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Hepatic and Small Bowel Mucormycosis after Chemotherapy in a Patient with Acute Lymphocytic Leukemia

Mucormycosis is a rare but invasive opportunistic fungal infection with increased frequency during chemotherapy-induced neutropenia. The clinical infections due to *Mucor* include rhinocerebral, pulmonary, cutaneous, gastrointestinal and disseminated diseases. The first two are the most common diseases and all entities are associated with a high mortality rate. Still hepatic involvement of *Mucor* is rarely reported. We experienced a case of hepatic and small bowel mucormycosis in a 56-year-old woman after induction chemotherapy for B-cell acute lymphocytic leukemia. Initial symptoms were a high fever unresponsive to broad spectrum antibiotics and pain in the left lower abdominal quadrant. It was followed by septic shock, deterioration of icterus and progressively elevated transaminase. An abdominal CT demonstrated multiple hypodense lesions with distinct margins in both lobes of liver and pericolic infiltration at small bowel and ascending colon. Diagnosis was confirmed by biopsy of the liver. The histopathology of the liver showed hyphae with the right-angle branching, typical of mucormycosis. The patient was managed with amphotericin B and operative correction of the perforated part of the small bowel was performed. However, the patient expired due to progressive hepatic failure despite corrective surgery and long-term amphotericin B therapy.

Key Words: *Mucormycosis; Liver; Intestine Small; Leukemia, Lymphocytic, Acute*

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INTRODUCTION

Mucormycosis is a fatal fungal infection caused by class Phycomycetes subdivided into the genera *Absidia*, *Rhizopus* and *Mucor* (1). The infection occurs most frequently in patients with hematologic malignancies (leukemia, lymphoma), transplanted patients receiving immunosuppressive therapy (5), ketoacidotic diabetes, malnutrition, renal or heart failure, and desferoxamine treatment for iron overload (2). Clinical entities of infection with *Mucor* include rhinocerebral, pulmonary, cutaneous, gastrointestinal and disseminated disease. The first two are the most common diseases and all entities associated with a high mortality rate (4). We report a disseminated mucormycosis case presenting hepatic involvement and multiple perforation of small bowel in a patient with B-cell ALL, who had neutropenia after chemotherapy, managed with long-term amphotericin B therapy and surgical debridement of perforated bowel.

CASE REPORT

A 48-year-old woman was found to have B cell acute lymphocytic leukemia (ALL) in November 1998. The patient received an induction chemotherapy for ALL of cytosine arabinoside (Ara-C), idarubicin, vincristine and prednisolone. Thereafter, she was referred with a neutropenic fever unresponsive to broad-spectrum antimicrobial therapy and diffuse abdominal pain, 17 days after chemotherapy. There was no history of frequent or unusual infections suggestive of immune deficiency. On physical examination, she was febrile (39℃) and in acute distress, with blood pressure of 110/70 mmHg, respiration of 20/min and pulse of 80/min. Initially, she was not icteric, and there was no lymphadenopathy or skin rash. The liver was palpable 1 cm below the right costal margin and spleen was not palpable. She had a localized left lower abdominal quadrant tenderness. The white blood cell count was 100/μL with 3% neutrophils, ALT 31 IU/L, AST 83 IU/L, total bilirubin 2.8 mg/dL, alkaline

