

## Case Report

# Hypertension as the Presentation of Disseminated *Rhizopus* in an Infant with Acute Myeloid Leukaemia

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**Abstract** Rhizomycosis is an angiotropic and life-threatening infection in immunocompromised patients. We report an infant with acute myeloid leukaemia who suffered from an intra-abdominal mass with progressive hypertension due to left renal, superior mesenteric and splenic arterial occlusions associated with *Rhizopus* infection, which was diagnosed by multidetector-row computed tomography and tissue biopsy. She underwent intensive management including surgery and liposomal amphotericin-B administration, but she died of progressive leukaemia. To the best of our knowledge, simultaneous infarction of three obstructed arteries in an infant with *Rhizopus spp.* infection has not been reported in the literature. We conclude rhizomycosis is a life-threatening infection in a child with leukaemia who has neutropenic status, and *Rhizopus spp.* infection may be associated with multiple arterial infarctions. Hence, early diagnosis, aggressive surgery, and adequate treatment are suggested.

**Key words** Hypertension; Infarction; Leukaemia; Rhizopus

### Introduction

Mucormycosis is a rare opportunistic infection and an angio-invasive mycosis with high morbidity and mortality rates caused by *Mucorales*, an order of the Zygomycetes

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class of fungi.<sup>1</sup> The most common mucormycosis genera are *Rhizopus* and *Mucor*. Mucormycosis has emerged as an increasingly important fungal infection during the past decade in haematopoietic stem cell transplant recipients and patients with haematologic malignancies.<sup>2</sup> After primary infection in the respiratory tract, gastrointestinal tract or mucocutaneous infection, mucormycetes may cause disseminated, metastatic disease through mycotic emboli with invasion of blood vessel walls by the hyphae.<sup>3</sup> The angio-invasive disease causes vascular thrombosis, tissue infarction, and destruction with subsequent ischaemia, necrosis, and suppurative pyogenic reactions.<sup>4,5</sup> Herein, we report an infant with acute myeloid leukaemia who suffered from intestinal fungal infection and progressive hypertension due to multiple arterial occlusions in the abdomen with *Rhizopus* infection, which was diagnosed via tissue pathology, fungal culture and multidetector-row computed tomography.

