematogenous dissemination mainly in the lung and liver (4, 6). Invasive G. capitatum infection is relatively rare, approximately 100 cases having been reported (1, 3, 4, 7, 8). Risk factors for systemic G. capitatum infection have been reported to be prolonged neutropenia, intensive chemotherapy, the use of broad-spectrum antibacterial agents and local disruption of skin and mucosal defenses (2, 9-11). Therefore, systemic G. capitatum infection is prone to occur in neutropenic patients with hematological malignancies such as acute leukemia, because patients receiving intensive chemotherapy, experience severe long neutropenic periods, and are often placed on a central venous catheter. Patients with conditions other than hematological malignancies are also susceptible to systemic infection by G. capitatum; an outbreak in an intensive care unit has been reported (3).
The diagnosis may usually be made by blood culture (4, 7). G. capitatum was detected by blood culture in the present case, however the lung also seemed to be involved even though there was not any pathological or mycological evidence; therefore, the route of the infection of G. capitatum was not clear. G. capitatum might have been in the lung as colonization and it increased in the neutropenic period during chemotherapy, and then went into the blood stream and systemic infection was completed. However, it was also likely that systemic infection of G. capitatum caused secondary disseminations in lung fields, because there were multiple small lesions in bilateral lobes of lung determined by CT. The multiple nodular shadows revealed by chest CT in the present case might be similar to those of previous reports, but there has been no clear explanation for the mechanism of formation of multiple lesions in the lung (2, 4). Another possibility was that G. capitatum might have invaded from skin via the central venous catheter, and then increased in the blood stream, and finally lung lesions appeared as dissemination. There is also a possibility that G. capitatum invaded as a translocation from the gastrointestinal tract, but it was difficult to confirm because there seemed to be no obvious abscess in the liver or spleen.

The prognosis of disseminated G. capitatum infection has been reported to be extremely poor, with a mortality rate of approximately 50-75% despite intensive antifungal therapy with AMPH-B, ITCZ or flucytosine (1-4, 6). Combination treatment with AMPH-B and 5-fluorocytosine has been recommended (2), as has the use of novel antifungal agents such as VRCZ and caspofungin (8). Although the patients treated with each of those new antifungal agents died (8), combination therapy with VRCZ and caspofungin may be effective for systemic G. capitatum infection (12, 13). In the present case, L-AMPH-B suppressed the infectious activity of G. capitatum. VRCZ also seemed to be effective in this case because chemotherapy had been continued without L-AMPH-B. The recovery from neutropenia may also have contributed to overcoming the infection, therefore using granulocyte colony stimulating factor (G-CSF) should be considered if the status of the infected patients permits.

In vitro susceptibility data on G. capitatum has been limited (14-16). In a previous report AMPH-B and VRCZ showed the lowest MICs of various antifungal agents against 23 G. capitatum isolates in vitro (14). Susceptibility to MCFG, which was used for the purpose of prophylaxis in this patient at the occurrence of systemic G. capitatum infection, was low, in keeping with an another report (17), so that the continuous use of MCFG as prophylaxis should only be performed under careful observation of clinical symptoms, especially in Japan where MCFG has been widely used. Our in vitro susceptibility data showed that MICs for AMPH-B and VRCZ were relatively low. Therefore, the clinical effectiveness appeared to be compatible with in vitro data in the present case. However, the correlation between in vitro and in vivo susceptibility requires further study.

We herein report a case of systemic infection by G. capitatum, a predominantly European pathogen, observed during chemotherapy for acute leukemia in Japan. In Japan, only a few other cases have been previously reported (17, 18), and the reason for the low occurrence of G. capitatum in Japan has not been known. However, the possibility that new or rare fungal pathogens might increase in prevalence like G. capitatum in the present case should be kept mind, because in recent years many novel agents for bacterial and fungal infections have become available and those agents might contribute to the control of many infections in Japan.

References


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