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Case Report

Fatal gastrointestinal mucormycosis in an immunocompetent patient: a case report and review of the literature

Juan Hu[1], Xinxin Zhou[2], Chengfu Xu[2], Lixiong Ying[3], Xia Zheng[1]

[1]Intensive Care Unit, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, Zhejiang, China; Departments of [2]Gastroenterology, [3]Pathology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, Zhejiang, China

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Abstract: Mucormycosis is an opportunistic, life-threatening infection caused by fungi of the class Zygomycetes, which typically develops in patients with immune deficiency. We report a rare case of gastrointestinal (GI) tract mucormycosis in a patient without any apparent precipitating factors. Despite receiving aggressive surgical debridement of the involved tissues and treatment with liposomal amphotericin B, he succumbed to life-threatening GI bleeding.

Keywords: Mucormycosis, immunocompetent patient, intestinal perforation

Introduction

Mucormycosis is a rare, devastating disease caused by a ubiquitous saprophytic mold growing in soil and organic matter that produces hyphae after inhalation or ingestion, and belongs to the order Mucorales. It is characterized by vascular invasion by the hyphae, leading to thrombosis and necrosis. Mucormycosis is mostly seen in immunocompromised patients and can be divided into six types: rhinocerebral, pulmonary, cutaneous, gastrointestinal (GI) tract, disseminated, and miscellaneous (including endocarditis, osteomyelitis and renal) [1-3]. Cases of GI mucormycosis in an immunocompetent host are rarely reported, but the mortality rate can be as high as 85% [3]. Here, we describe a case of a male patient with no underlying disease who succumbed to GI bleeding caused by intestinal mucormycosis.

Case report

A 75-year-old male presented to a local hospital with fever (the highest temperature > 39°C) and diarrhea for 1 day. Despite antibiotic therapy and supportive treatment, his symptoms continued and he developed syncope, acute renal failure, and hypovolemic shock, and was transferred to the intensive care unit of a local hospital where he was intubated and administered vasopressors and continuous renal replacement therapy.

After 2 days, the fever and diarrhea were controlled, but he developed GI bleeding and was admitted to our hospital. The diagnosis at the time of admission was acute idiopathic enteritis, maldistributive shock, acute kidney injury (AKI), coagulation dysfunction, digestive tract hemorrhage, and mild anemia. Antibiotics were switched to Tienam plus levofloxacin instead of cefradine plus levofloxacin, and active supportive treatment was continued. The patient improved, with a body temperature of 36.2-38.3°C, and mechanical ventilation was stopped on the sixth day after admission to our hospital. Moreover, he maintained normal defecation after admission, and enteral nutrition was initiated on the eighth day. His diarrhea (1,500 mL loose stools per day) returned after starting enteral nutrition. A physical examination revealed mild abdominal tenderness. Ultrasonography of the abdomen showed a separated seroperitoneum. We then stopped enteral nutrition and his diarrhea resolved soon thereafter.

However, at noon on day 14, he developed a severe stomachache with polypnea, polycardia,