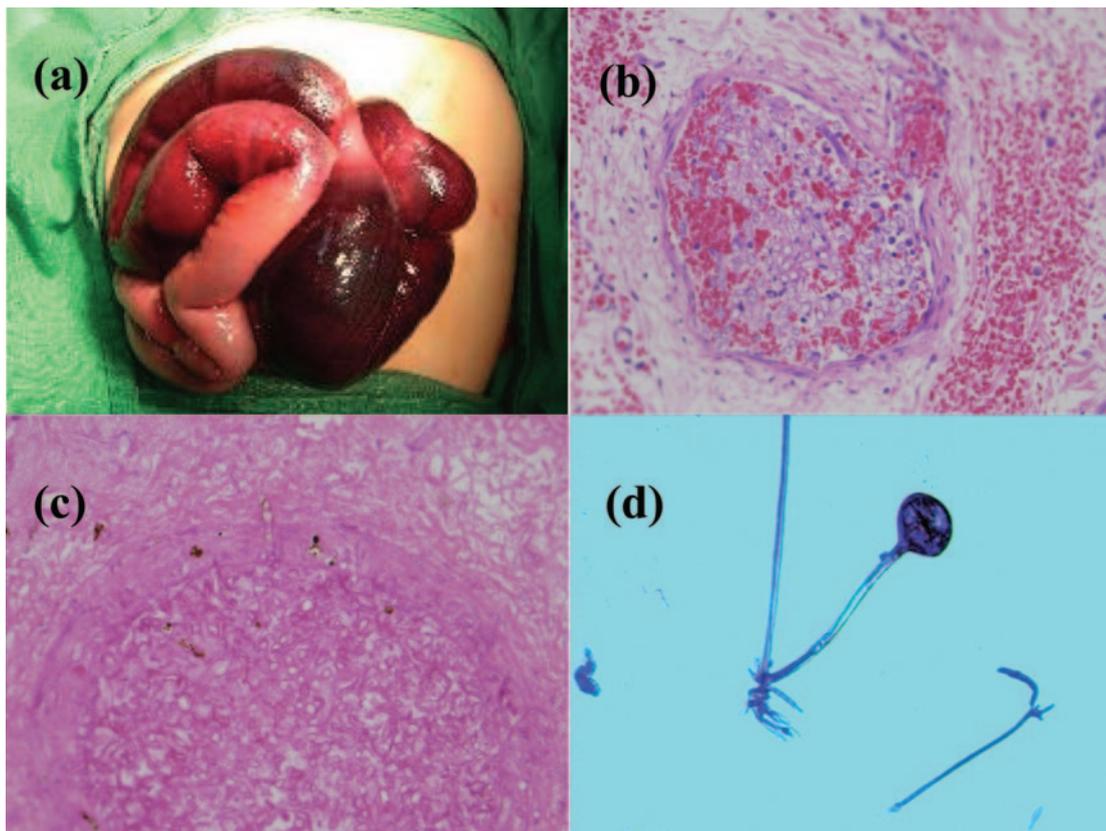
### Case Report

A 7-month-old girl had a history of full-term birth, with birth weight of 3880 gm, was in good health, and had met

fair development milestones. She became febrile (38.5°C) and some blood-tinged material in her diaper and gross haematuria were noted. Multiple petechiae over her trunk and face were also found. She was brought to Taichung Veterans General Hospital for examination. A complete blood count showed a haemoglobin level of 6.9 g/dL, a white blood cell count of  $197.7 \times 10^9$  cells/L, and a platelet count of  $10 \times 10^9$  cells/L. The peripheral blood smear revealed 49% of white blood cells were blasts. The surface markers study of bone marrow blasts showed CD33 was 94%, CD15 was 93% by flow cytometry, and acute myeloid leukaemia was diagnosed. Idarubicin (9 mg/m<sup>2</sup>/day for 3 days) and cytosar (100 mg/m<sup>2</sup>/day continuous intravenous drip for 7 days) under the Taiwan paediatric oncologic group acute myeloid leukaemia protocol were administered on 8 November 2012.

Her body temperature elevated to 38.7°C and her absolute neutrophil count was  $0.3 \times 10^9$  cells/L on 16 November 2012. Broad spectrum antibiotics including meropenem and vancomycin were given due to febrile neutropenia. She also

had received granulocyte colony-stimulating factor (5 mcg/kg/day) since the first day of febrile neutropenia as well as empiric antifungal agent oral fluconazole (5 mg/kg/day) and nystatin 3 days later. However, she suffered from progressive abdomen distension and vomiting during the following week. The abdominal X-ray revealed a distended abdominal wall and subcutaneous emphysema over the left lower quadrant area. Abdominal computed tomography showed massive ascites, crowding of the bowel loop over the central portion of the abdomen and dilatation of the bowel loop over the left middle abdomen. The liver, spleen, and kidneys revealed no significant abnormal finding. Intestinal obstruction with ascites was diagnosed and the girl underwent abdominal surgery on 26 November 2012. Gangrenous change of the proximal jejunum and ischaemia of the splenic flexure of the colon (Figure 1) were found during surgery. Thus, 20 cm of the jejunum and 5 cm of the colon were excised. The pathologic report of intestinal specimens showed extensive fungal infection and marked



**Figure 1** (a): Photograph showing the gangrene change of the proximal jejunum. (b, c): Histological tissue sections of the jejunum illustrating irregular-sized hyphae, where (b) (eosin/H&E stain) shows invasion of the blood vessel and haemorrhagic infarct. (c) (eosin/H&E stain) showing the blood vessels of resection margins invaded by fungal hyphae. (d): Lactophenol blue wet-mount microscopy illustrating the broad, ribbon-like hyphae with absence of transverse septa and root-like rhizoids typical of *Rhizopus* species.

haemorrhagic infarctions were noted in the jejunum and colon (Figure 1). Liposomal amphotericin-B (5 mg/kg/day) was administered. Four sets of bacterial and fungal cultures from blood samples were sterile. Her serum also tested negative for *Aspergillus* galactomannan. Two sets of fungal cultures from the intestinal tissue specimens were positive within 24 hours for a cotton-like, white-gray fungus without reverse pigment growing at 28° and 37°C. Growth was inhibited by cycloheximide. Microscopically, the isolate had broad aseptate hyphae, a white to gray-brown thallus formed from stolons with long unbranched sporangiophores, which were produced by root-like hyphae (rhizoids) (Figure 1). These characteristics were used to identify the fungus as *Rhizopus* spp, and thus the patient was diagnosed with intestinal rhizomycosis infection.

