CASE REPORT

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Breakthrough disseminated zygomycosis induced massive gastrointestinal bleeding in a patient with acute myeloid leukemia receiving micafungin

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Abstract A 69-year-old man, who had been receiving prednisolone for 11 months for treatment of interstitial pneumonia, was diagnosed with acute myeloid leukemia. During induction therapy, he developed severe pneumonia. Although meropenem and micafungin were started, he died of circulatory failure owing to massive gastrointestinal bleeding. Autopsy specimens obtained from the stomach revealed fungal hyphae, which had invaded diffusely into submucosal vessels and caused the massive gastric bleeding. The same hyphae were also observed in both lungs. A diagnosis of disseminated zygomycosis was confirmed by its characteristic histopathological findings. Because zygomycetes are spontaneously resistant to the newer antifungal agents, such as voriconazole or micafungin, it seems likely that the prevalence of zygomycosis as a breakthrough infection may increase in the future. Zygomycosis is a rare, but life-threatening, deep fungal infection that appears in immunologically or metabolically compromised hosts.1 Because its clinical manifestation is similar to that of invasive aspergillosis, cultures are often negative and no reliable serologic tests are currently available; therefore, antemortem diagnosis is usually difficult. In addition, because zygomycetes are spontaneously resistant to most antifungal agents, except for amphotericin B, it seems likely that zygomycosis might occur as a breakthrough infection associated with the use of newer antifungal agents, such as voriconazole or micafungin. In fact, in the voriconazole era, the incidence of zygomycosis in patients with hematological malignancies has been reported to be increasing.2,3 Here, we report a case of breakthrough disseminated zygomycosis, which resulted in massive gastrointestinal bleeding, in a patient receiving micafungin.

Introduction

Zygomycosis is a rare, but life-threatening, deep fungal infection that appears in immunologically or metabolically compromised hosts.1 Because its clinical manifestation is similar to that of invasive aspergillosis, cultures are often negative and no reliable serologic tests are currently available; therefore, antemortem diagnosis is usually difficult. In addition, because zygomycetes are spontaneously resistant to most antifungal agents, except for amphotericin B, it seems likely that zygomycosis might occur as a breakthrough infection associated with the use of newer antifungal agents, such as voriconazole or micafungin. In fact, in the voriconazole era, the incidence of zygomycosis in patients with hematological malignancies has been reported to be increasing.2,3 Here, we report a case of breakthrough disseminated zygomycosis, which resulted in massive gastrointestinal bleeding, in a patient receiving micafungin.

Case report

A 69-year-old man, with known interstitial pneumonia, was admitted to our hospital with thrombocytopenia and an abnormal leukocyte count and was diagnosed with acute myeloid leukemia (M4 according to the French-American-British [FAB] classification). He had been receiving prednisolone 20–40 mg per day for 11 months to treat persistent respiratory symptoms resulting from the interstitial pneumonia. He also had steroid-induced diabetes mellitus, with a hemoglobin (Hb) A1c level of 7.4%. Induction chemotherapy with idarubicin and cytosine arabinoside for acute leukemia was initiated. On the fifth day after the initiation
of the chemotherapy, he developed sudden dyspnea and had a temperature of 38.9°C. His absolute neutrophil count (ANC) had decreased to 80 μl⁻¹. Physical assessment revealed no infectious focus, and no evidence of infection was found on chest X-rays or on computed tomography (CT) scans. Two sets of blood cultures were negative and no clinically significant organisms grew from sputum cultures. Tests for circulating galactomannan antigen assay and serum 1,3-β-D-glucan were also negative. However, considering his neutropenic state, the induction chemotherapy was discontinued and empirical treatment with meropenem 2 g per day and micafungin 150 mg per day was started for the treatment of febrile neutropenia. Considering the possibility of a detrimental effect on the underlying interstitial pneumonia related to his febrile condition, intermittent methylprednisolone, 125 mg per day, was initiated to relieve his respiratory condition. Intravenous insulin therapy was also started for his hyperglycemia.

On the eleventh day, he had symptoms of severe chest pain and developed respiratory failure. A chest X-ray and CT scan revealed pneumonia in the upper-left pulmonary lobe. These findings were consistent with invasive pulmonary aspergillosis. He was intubated and granulocyte colony-stimulating factor (G-CSF), 300 μg per day, was started. His respiratory condition was stabilized by mechanical ventilation. Because a sputum survey taken from the tracheal tube revealed abundant methicillin-resistant Staphylococcus aureus (MRSA) with phagocytosis, arbekacin, an aminoglycoside antibiotic with anti-MRSA activity, was added, at 200 mg per day. On the seventeenth day, because his ANC exceeded 2000 μl⁻¹, G-CSF was discontinued; however, his general condition showed no significant change. On the seventeenth day, he suddenly developed circulatory failure with massive tarry stool and his hemoglobin level decreased, from 9.1 g/dl to 5.4 g/dl. However, his clinical condition did not allow for invasive medical intervention, except for blood transfusions, and he died on the eighteenth day (Fig. 1).

Autopsy findings showed expansion of the stomach with a massive hematoma collection, with mucosal erosion. Microscopic findings revealed many fungi with broad, rarely septate hyphae of uneven diameter, branching at 90° angles and invading tissues with an angiocentric tendency, causing...

**Fig. 1.** Clinical course. AMK, Amikacin; ABK, arbekacin; MEPM, meropenem; MCFG, micafungin; G-CSF, granulocyte colony-stimulating factor; mPSL, methylprednisolone; DNR, daunomycin; Ara C, cytarabine; RCC, red cell concentrates, WBC, white blood cell count, Neut, neutrophil count; HGB, hemoglobin; Alb, albumin; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein, sBP, systolic blood pressure; SpO₂, pulse oximeter saturation; FiO₂, inspired oxygen fractional concentration.

### Laboratory Values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Admission</th>
<th>Day 1</th>
<th>Day 5</th>
<th>Day 11</th>
<th>Day 17</th>
<th>Day 18</th>
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<tr>
<td>SpO₂ (%)</td>
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<td>97</td>
<td>96</td>
<td>87</td>
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<td>O₂ delivery (/min)</td>
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<td>WBC (μL)</td>
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<td>45600</td>
<td>45600</td>
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<td>Neut (μL)</td>
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<td>48600</td>
<td>45600</td>
<td>45600</td>
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<td>HGB (g/dl)</td>
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<td>Alb (mg/dL)</td>
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<td>Cr (mg/dL)</td>
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<td>CRP (mg/dL)</td>
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<td>1,3-β-D-glucan (pg/ml)</td>
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<td>(-)</td>
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<td>Pneumonia shadow</td>
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<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
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