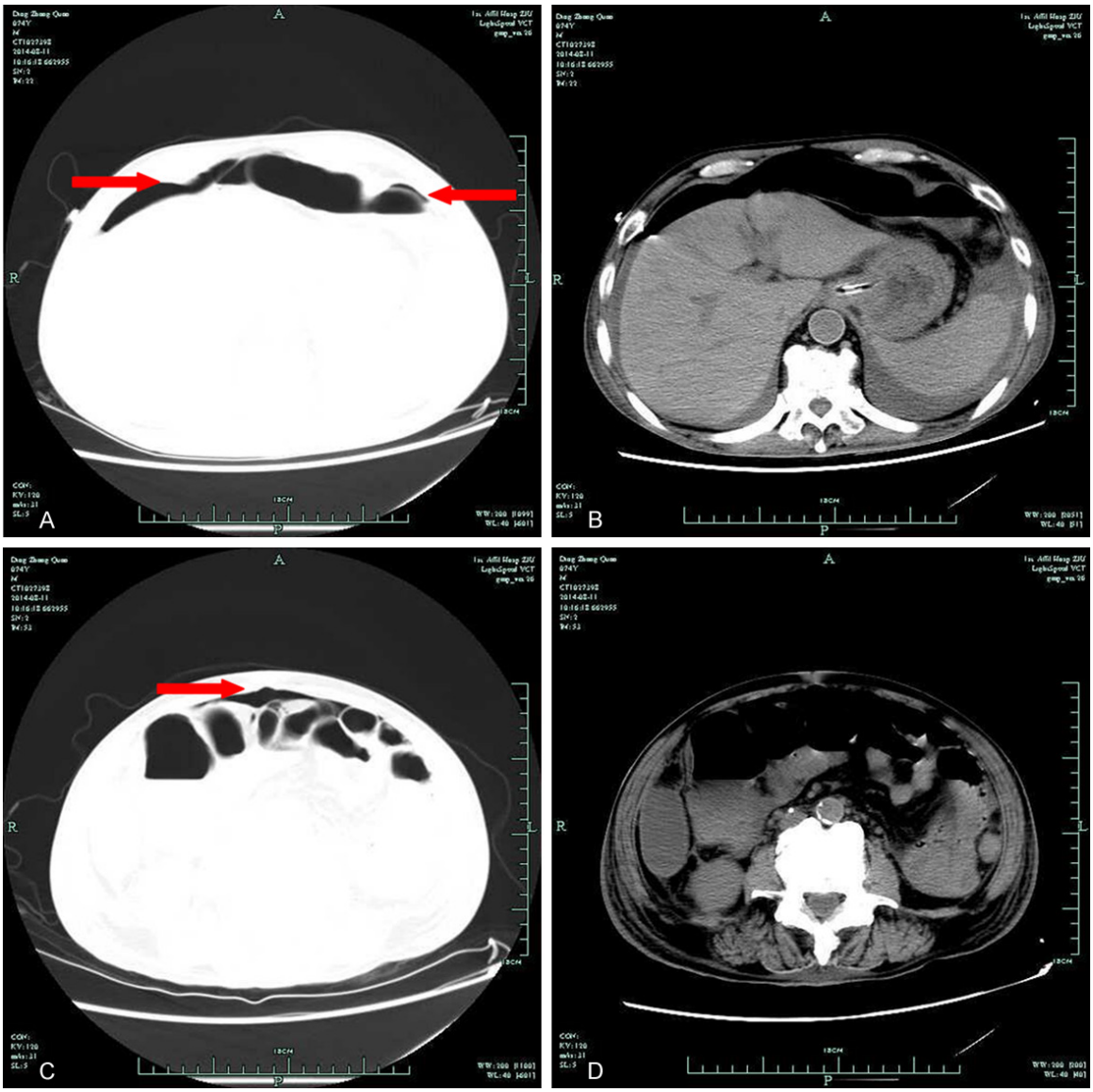

Figure 1. An abdominal CT scan documents intraperitoneal free gas. A and C. Adjustment pictures to display intraperitoneal free gas as red arrows showed; B and D. Original pictures.

and hypotension (77/35 mmHg), and physical examination of his abdomen revealed tenderness, tension, and rebound pain. A computed tomography (CT) scan (**Figure 1**) showed intraperitoneal free gas and large peritoneal effusions, suggestive of an intestinal perforation. Regarding the cause of the intestinal perforation, there was no evidence of autoimmune disease (antinuclear antibody negative). Infection was considered, as fever and diarrhea were his initial symptoms. A laboratory examination suggested active inflammation. No pathogenic bacterium was identified, but a stool culture grew *Candida krusei*. Although the symptoms were, to an extent, controlled by antibiotic therapy (levofloxacin 500 mg qd for 5 days, imipenem-cilastin sodium 1.0 q 6 h for 8 days, piperacillin-tazobactam 4.5 g q 8 h for 5 days, and caspofungin 50 mg qd for 11 days) and active supportive treatment, the intestinal perforation caused us to consider non-specific pathogens. Although tests for serum tumor markers were negative, GI tumors and lymphoma were also considered. CT showed a dilated intestinal canal, therefore intestinal obstruction was excluded. To make a definite diagnosis, we performed an exploratory laparotomy, which showed a large amount of turbid ascites, expansion and