The girl's general condition was stabilised after the operation but progressive and persistent tachycardia (average heart rate of more than 180 beats/minute) and hypertension (average blood pressure above 187/110 mmHg) were found 8 days after surgery. Echocardiography and electrocardiogram were done and normal heart function was noted, except for sinus tachycardia. Renal artery obstruction was suspected, so abdominal multidetector-row computed tomography was performed to assess the abdominal vascular anatomy. The images showed total occlusion of the left renal artery, superior mesenteric artery, and splenic artery with infarctions of the left kidney and spleen (Figure 2). The renal functions were checked and showed normal results. The girl received antihypertension agent (intravenous Labetalol) treatment, but catheterisation and thrombolytic agents were withheld due to refractory thrombocytopenia. Chemotherapy was also withheld owing to the invasive fungal infection and unstable vital signs. Her hypertension and tachycardia were brought under control after one week. Unfortunately, progressive hyperleukocytosis with blasts was found by peripheral blood smear, and multiple progressive small nodules were noted over the girl's scalp, trunk, and limbs, which were diagnosed as leukaemia infiltration by mass biopsies. The girl died of refractory leukaemia and invasive fungal infection on 20 December 2012, despite liposomal amphotericin-B treatment for three weeks.

## Discussion

According to a systematic review and analysis of reported cases conducted by Zaoutis et al,<sup>1</sup> high-risk factors for developing mucormycosis include young age, infantile acute

myeloid leukaemia under chemotherapy, neutropenic status, and usage of broad spectrum antibiotics. All of these factors were found in the present case. Zygomycetes infection is characterised by tissue infarction and necrosis due to angio-invasive hyphae. Once established, the disease is rapidly progressive and is often fatal, as in the present case. The portals of entry of zygomycetes are usually the respiratory tract, the skin, and, less frequently, the gut when fungal spores are inoculated, inhaled, or ingested.<sup>6</sup> Gastro-intestinal mucormycosis is considered a rare manifestation. It is mainly described in premature neonates, where it presents as necrotising entero-colitis.<sup>3,7</sup> After primary infection, zygomycetes may cause disseminated, metastatic disease through mycotic emboli. Characteristically, invasion of blood vessel walls by the hyphae occurs and contributes to necrotic and ischaemic appearance of tissue.

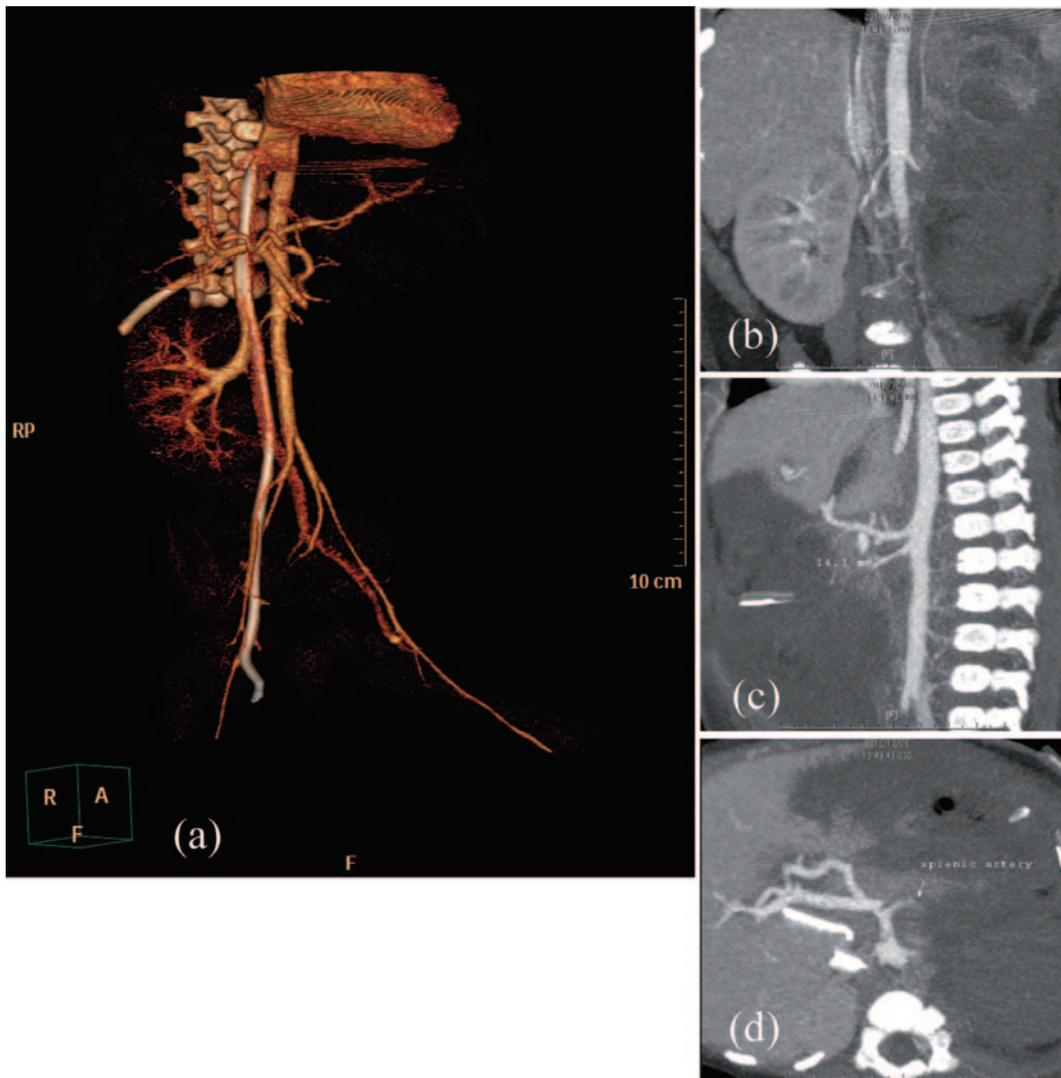
Clinical diagnosis of mucormycosis is difficult, and is often made at the last stage of the disease or post-mortem.<sup>5</sup> Unlike aspergillosis, there is no available biomarker such as galactomannan to aid in early diagnosis. Histologically, the diagnosis of mucormycosis is relatively easy in the case of rhino-orbital and mucocutaneous involvement. However, when deep tissues are invaded, samples are difficult to acquire, and therefore it may be particularly challenging to obtain the correct diagnosis. Even with vessel invasion, zygomycetes are not isolated easily from blood culture, as was shown in our patient. de Mol and Meis,<sup>8</sup> reported an adult who suffered from the left renal artery obstruction-induced kidney infarction caused by *Rhizopus*. To our knowledge, the present study is the first reported case of an infant with simultaneous obstruction of three arteries and *Rhizopus* spp. infection.