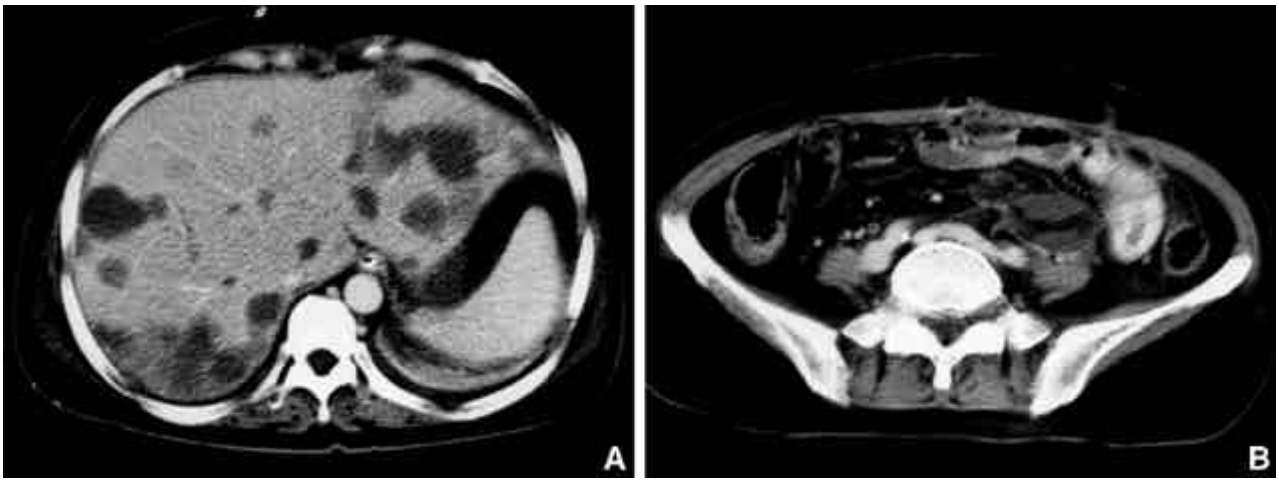

Fig. 1. Abdominal CT presents variable-sized, multiple, well circumscribed hypodense lesions (A) and also pericolic infiltration and wall thickening at ascending colon, mesentery and omenta (B). The masses in both hepatic lobes surrounding the vessels without a mass effect should suggest an angioinvasive organism. This lesion presents necrosis of liver tissue due to fungal thrombosis.

phosphatase 210 IU/L, and bicarbonate 20.8 mmol/L. A chest radiograph showed no specific abnormality. An abdominal ultrasonogram taken at another hospital demonstrated diffuse bowel wall thickening and increased mesenteric echogenicity. An abdominal CT in the emergency room showed precolic infiltration at ascending colon, mesentery and ometum, with concentric wall thickening of small bowel and ascending colon. Stool and urine cultures were negative. But three sets of blood cultures were positive for *Escherichia coli*. Susceptible therapy with ceftazidime and amikacin was initiated, targeting for colitis.

In December 1998 during 7 days of persistent fever, the patient was transferred to the intensive care unit because she developed septic shock with pulmonary edema, loss of consciousness and progressively aggravated liver function (total bilirubin 5.5 mg/dL, AST 200 IU/L, ALT 300 IU/L), despite sustained adequate antibiotic therapy. We changed vancomycin and imipenem. A CT scan which was done to rule out intra-abdominal infection (abscess) revealed variable-sized, multiple, well circumscribed low-attenuation in both hepatic lobes, similar to multiple liver abscess and small bowel (especially ileal loop) perforation (Fig. 1). As these findings suggested systemic fungal infection, amphotericin B (0.7 mg/kg) was started. At the same time sono-guided biopsy of liver was performed and some bloody material could be aspirated, in which a single, broad nonseptated hyphae with typical right angle was found on microscopic examination (Fig. 2). An emergency exploratory laparotomy was done, revealing a multiple perforation in the wall of the small bowel with necrosis from 70 cm of Treiz ligament to 60 cm of ileocecal valve. Complete resection of perforated small bowel and end-to-end anastomosis was carried out. Pathologically the bowel is necrotic and perforated at multiple sites. There were extensive fungal proliferation in the necrotic tissue and vascular space (Fig. 3).

