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Two Cases of Disseminated Mucormycosis in Patients following Allogeneic Bone Marrow Transplantation

We describe two cases of disseminated mucormycosis following allogeneic bone marrow transplantation (BMT). Both patients were suffering from chronic graft-versus-host disease (GVHD) and treated with prolonged administration of corticosteroid. In both cases, the initial symptoms were high fever and left flank pain. Involved organs were the spleen, right kidney and the right lung in one case, and the spleen and the brain in the other. The diagnosis was confirmed by pathology after splenectomy. One patient, in whom the immunosuppressesants could be discontinued, was treated with prolonged conventional and liposomal amphotericin B and 5-fluorocytosine. The other, in whom the immunosuppressants could not be discontinued due to extensive GVHD, was unresponsive to amphotericin B, and eventually died from the fungal infection. Although mucormycosis, especially the disseminated form thereof is infrequent, it should be considered in high-risk patients because early diagnosis and timely therapy combining antifungal drug or surgery and reduction of immunosuppression appear to improve the prognosis.

Key Words : *Mucormycosis; Immunocompromised Host; Bone Marrow Transplantation; Amphotericin B*

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INTRODUCTION

Invasive fungal infections play a key role in contributing to morbidity and mortality in hospitalized patients, especially those who are profoundly immunocompromised such as patients on bone marrow transplantation (BMT). Although a variety of yeasts and molds can cause invasive fungal infections, Candida and Aspergillus species account for the majority of the infections. Recently, other less common fungal isolates, such as Zygomycetes, are recognized as opportunistic pathogens with a increasing frequency (1, 2).

Mucormycosis is an opportunistic infection caused by fungi of the order Mucorals, class Zygomycetes. Fungal spores are dispersed into the air from decaying material, and the portal of entry for human infections is via the inhalation route. Zygomycetes has a tendency for vascular invasion and tissue necrosis, with resultant hemorrhage and necrotic lesions. The major clinical diseases can be divided into five forms according to the site of involvement: rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated mucormycosis. Disseminated mucormycosis is an extremely rare condition with high mortality rate and generally occurs in severely immunocompromised patients (3-5).

Several cases of mucormycosis were reported in Korea, including disseminated form after chemotherapy in a patient with acute lymphocytic leukemia (6). Now, we first report two cases of disseminated mucormycosis following BMT in Korea. One was successfully treated with combination of surgery, conventional and liposomal amphotericin B with discontinuing immunosuppressants and the other died despite surgery and amphotericin B. In the latter patient, immunosuppressants could not be discontinued due to extensive graft-versus-host disease (GVHD).

CASE REPORTS

CASE 1

A 35-yr-old man was admitted through emergency room due to sudden development of high fever and left flank pain. Thirteen months before he had been diagnosed as acute myelogenous leukemia (M5), and had received allogeneic BMT five months after the diagnosis. He was suffering from steroid-induced diabetes and was on combined immunosuppressive therapy with prednisolone (40 mg/day) and cyclosporine (300 mg/day) for extensive chronic GVHD.

On physical examination, there was tenderness on the left costovertebral angle with hepatosplenomegaly. At this time the leukocyte count (and neutrophil count) was within normal range. Urinalysis revealed pyuria. A chest radiograph showed focal pneumonic infiltration in the right lower lung field. Empirical antibiotics with cefoperazone/sulbactam, amikacin was started. Blood, sputum, and urine cultures were repeatedly negative for fungi and bacteria. Chest and

abdomen computed tomography (CT) scan showed pseudoaneurysm in the spleen (Fig. 1), abscess in the right kidney, and pneumonic infiltration in right middle lobe of the lung. On day 6, splenectomy was performed and showed characteristically broad, irregular, and non-septate hyphae. Cyclosporine therapy was discontinued in an attempt to restore host defenses. Prednisolone was also tapered to physiologic dosage without aggravation of chronic GVHD. Amphotericin B with 5-fluorocytosine (75 mg/kg/day) was started to a dose of 1 mg/kg/day and was later replaced by liposomal amphotericin B (4 mg/kg/day) because of deterioration of renal function. Total accumulated dosage of amphotericin B was 6.69 g (conventional amphotericin B, 0.79 g, liposomal amphotericin B, 5.9 g in 45 days).