The treatment of mucormycosis requires a rapid diagnosis, correction of predisposing factors, surgical resection, debridement, and administration of appropriate antifungal agents.<sup>2</sup> Surgery appeared to improve the outcome, except in the case of gastrointestinal zygomycosis in children.<sup>1</sup> Survival increased to 70% for patients treated with a combination of surgery and antifungal therapy compared to 57% for those treated with surgery or medication alone.<sup>1,7</sup> Among patients treated with antifungal therapy, liposomal amphotericin B was the most commonly used for zygomycosis with less nephrotoxicity compared with amphotericin B deoxycholate. Other antifungal posaconazole or caspofungin can be used in combination with amphotericin B in case of treatment failure or as a substitute for serious side effects.<sup>9</sup> Posaconazole has largely been used as salvage therapy or in cases of intolerance to amphotericin B, with a success rate of 60%.<sup>2</sup>

Most azoles, including fluconazole and voriconazole, are ineffective against zygomycetes. Unfortunately, our patient initially received fluconazole and nystatin as empiric antifungal agents to treat her febrile neutropenia. The role of iron chelation (e.g., deferasirox) is controversial. It has been reported the iron chelator deferasiron protects mice against mucormycosis; however, a recent double-blinded, phase 2 study on deferasirox with liposomal amphotericin B treatment for mucormycosis failed to demonstrate a benefit of combination treatment.<sup>2</sup> According to a report by the Working Group on Zygomycosis of the European Confederation of Medical Mycology, the overall mortality rate of zygomycosis

was 47%.<sup>10</sup> In high-risk patients, including haematopoietic stem cell transplantation recipients, with mucormycosis, the disease-related mortality rate has been shown to be at least 75%.<sup>2</sup> Our patient received aggressive surgery with adequate dosage of an antifungal agent to treat rhizomycosis. Her hypertension and tachycardia were brought under control after treatment; however, she died from progressive leukaemia.

We conclude that rhizomycosis is a life-threatening infection in an infant with leukaemia who has neutropenic status and may be associated with multiple arterial infarctions; hence, early diagnosis, aggressive surgery, and adequate treatment are suggested.



**Figure 2** (a) Multidetector-row computed tomography of the abdomen revealed occlusions in the left renal artery (b), superior mesenteric artery (c), and splenic artery (d) with infarction of left kidney and spleen.

## Conflict of Interest

We declare that we have no conflict of interest.

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