During 3 weeks of treatment with amphotericin B (postoperative day 14), the patient's fever resolved and white blood cell count restored slowly without full recovery of cell count. But in the follow up CT scan, subtle regression of the lesions was observed and examination of a bone marrow biopsy specimen showed

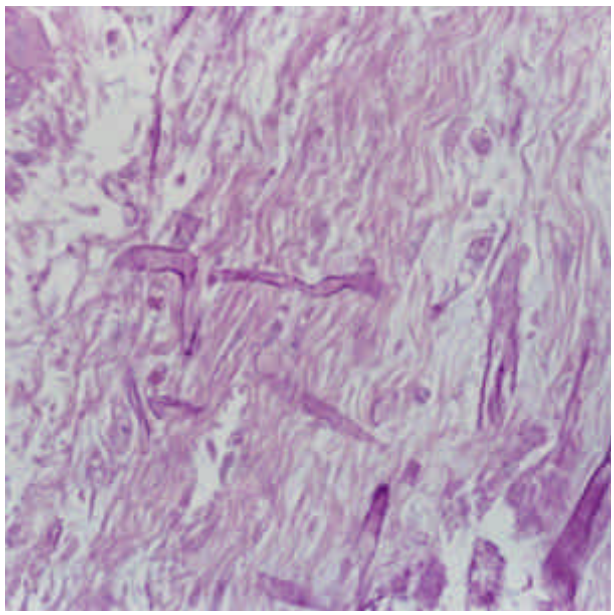

Fig. 2. The most characteristic features of the histopathology are the perivascular and blood vessel invasions resulting in arterial thrombosis and subsquent necrosis. Mucorales appear in tissue as irregularly shaped, broad hyphae with the right angle branching (H&E, ×400).

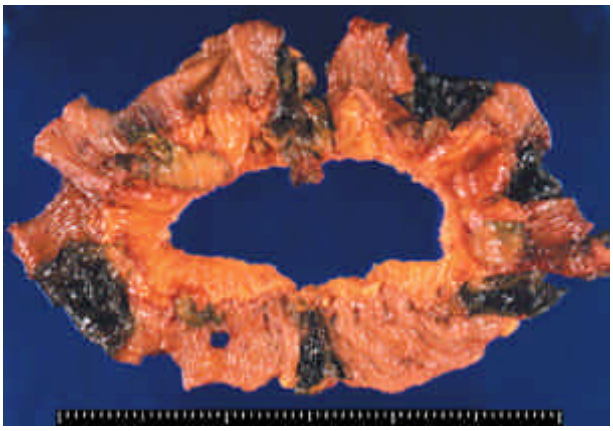

Fig. 3. In the perforated small intestine, the serosa shows six segmental necrotic areas which are greenish yellow and necrotic. There are extensive fungal proliferation in the necrotic tissue and vascular space.

complete remission 1 month after antifungal therapy. Although clinically she was tolerable, her illness was characterized by progressive hepatic failure with feature that clinically suggested viral hepatitis with jaundice (total bilirubin 10 mg/dL, AST 400 IU/L, ALT 500 IU/L). But viral markers of hepatitis were negative.

In January 1999, Amphotericin B liposomal complex (ABLC; 2 mg/kg/day) was initiated and broad spectrum antibiotics continued. Surgical resection of the hepatic lesion was not considered to be an alternative because of multiple extension. After 8 days of treatment with ABLC (total 1,200 mg), it was discontinued due to economical problems, and the patient was returned to conventional amphotericin B.

In postoperative day 20, fever recurred and purulent discharge with tenderness appeared on surgical wound site. Fistulogram confirmed a small size of gastrocutaneous fistula. As the general condition and laboratory finding of the patient was poor and severely deteriorated, the fistula was not able to be surgically operated. The culture of discharge from the wound grew *Citrobacter freundi* and vancomycin resistant enterococci (VRE). Ampicillin and imipenem were prescribed for the bacteria.

In April 1999, she received a total 8 g of amphotericin B during hospitalization period of three months. Follow-up CT scan showed no interval change compared with the previous examination. Despite amphotericin B therapy, the condition of the patient became worse and she finally died of progressive hepatic failure.

DISCUSSION

Disseminated mucormycosis is an uncommon filamentous mycosis which most frequently occurs in severely immunocompromised patients and associated with a very high mortality rate (3). Although mucormycosis occurs less commonly than candidiasis, aspergillosis in immunodeficient state, it is an increasing incidence, probably caused by more aggressive therapy of the underlying disease. It is also an important and potentially treatable infection (12, 13).