He was successfully treated with combination of splenectomy, prolonged use of conventional and liposomal amphotericin B and 5-fluorocytosine, and discontinuing of cyclosporine and prednisolone. During the 1-yr period of follow-up after antifungal therapy, he was in good health without relapse of the infection.

CASE 2

A 39-yr-old man was admitted due to development of fever and left flank pain. Eight months before he had been diagnosed as chronic phase of chronic myelogenous leukemia and had received allogeneic BMT three months after the diagnosis. The post-BMT course was complicated by steroid-induced diabetes, veno-occlusive disease, drug-induced hepatotoxicity, and cytomegalovirus infection. Two weeks before this event, the patient was readmitted due to extensive chronic GVHD involving the liver and gut, which was successfully treated with tacrolimus and prednisolone.

On physical examination, hepatosplenomegaly was detected. Laboratory investigation showed liver failure with coagulation abnormality but leukocyte count was within normal range. Chest radiographs were normal. Cefoperazone/sulbactam, amikacin, and teicoplanin were started. Cultures of blood, sputum, and urine were all repeatedly negative. Abdomen CT scan showed splenic abscess with peritoneal leakage. On day 10, splenectomy was performed and histologic examination revealed broad, irregular, and non-septate hyphae. Splenic arterioles were thrombosed and contained the same hyphae (Fig. 2). Amphotericin B was started to a dose of 1 mg/kg/day and was later replaced by liposomal amphotericin B (4 mg/kg/day). Because chronic GVHD were aggravated during the course of tapering tacrolimus and prednisolone, immunosuppressants could not be tapered.

The patient's condition progressively deteriorated with lethargy, confusion, stiff neck, and subsequent coma (day 20). Cerebrospinal fluid did not show any leukocytes, and cultures for bacteria, fungus, and virus were all negative. The brain magnetic resonance scan revealed a lesion in the right occipito-parietal cerebral hemisphere (Fig. 3). The patient died on day 23 and the death was related with disseminated mucormycosis. He had received amphotericin B until his

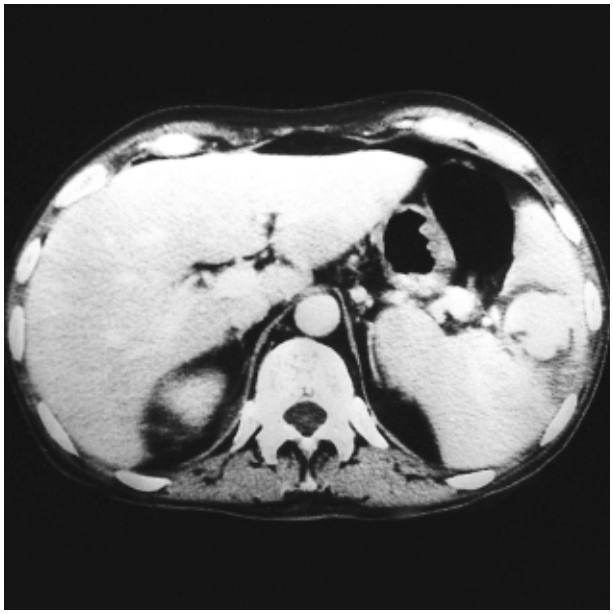

Fig. 1. Abdominal CT reveals splenomegaly, and a well defined highly enhanced lesion with non-enhanced peripheral portion about 4×3 cm in diameter in the perihilum of the spleen, which is most likely the intrasplenic pseudoaneurysm with peripheral thrombi formation.

