Disseminated Pulmonary Mucormycosis Involving the Jejunum in an Acute Lymphoblastic Leukemia Patient

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Case report

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Abstract

**Background:** Pulmonary mucormycosis and aspergillosis with disseminated mucormycosis involving gastrointestinal is a very rare but lethal infection leading to extreme mortality.

**Case presentation:** A 51-year-old female was admitted in the hematology clinic following persistent fever. Bone marrow pathology was done on the third day and the common type of acute B-lymphocytic leukemia (B-ALL) with the IKZF1 mutation was diagnosed. IVCP program was prescribed as initial treatment. After five days, broad spectrum antibiotics and voriconazole were started due to febrile neutropenia. Forty-nine days after admission, based on characteristics of the clinical pulmonary symptoms, the feature of the computed tomography (CT) and the morphological profile of the hyphae, we switched the antifungal therapy to intravenous amphotericin B (AmB) with an initial dose of 0.5 mg/kg/d. On day sixty-two, according to the abdominal CT and clinical symptoms, intestinal perforation was diagnosed and emergency surgical management was performed. Histopathology of specimens from the jejunum and ileum showed broad septate fungal hyphae. L-AmB was added to 1.0 mg/kg/d for one week, followed by fever resolution. Considering the relief of symptoms and regression of lesions on imagery, our strategy switched to oral posaconazole 0.8 g/d. The patient was discharged in good condition for continuous therapy with antifungal agents and for follow-up at the outpatient clinic.

**Conclusions:** Direct microscopic testing with calcofluor white is the key to rapid diagnosis of mucormycosis, and early administration of active antifungal agents at optimal doses and complete resection of all infected tissues led to improved therapeutic outcomes.

Background

Mucormycosis is a life-threatening and opportunistic infection leading to high mortality in immunocompromised individuals [1–3]. This lethal infection usually occurs in patients with uncontrolled diabetes, neutropenia, hematologic malignancies (HM) or corticosteroid treatment [4]. The incidence of mucormycosis has been increasing in recent decades, mainly due to the growth of the number of patient groups presenting with these predisposing conditions and our medical advances in diagnosing the infection [1, 5, 6]. In patients with HM, the main clinical form is pulmonary mucormycosis (PM) [7–9], and the most representative risk factors associated with PM include neutropenia and corticosteroids [8]. The onset of pulmonary mucormycosis is acute, the progression is rapid [10], and the reported mortality ranges from 20–100% in adults, depending on the underlying risk factors, site of infection and treatment [11, 12]. Gastrointestinal mucormycosis (GIM) is the least frequent form, constituting only 4–7% of all cases [13]. Because of the nonspecific clinical hallmarks of GIM, the diagnosis is often delayed or missed, and mortality remains high at 57% [14]. However, in patients with prolonged neutropenia and in those with disseminated disease, mortality is 90–100% [4, 15].

Case Presentation
On July 18, 2019, a 51-year-old female presented to the hematology clinic complaining of an approximately one-month history of fatigue and reported a fever lasting for 24 hours. On admission, physical examination revealed a distended spleen. Other systemic examinations were unremarkable. At presentation, her body temperature was 37.4 °C, her blood pressure was 115/71 mmHg, and her pulse was 80 bpm. Her blood work showed an elevated white blood count of $33.17 \times 10^9$/L, hemoglobin 68 g/L, and platelets $44 \times 10^9$/L, and the percentage of primitive cells was 95% in peripheral blood.

The timeline of diagnosis and targeted therapy is shown in Table 1. Fever was relieved by anti-biotherapy introduction. The common type of acute B-lymphocytic leukemia (B-ALL) with the IKZF1 mutation was diagnosed by bone marrow pathology. Considering her history of familial diabetes and percutaneous coronary intervention (PCI), the chemotherapy program was initiated with a low dose of vindesine sulfate and dexamethasone and oral prophylactic treatment with fluconazole simultaneously. One month later, bone marrow pathology was repeated and showed 12% blast cells. A high-intensity IVCP program was performed. After 5 days, broad spectrum antibiotics and voriconazole were started due to febrile neutropenia.
| Time | Clinical features       | Biology results                  | Therapy strategies                                                                 |
|------|-------------------------|----------------------------------|-----------------------------------------------------------------------------------|
| D1   | Fever                   | High level of CRP                | Levofloxacin 0.6 g/d and cefoperazone/sulbactam 9 g/d IV                         |
| D3   | Bone marrow pathology   | B-ALL                            | Chemotherapy introduction (vindesine sulphate 4 mg per week and dexamethasone 10 mg/d IV); prophylactic therapy (fluconazole 0.1 g/d p.o.) |
| D33  | Repeated bone marrow pathology | Not completely relieved          | Chemotherapy switched to IVCP (idarubicin 10 mg/d1-3, vindesine sulphate 4 mg per week, CTX 1.2 g/d 1,15, and dexamethasone 10 mg/d IV) |
| D39  | Neutropenia             |                                  | Antifungal combined therapy (voriconazole 0.4 g/d p.o.)                           |
| D41  | Persistence of fever    | High level of CRP                | Levofloxacin 0.6 g/d and cefoperazone/sulbactam 9 g/d IV                         |
| D49  | Febrile neutropenia and cough | Rising of CRP rate; abnormal chest CT scan | Switched antibiotherapy therapy (meropenem 3 g/d and linezolid 1.2 g/d IV)         |
| D51  | Filamentous fungi detected in sputum |                    | Switched antifungal therapy (AmB 0.4 mg/kg/d IV)                                  |
| D57  | Fever resolution        |                                  |                                                                                   |
| D62  | Abdominal pain and fever | Blood pressure 85/33 mmHg; high level of CRP | Adjusted to tigecycline 0.1 g/d, combined L-AmB 0.5 mg/kg/d and voriconazole 0.4 g/d IV |
| D63  | Abnormal abdominal CT scan, acute peritonitis |                            | Emergency surgery                                                                 |
| D64  | Hypha detected in jejunum histopathology |                          | Adding L-AmB dose to 1.0 mg/kg/d IV                                             |
| D66  | Fever resolution        |                                  |                                                                                   |
| D83  | Repeated bone marrow pathology | Completely relieved              | Adding L-AmB dose to 1.2 mg/kg/d IV                                             |