Hepatic involvement is usually presented with pulmonary or gastrointestinal infection and is considered a part of the disseminated disease (8, 11). Gastrointestinal mucormycosis is rare, even in patients with leukemia and lymphoma. Generally, intrinsic abnormalities of the gastrointestinal tract, such as amebic colitis, typhoid, pellagra and kwashiorkor (1) are predisposed to mucormycosis. In gastrointestinal involvement, the stomach is the most frequent site of involvement, with colon and small bowel following (1, 14, 15). Unlike rhinocerebral mucormycosis, the signs and symptoms are obscure in many cases by the underlying disease in gastrointestinal involvement. Especially cytosine arabinoside (Ara-C), which was frequently considered to be a treatment for acute leukemia, will damage gastrointestinal mucosal barrier and through this damaged mucosa, fungi easily invade blood vessel, grow intravascularly and cause thrombosis, infarction, bleeding and dissemination. Fungi metastasize to liver via portal system, and form abscess, particularly in chemotherapy-induced granulocytopenia (11, 12). Because the disseminated mucormycosis has variable clinical manifestations and requires examination of a tissue specimen for diagnosis, it has been infrequently diagnosed before death (8).

This case presents a typical multiple hypodense mass lesions in CT findings. The hypodense hepatic lesions surrounding vessels without a mass effect suggest an angioinvasive organism. This lesion presents necrosis of liver tissue due to fungal thrombosis. The CT finding are not pathognomonic but are valuable in narrowing the differential diagnosis. The differential diagnosis include infection with fungi of the genera *Aspergillus*, *Candida*, *Cryptococcus*, the order Mucorales, and the species *Pseudomonas aeruginoginosa* (10). Also magnetic resonance imaging (MRI) may reveal abnormalities in the involved structures. But due to a lack of comparative studies, the benefits of CT versus MRI are not known. MRI may be prefered for the diabetic patients in whom intravenous contrast agents may be contraindicated (4).

Culture and pathological examinations of biopsy specimen are the only definite diagnosis of mucormycosis. The most characteristic features are perivascular and blood vessel invasions that result in arterial thrombosis and subsquent necrosis. Mucorales appear in tissue as irregularly shaped, broad hyphae with the right angle branching (15).

Successful therapy involves repeated surgical debridement and adjunctive therapy with intravenous amphotericin B (1, 4, 9). Dosage of amphotericin B of 0.7-1.0 mg/kg/day should be used, although a dosage of 2 mg/kg/day may be required for treatment of patients who have aggressive and rapidly progressive infection (1). Also the efficacy of lipid formulations of amphotericin B against invasive opportunistic fungal infections appears to be similiar to that of conventional amphotericin B at equivalent doses (15). Gonzalez et al. reported successful treatment of disseminated mucormycosis in a neutropenic patient with amphotericin B lipid complex and granulocyte colony stimulating factor (9). Although we changed conventional amphotericin B to AmBisome with higher dosage with expectations of improving the hepatic lesions, the necrotic lesion in the liver did not lead to interval change. Our patient did not respond to a long-term amphotericin B therapy (total 8 g) after complete resection of perforated small bowel. The treatment failure was probably caused by several factors: First, the resection of long-perforated segment of small bowel led to the inadequate nutrition despite of intravenous supply. Second, large multiple hepatic necrotic lesions impaired liver function progressively. Third, long-term antibiotics therapy might promote combined bacterial or fungal infections (12). Lastly, a lack of full restoration of granulocyte slowed down therapeutic effects, which attributed to the recurrence of ALL.

The prognosis of the underlying disease is an important factor for the outcome of the infection due to mucormycosis. If patients who have mucormycosis receive carefully coordinated surgical and medical treatment, it should be possible to reduce the mortality rate of mucormycosis to >20% (14).

In conclusion, biopsy with histologic confirmation and culture may lead to earlier diagnosis and intravenous amphotericin B with surgery and with adequate supportive care may help in successful treatment (8).

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