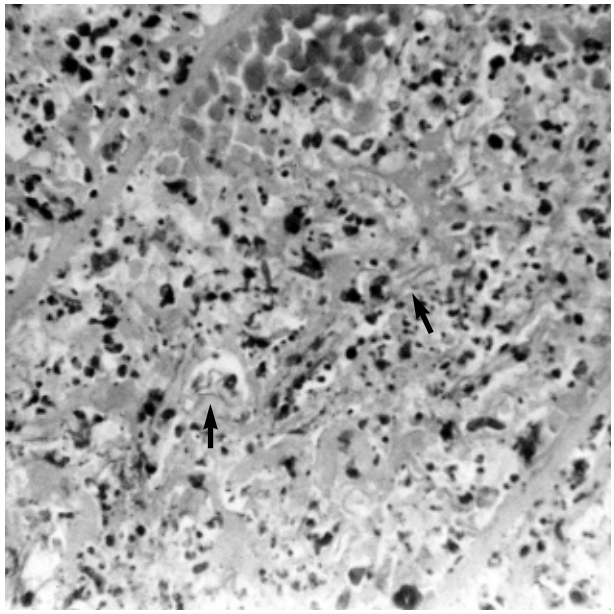

Fig. 2. Intramural thrombi and broad, non-septate, irregular hyphae invading blood vessels in splenic tissue (hematoxylin-eosin staining, ×400, arrows).

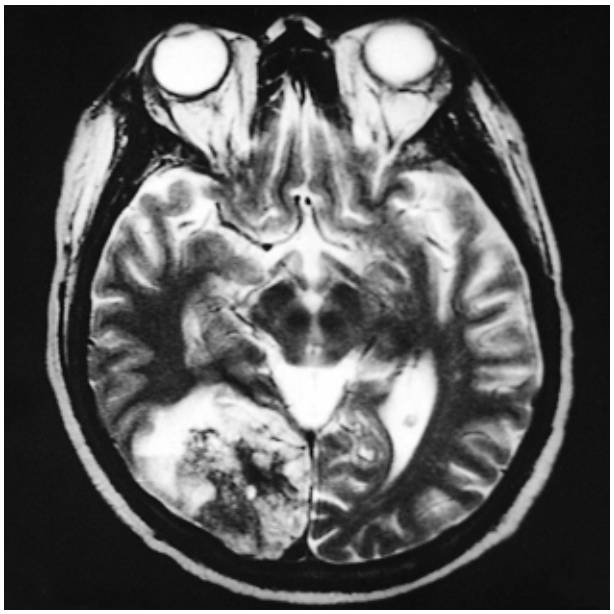

Fig. 3. Magnetic resonance scan of the brain. This T2-weighted scan shows an extensive right occipital lobe abscess with much surrounding edema.

death (total dose, conventional amphotericin B 0.15 g, liposomal amphotericin B 1.95 g in 13 days)

DISCUSSION

Mucormycosis is an uncommon filamentous mycosis which most frequently occurs in immunocompromised patients. Although the epidemiological data on this fungal infection are at best scanty, it would appear that the incidence of this complication has increased in patients with hematological malignancies during the last decade probably due to the more severe and prolonged post-chemotherapeutic neutropenia caused by the use of more aggressive treatments (4). Morrison et al. reported on the detection of mucormycosis infection in 0.9% during the post-BMT period (2). Several risk factors for mucormycosis such as prolonged neutropenia, poorly controlled diabetes, prolonged use of steroids, and impaired immune system were usually present in the BMT recipients, in whom the infections are likely to progress more rapidly (7, 8). Both of our patients were not neutropenic when mucormycosis developed. But they all were diabetics, using immunosuppressants including corticosteroids, and their immune system, such as cell-mediated immune responses, was impaired due to chronic extensive GVHD.

The spectrum of mucormycosis seen in the BMT population may be different from that seen in patients with diabetes and leukemia. The classic rhinocerebral type of infection is not common in the BMT population (2, 7). In either of our patients, sinonasal region was not involved, suggesting that it may not be the main port of entry. In disseminated forms, mucor enters through the respiratory tract and invades the lung and arrives at other sites by embolic dissemination (1). The most common site of spread is known to be the brain, but metastatic necrotic lesions have also been found in the spleen, heart, and other organs. Disseminated mucormycosis is usually diagnosed after the death of the patient from the infection. Occasionally metastatic cutaneous lesions permit an earlier diagnosis (3, 5). In our cases, the infection was first detected in the spleen and cutaneous lesions were not present. It would be reasonable to assume that other lesions also due to mucormycosis. But the concept should be reminded that more than one microorganism can simultaneously infect such immunocompromised patients like ours (9, 10). Although we did not perform repeated biopsies and cultures in other sites, if there were clinical clues that suggest two or more different infectious processes (development of new lesions while receiving therapy, progression of disease, or abnormal presentation of fungal infections, etc), it would be essential to obtain specimens repeatedly from the affected sites.