D day, CRP C-reactive protein, IV intravenous, B-ALL acute B-lymphocytic leukemia, p.o. per os, CT computed tomographic, CTX cyclophosphamide, AmB amphotericin B, L-AmB liposomal amphotericin B
On day 49, significant pulmonary symptoms, such as productive cough, occurred, along with a persistent fever. Computed tomography (CT) showed a massive high-density shadow in the right superior lobe (Fig. 1) and rising levels of C-reactive protein (CRP). Blood culture was sterile, and serologies for (1,3)-beta-D-glucan, galactomannan (GM), syphilis, acquired immunodeficiency syndrome and hepatitis A–E were negative. Polymerase chain reaction for cytomegalovirus and EB virus were negative. Anti-biotherapy was switched to meropenem and linezolid, but there was no obvious relief in symptoms. Microbiological tests were implemented with low respiratory tract specimens. Classically, microscopic evaluation with Gram (Fig. 2a) and calcofluor white (Fig. 2b) staining revealed filamentous hyphae; one type was uniformly thinner, septate, and branching at acute angles, and the other had a variable width, was nonseptate, and had branching filamentous hyphae and a ribbon-like appearance. Cultures of specimens on Sabouraud dextrose agar (SDA) showed the features as *Mucorales*. Colonies appeared cotton and white-gray, both on the surface and reverse side (Fig. 2c). Lactophenol cotton blue staining revealed irregularly branching sporangiophores terminating prominently, and sporangioles borne off the vesicles (Fig. 2d). *Cunninghamella bertholletiae* was identified by mycological characteristics and ITS-based sequencing (accession no. MT470208). DNA sequences were analyzed using NCBI BLAST (https://blast.ncbi.nlm.nih.gov/Blast.cgi). Another pathogen isolated from specimens was *Aspergillus flavus*.

Based on the characteristics of the filamentous hyphae, we switched the antifungal therapy to intravenous amphotericin B (AmB) with an initial dose of 0.5 mg/kg/d. Persistent fever was resolved, but unexpectedly, acute abdominal pain with high fever and a “sudden drop” in blood pressure appeared on day 62. Anti-biotherapy was adjusted to tigecycline combined with liposomal amphotericin B (L-AmB). At midnight, the abdominal pain worsened, and acute diffuse peritonitis was considered. CT showed some free abdominal gas under the diaphragm, and peritoneal fluid was detected (Fig. 3). Emergency surgical management, including partial resection of the jejunum and ileum, was performed. There were 9 perforations in the jejunum 190 cm-210 cm from the curved ligament, with an aperture of approximately 1–2 cm, and a perforated ileum was detected approximately 25 cm from the ileocecal part.
Histopathology of specimens from the jejunum and ileum showed broad septate fungal hyphae (Fig. 4). Cultures of specimens from the jejunum also showed features such as *Mucorales*, and *Cunninghamella bertholletiae* was identified according to the same protocols mentioned above. Antifungal susceptibility tests according to Clinical and Laboratory Standards Institute (CLSI) M38-A2 [16] were implemented. The susceptibility profiles of *C. bertholletiae* showed fluconazole 256 µg/ml, itraconazole 0.5 µg/ml, posaconazole 0.5 µg/ml, voriconazole 8 µg/ml, AmB 2 µg/ml, flucytosine 64 µg/ml and echinocandins all 8 µg/ml. The susceptibility profiles of *A. flavus* showed itraconazole 1 µg/ml, posaconazole 0.5 µg/ml, voriconazole 0.25 µg/ml, and AmB 2 µg/ml.

L-AmB was added to 1.0 mg/kg/d for one week, followed by fever resolution. She was covered pre- and postsurgery with L-AmB for 8 weeks. Considering the relief of symptoms and regression of lesions on imagery, our strategy switched to oral posaconazole 0.8 g/d. The patient was discharged in good condition for continuous therapy with antifungal agents and for follow-up at the outpatient clinic.