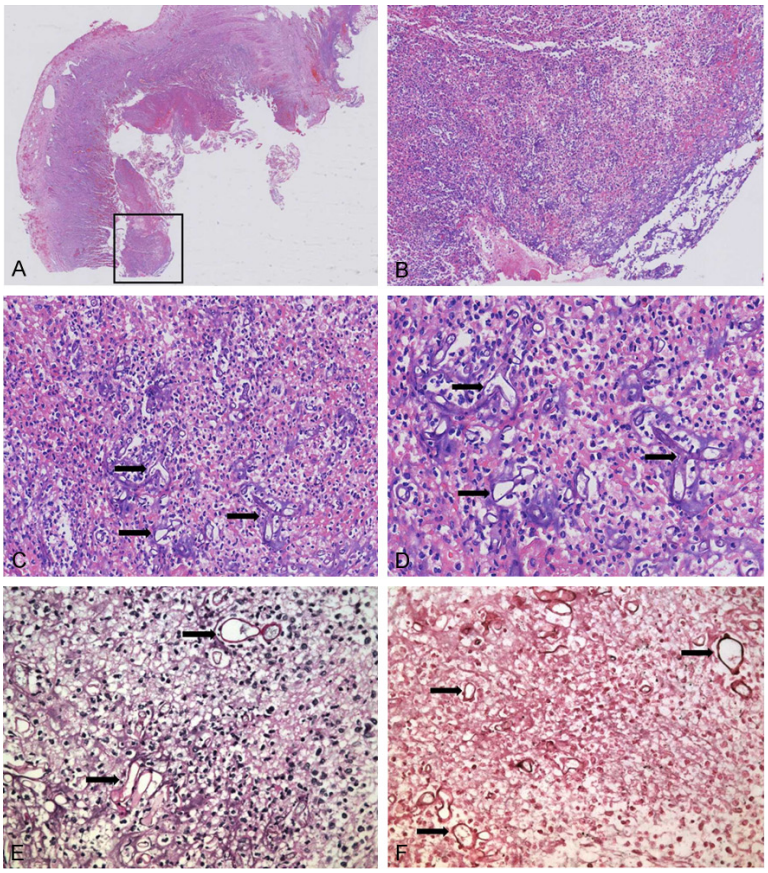

Figure 2. Representative slides from resection material demonstrating fungal enteritis (mucormycosis) with extensive necrosis evidenced by irregular branching, broad non-septate fungal hyphae (A. HE; B. HE, × 100; C. HE, × 200; D. HE, × 400; E. PAS (Periodic Acid-Schiff stain), × 400; F. Periodic acid-silver Metheramine, × 400).

aerification of the colon, adhesive right hemicolon, a mass of excrement on the right side of the colon side ditch, and a 2.0 × 2.0 cm perforation in the ileum (30 cm distal to the ileocecal junction) together with flowing excrement. Beyond the ileum, no space-occupying lesion was found, and ileocecal junction resections and enterolysis were performed without an ileostomy. The margins of the perforation were submitted for histopathological examination, which revealed multiple necrotic fragments of tissue from the perforation margin and incrassate walls of intestinal and mesenteric veins around the perforation, with hyalinization of the necrotic tissue and hyphal structures, indicative of mucormycosis (**Figure 2**). Intravenous liposomal amphotericin B was added to the therapeutic regimen on day 24. Unfortunately, the mucormycosis continued to progress and the patient died due to life-threatening GI bleeding on day 36. No autopsy was performed.