The hallmarks of mucormycosis are vascular invasion and tissue necrosis. Typically, the fungi appear as broad (10 to 20 μm in diameter), non-septate hyphae with branches occurring at right angles. We found the typical fungi in the splenic arterioles with intramural thrombi.

Oral antifungal prophylaxes are known to be unable to prevent mucormycosis (1, 2). Zygomycetes are resistant to triazole and nystatin, and whether the use of intranasal, aerosolized, or parenteral amphotericin B can play a role in preventing mucormycosis is still uncertain. Both patients in this report had received prophylactic fluconazole during the neutropenic period during the BMT and following 3 and 4 months, respectively.

Therapy of mucormycosis consists of rapid correction of the predisposing factors, surgical debridement of necrotic tissue whenever feasible, antifungal therapy, and adjunctive therapy such as hyperbaric oxygen, granulocyte colony stimulating factor, and granulocyte transfusion (3, 11, 12). Both of our patients underwent splenectomy and received conventional and liposomal amphotericin B.

The differences between the two lie in the possibility of discontinuation of immunosuppressants, days after the BMT, the duration of antifungal therapy, total dosage of amphotericin B, and the difference of potency of immunosuppressant between cyclosporine and tacrolimus (Table 1).

In hematologic patients the most important good prognositc factor is the outcome of the hematologic disease (4). The importance of reversing underlying factors is evident in the experience with mucormycosis. In the former of this two cases, discontinuation of immunosuppressants, lower potency of immunosuppressants used, and longer days after BMT, all of which may mean the more possible immune restoration, were the reason for good prognosis. The prolonged use of amphotericin B is known to be correlated with a good

Table 1. Characteristics of the patients with disseminated mucormycosis after bone marrow transplantation

	Case 1	Case 2
Sites of infection	lung, spleen, kidney	spleen, brain
Days after BMT*	+259	+142
WBC ($\times 10^9$/L)*	6.4	9.4
Steroid-induced Diabetes	Yes	Yes
Chronic GVHD grade	Extensive (skin, liver, oral mucosa)	Extensive (skin, liver, gut)
Immunosuppressants used* (mg/day)		
Cyclospirine	300	–
Tacrolimus	–	4
Prednisoline	40	30
Antifungal therapy (total dose in grams)		
Ampho B	0.79	0.15
Lip Ampho	5.9	1.95
5-FC	112.5	
Duration of antifungal therapy (days)	43	13
Outcome	Survived at the time of follow-up 1 yr later	Death related to Infection

BMT: bone marrow transplantation; GVHD: graft-versus-host disease; Ampho B: amphotericin B; Lip Ampho: liposomal amphotericin B, 5-FC: 5-fluorocytosine.
*At the time of infection.

prognosis (4, 7). However, one should not lose a sight of the fact that the correlation between the high total dosage, long duration of use of amphotericin B and the cure of patients could be simply due to the longer survival of these patients. In these reports, favorable prognosis might be actually due to the longer survival of patient rather than having received the high total dosage of amphotericin B with longer duration.

The use of lipid formulations of amphotericin B has recently been implicated for the treatment of systemic fungal infections to reduce the toxicity of conventional amphotericin B. In a few cases, liposomal amphotericin B has been reported to be efficacious for the treatment of mucormycosis. However, further studies are needed to assess whether these compounds are truly efficacious for the treatment of this systemic fungal infection (3, 11).

In conclusion, careful clinical and radiologic examinations are the key to early diagnosis of mucormycosis, especially in the disseminated form, in immunocompromised patients. Early histologic confirmation certainly lead to early and proper treatment i.e., antifungal therapy and surgical approach. Successful outcome is attributed to early diagnosis in conjunction with not only surgery or antifungal therapy, but correction of risk factors such as discontinuation or tapering of immunosuppressants.

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