**Discussion And Conclusions**

Mucormycosis and aspergillosis are opportunistic fungal infections that can lead to life-threatening complications and occur most commonly in individuals with neutropenia and prolonged immunosuppressive therapy [17]. An epidemiological article of 929 cases of mucormycosis found a correlation between the patient survival and the species within the *Mucorales*, given the conclusion of *Cunninghamella spp.* causing the highest percentage of crude mortalities and being an independent risk factor for death in the multivariate analysis [18]. As the most representative etiologic agent, *C. bertholletiae* occurs less frequently but causes refractory and fatal infections. A review of 15 cases of mucormycosis caused by *Cunninghamella spp.* indicated a patient population mainly consisting of neutropenia and transplantation [19]. Gastrointestinal mucormycosis (GIM) is the rarest type of *Mucorales* infections, constituting only 4–7% of all cases, with a mortality rate of 85–90% [14]. The successful management of the aggressive illness requires early surgical debridement, control of underlying disease and suitable antifungal therapy [20]. The jejunum is the least infected, and only a few cases of jejunal mucormycosis have been reported. A typical characteristic of pathophysiology of *Mucorales* infection is angioinvasion with thrombosis and thus necrosis of an affected part of the intestine. This will produce acute abdominal pain, possible bleeding or perforation [20, 21]. To the best of our knowledge, this is the first report of disseminated mucormycosis involving the jejunum in B-ALL patients caused by *C. bertholettiae* in China.

Early diagnosis of mucormycosis is the key to treatment and prognosis. And the definitive diagnosis of mucormycosis depends on a combination of histopathological findings and standard mycological methods, as well as DNA sequencing of the internal transcribed spacer (ITS) region, which has been suggested as a valuable target for identification at the genus and the species level by the CLSI guidelines [22]. Successful management of mucormycosis is on the basis of a multimodal manner, including reversal or revocation of underlying predisposing factors, early administration of suitable antifungal agents, thorough resection of all infected tissues [23, 24]. According to the guidelines of ECIL-6 and
ECMM-ESCMID, AmB and L-AmB are recommended as the first-line antifungal agent approved for the therapy of invasive mucormycosis [25]. High-dose L-AmB (10 mg/kg/day) immediately administered upon suspicion of mucormycosis greatly suppressed the infection in its early stage [26]. However, in the absence of surgical debridement for infected tissue, antifungal therapy alone is rarely curative [4].

Our aim in this report is to highlight the need for a high clinical suspicion for *Mucorales* infection in neutropenic, immunocompromised and diabetic patients. Direct microscopic testing with calcofluor white is the key to rapid diagnosis. In addition, effective multidisciplinary communication with consulting physicians, such as hematologists, pulmonologists and microbiologists, as well as immediate initiation of treatment, including surgical resection, can lead to improved patient outcomes in managing this rare but devastating disease and lay a solid foundation for the subsequent treatment of original disease.

**Abbreviations**

AmB: amphotericin B; BALF: Bronchoalveolar lavage fluid; B-ALL: B-acute lymphocytic leukemia; CLSI: Clinical and Laboratory Standards Institute; CRP: C-reactive protein; CT: Computed tomography; CTX: cyclophosphamide; D: day; ECMM-ESCMID: European confederation of medical mycology-The European Society for Clinical Microbiology and Infectious Diseases; ECIL-6: European conference on infections in leukaemia; GIM: Gastrointestinal mucormycosis; HM: hematologic malignancies; IKZF1: Ikaros family zinc finger 1; ITS: internal transcribed spacer; IV: intravenous; IVCP: intravenous cyclophosphamide; L-AmB: liposomal amphotericin B; PCI: percutaneous coronary intervention; PM: pulmonary mucormycosis; p.o.: per os; SDA: Sabouraud dextrose agar; WBC: White blood cell count.

**Declarations**

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**Authors’ contributions**

The first draft of the manuscript was produced by LW, LZ and ZH. All authors reviewed, edited, and approved the final versions of the submitted manuscript. LW, ZC, YY, QM and YW were major contributors in analyzed and interpreted the patients data. LW, ZC, LZ and ZH were major contributors in writing the manuscript. YF performed the histological examination of the jejunum. All authors read and approved the final manuscript.

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**Availability of data and materials**

All the data supporting our findings is contained within the manuscript.

**Ethics approval and consent to participate**

**Consent for publication**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

**Competing interests**

The authors declare that they have no conflict of interest.

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**Figures**
Figure 1

A close-up chest CT scan of the right lung shows a massive high-density shadow (arrow) in the superior lobe.

Figure 2

a Gram stain and b calcofluor white stain showed two different hyphae: one is uniformly thinner, septate, and branching at acute angles. The other is a variable width with ribbon-like appearance (20× magnification). c Macroscopic and d microscopic appearances of C. bertholettiiae.
Figure 3

The thinner arrow shows free abdominal gas under the diaphragm, and the wider arrow shows peritoneal fluid.
Figure 4

Photomicrographs from the jejunum showed acute necrotizing angioinvasion with abundant broad, nonseptate fungal hyphae (arrow) consistent with mucormycosis (a, hematoxylin and eosin stain; b, calcofluor white stain; 20× magnification).