Discussion

Mucormycosis is a rare and often life-threatening disease that is commonly seen in patients with risk factors that include hematological or solid malignancies, neutropenia, trauma, use of corticosteroids, solid organ, or stem cell transplant, diabetic or metabolic acidosis, iron overload or deferoxamine use, malnourishment, barrier disruption by a catheter, premature birth, and previous exposure to antifungal agents, such as voriconazole and echinocandins [4, 5]. Other risk factors include widespread use of newer, broad-spectrum antifungal agents, such as voriconazole and echinocandins [5].

Mucormycosis can occur in many parts of the human body. The most common sites of mucormycosis are the sinuses (39%), lungs (24%), skin (19%), brain (9%), GI tract (7%) and kidneys (2%), in addition to disseminated infection (3%) [3]. GI tract infections are rare. Among non-transplant patients, the most frequently involved site is the stomach (67%), followed by the colon (21%), small intestine (4%), and esophagus (2%) [6]. Almyroudis et al. reported that among solid organ transplant recipients the incidence of GI mucormycosis was 11.2% (13 of 116 patients), and involved the stomach (69.2%), colon (7.6%), esophagus (7.6%), and liver (7.6%) [7].

Studies of GI mucormycosis in an immunocompetent host are rare. We searched the PubMed database for cases of GI mucormycosis in immunocompetent adults reported in the English literature. A total of 12 cases were retrieved and these cases are summarized in **Table 1**. Almost all of the cases reported in the literature had different underlying initial symptoms, such as fever, respiratory symptoms, hematochezia, or hematemesis. However, the patient's condition tended to deteriorate rapidly. Of the 12 patients reviewed, only 1 was cured without recurrence.

Table 1. Summary of cases of gastrointestinal mucormycosis in immunocompetent adults

Year	Sex	Age	Location	Clinical presentation	Diagnosis	Treatment		Result
						Surgery	Antifungal therapy	
1999 [8]	Male	54	Small bowel	Constipation, abdominal tenderness, hypotensive	Laparotomy, biopsy	Yes	Liposomal Amp B	Death
2006 [9]	Female	58	Sigmoid	Haematochezia	Surgery, biopsy	Yes	No	Death
2008 [10]	Male	28	Stomach	Fever, abdominal pain and bloody diarrhea, GI bleeding	Laparotomy, biopsy	Yes	Amp B (deoxycholate)	Death
2011 [11]	Female[#]	70	Ascending colon	GI bleeding	Colonoscopy, biopsies	No	No	Death
2012 [12]	Male	69	Colon	Abdominal pain,	Laparotomy, biopsy	Yes	Amp B	Death
2012 [13]	Male[$]	32	Stomach	Hematemesis	Surgery, biopsy	Yes	Amp B	Death
2012 [14]	Male	58	Stomach	GI haemorrhage	Surgery, biopsy, autopsy	Yes	Amp B	Death
2015 [15]	Female[*]	58	Colon	Lower GI hemorrhage	Laparotomy, biopsy	Yes	Amp B and micafungin	Death
2016 [16]	Male[$]	56	Stomach	Dyspepsia, intermittent hematemesis, pain and distention of abdomen	Upper GI endoscopy, biopsy	No	Antifungal treatment	Recovered
2017 [17]	Male	66	Duodenum, jejunum	Abdominal distension, nausea, and fever, GI bleeding	Gastroscopy, biopsy	Yes	Amp B	Death
2017 [18]	Female	53	Stomach	Hematemesis	Upper endoscopy, laparotomy	Yes	No	Death
2017 [19]	Male	22	Duodenum	Recurrent hematemesis and melena	Oesophago-gastro-duodenoscopy, biopsy	No	No	Death

#: Admitted with septic shock secondary to community acquired pneumonia, and receive eight days of steroidtherapy (hydrocortisone 100 mg tid) before GI bleeding. $: Alcoholic liver disease with cirrhosis. *: Admitted with upper respiratory tract infection and receive intravenous solumedrol (40 mg q8 h) for 14 days and antifungal (fluconazole 400 mg daily) before GI hemorrhage. GI: gastrointestinal; Amp B: amphotericin B.

Guidelines did not include any recommendations for the methods of diagnosis of mucormycosis infections. Mucormycosis is not detectable in the blood or cerebrospinal fluid (CSF). Clinical features of GI mucormycosis are nonspecific, including abdominal pain and distention, nausea and vomiting, hematemesis, hematochezia, and intestinal perforation with peritonitis [20]. Delays in diagnosis and initiation of treatment are associated with an increased mortality rat [21]. Biopsy with histopathological and culture evaluation is the best current method to detect mucormycosis infections. The histopathological hallmark of mucormycosis infection is vascular invasion, causing thrombosis and infarction, or secondary hemorrhages of neighboring tissues; focal areas of granulomatous inflammation are occasionally present [22, 23]. The diagnosis is established histopathologically by the presence of characteristic broad, branching and non-septate hyphae in freshly infected tissues, usually in association with extensive angioinvasion, with resultant vascular thrombosis and infarction. Newer diagnostic modalities include serology and multiplex polymerase chain reaction (PCR), which we did not perform. The antigen test has low sensitivity and specificity [24].

There are no current Infectious Diseases Society of America (IDSA) grade A or I classifications to guide antifungal therapy for the successful treatment of mucormycosis. The current management is largely based on case reports, animal studies, and *in vitro* data [25]. Successful treatment of GI mucormycosis involves early diagnosis, elimination of the underlying predisposing factors, aggressive surgical debridement of involved tissues, and antifungal therapy. One study reported a twofold increase in mortality at 12 weeks when treatment was delayed and amphotericin B was initiated > 6 days after diagnosis (82.9% vs. 48.6%) [21]. In our case, prompt and extensive surgical debridement was performed to remove all necrotic tissue. A meta-analysis of published reports of mucormycosis suggested that the survival rate is dependent on the treatment strategy: 3% for patients who received neither surgery nor antifungal therapy, 57% with surgery alone, 62% with antifungal therapy alone, and 70% for those who underwent both surgery and antifungal therapy [3].

Intravenous amphotericin B (including its deoxycholate salt and lipidic form) is the reference antifungal therapy for GI mucormycosis, and the recommended doses range from 1 to 1.5 mg/kg/day for amphotericin B deoxycholate and from 3 to 5 mg/kg/day for amphotericin B in its lipidic form. The optimal duration of antifungal chemotherapy is not clear but should

be guided by the resolution of all associated symptoms and findings. In immunocompromised patients, maintenance therapy/secondary prophylaxis must be considered [26, 27]. Posaconazole, a second-line agent, is used as a step-down therapy for patients who have responded to amphotericin B, and rarely as salvage therapy for patients who do not respond to or cannot tolerate amphotericin B [28]. Moreover, rifampicin enhances the fungicidal action of amphotericin B [29] and colistin *in vitro* against Mucorales spores and mycelia [30].

In the case reported herein, a 75-year-old male, who was not immunocompromised and did not have any apparent precipitating factors, died of GI bleeding attributed to GI mucormycosis. The time from onset of fever and diarrhea to starting liposomal amphotericin B was 29 days, which contributed to the unfortunate outcome.

GI mucormycosis has a low morbidity rate and high mortality rate, and delays in diagnosis are associated with an increased mortality rate. GI mucormycosis is typically not considered until histopathological examination, which frequently leads to treatment failure. If a patient with no history of underlying disease or no evidence of an immunocompromised state develops an unexplained fever, diarrhea, or intestinal perforation, then alimentary tract hemorrhage or GI mucormycosis should be considered. Treatment success is dependent on early diagnosis and prompt administration of antifungal therapy. Therefore, urgent surgical debridement of infected and necrotic tissue is also suggested. Further studies of gastric mucormycosis will enhance our knowledge of the condition and improve the survival rate.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xia Zheng, Intensive Care Unit, The First Affiliated Hospital, College of Medicine, Zhejiang University, 79 Qingchun Road, Hangzhou 310003, Zhejiang, China. Tel: +86-13958174689; E-mail: zxicu@zju.edu.cn

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