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Total Gastric Necrosis Due to Mucormycosis: A Rare Case of Gastric Perforation

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Statistical Analysis C
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Conflict of interest: None declared

Patient: Female, 52
Final Diagnosis: Gastric mucormycosis
Symptoms: Sepsis • surgical abdomen
Medication: Liposomal amphotericine b
Clinical Procedure: Total gastrectomy
Specialty: Surgery

Objective: Rare disease


Background: Spontaneous gastric perforation is usually a complication of peptic ulcer disease, or a postoperative complication resulting from gastric torsion. Mucormycosis (or zygomycosis) is an uncommon opportunistic fungal infection that is usually seen in immunocompromised patients and is associated with significant morbidity and mortality. This report is of a rare case of spontaneous gastric perforation due to mucormycosis infection.

Case Report: A 52-year-old woman, with a past medical history of heroin abuse, diabetes mellitus, hypertension, and chronic kidney disease treated by dialysis, presented to the emergency department with cellulitis of the arms. Following hospital admission, her medical condition deteriorated, and she developed septic shock and multiorgan failure, requiring transfer to the intensive care unit (ICU), where she was diagnosed with a perforated hollow viscus as the cause. Surgical exploration showed that the mucosa of the stomach was necrotic and perforated, but the remaining bowel appeared normal. Total gastrectomy was performed, and a jejunostomy feeding tube was inserted. Histopathology of the gastric tissue confirmed infection with mucormycosis. The patient was treated with adjunctive liposomal amphotericin B, her condition improved, and she was extubated on postoperative day 2. However, the patient died on postoperative day 21 due to sepsis and multiorgan failure.

Conclusions: Mucormycosis is an opportunistic angioinvasive fungal infection, and gastric perforation is a rare clinical presentation. However, knowledge of the association between gastric necrosis and perforation and mucormycosis infection might lead to early diagnosis and treatment and reduce patient morbidity and mortality.

MeSH Keywords: Amphotericin B • Gastrectomy • Mucormycosis • Necrosis • Stomach Rupture

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Background

The stomach is a highly vascularized organ. Spontaneous gastric perforation secondary to necrosis of the stomach is an unusual surgical finding. Mucormycosis (or zygomycosis) is an uncommon fungal infection occurring in immunocompromised hosts. A previously published study has shown that the annual incidence of mucormycosis in the general population is 1.7 cases for every 1 million individuals, which is equivalent to approximately 500 affected Americans each year [1]. This rare angioinvasive fungal infection, mucormycosis, can cause infections that are rhinocerebral, pulmonary, cutaneous, gastrointestinal, renal, or disseminated, but primary gastrointestinal infection is an uncommon clinical presentation with a prevalence of only 7% of reported cases [2].

This report is of a rare case of invasive gastric mucormycosis presenting with gastric perforation, due to complete transmural gastric necrosis, in a patient with a history of heroin abuse and uncontrolled diabetes.

Case Report

A 52-year-old woman, with a past medical history of heroin abuse, diabetes mellitus, hypertension, and chronic kidney disease treated by dialysis, presented to the emergency department with cellulitis of the arms, associated with infection of needle injection sites. The patient was initially admitted to the ward and managed with broad-spectrum intravenous (IV) antibiotic therapy, piperacillin/tazobactam (Tazocin) 2.25 gm three times a day, and underwent surgical drainage of the abscesses of her arms. The patient was later transferred to the intensive care unit (ICU) due to a sudden deterioration in her medical condition, including the onset of severe abdominal pain associated with sepsis.

On physical examination, she was hemodynamically unstable, with a blood pressure of 80/50 mmHg, her temperature was 38°C, and her heart rate was 120 beats per minute. Her abdomen was moderately distended with absent bowel sounds, diffuse guarding, and rigidity. Her laboratory results showed metabolic acidosis and elevated an elevated white blood cell (WBC) count of 31,000 per microliter of blood. The patient was resuscitated with adequate IV hydration and stabilized with inotropes.

In view of the symptoms and clinical findings in this patient, enhanced computed tomography (CT) of the abdomen and pelvis was done, which showed an edematous gastric wall and free intraperitoneal air, indicating a perforated hollow viscus (Figure 1). The patient was urgently moved to the operating room where an exploratory laparotomy was done. At

laparotomy, a large amount of turbid bilious fluid was present and a gastric perforation was seen in the prepyloric area, associated with transmural gastric necrosis (Figure 2). The rest of the bowel appeared to be grossly normal. An intraoperative upper endoscopy was done and confirmed the viability of the esophagus but due to hemodynamic instability, the patient underwent total gastrectomy with the insertion of a nasogastric tube and a jejunostomy feeding tube.

The histological examination of the stomach showed extensive ulceration of the gastric mucosa, dense acute inflammation involving the full-thickness of the gastric wall involving serosa, and multiple epithelioid granulomas. There were broad budding fungal organisms present, with right-angled budding hyphae present, and angioinvasion was found in the ulcer bed. The histological findings were those of mucormycosis (Figure 3). Special histochemical stains, including periodic acid-Schiff (PAS) (purple) and the Grocott-Gömöri methenamine silver stain (GMS) (black) confirmed the presence of invasive mucormycosis (Figure 4).

The early postoperative course was satisfactory and on postoperative day 2, the patient was successfully extubated, and treated with broad-spectrum antimicrobial medications that included meropenem 500 gm three times daily, metronidazole 500 three times daily, and caspofungin 50 mg once daily. On postoperative day 4 (10 days after hospital admission), because histology had confirmed a diagnosis of mucormycosis, the patient was treated with adjunctive liposomal amphotericin B, 5 mg/kg once daily. However, the patient died on postoperative day 21 due to sepsis and multiorgan failure.

Discussion

Mucormycosis (or zygomycosis) is a life-threatening opportunistic infection caused by angioinvasive fungi of the subphylum Mucoromycotina, order Mucorales [3]. The mechanism of transmission usually occurs via inhalation of the sporangiospores or as direct inoculation into the disrupted mucocutaneous surface in immunocompromised individuals [4].

Mucormycosis commonly presents with five clinical patterns and may affect the pulmonary, rhinocerebral, gastrointestinal, cutaneous, or central nervous systems. Dissemination may also occur due to the highly invasive nature of this fungal organism. Dissemination is a term used to describe an infection that affects two or more noncontiguous organ systems [5]. Disseminated mucormycosis most commonly affects the lungs and brain most often, with the infection usually originating in the lungs [6]. Pulmonary and rhinocerebral forms are the most common forms of infection, while primary gastrointestinal mucormycosis is very uncommon.

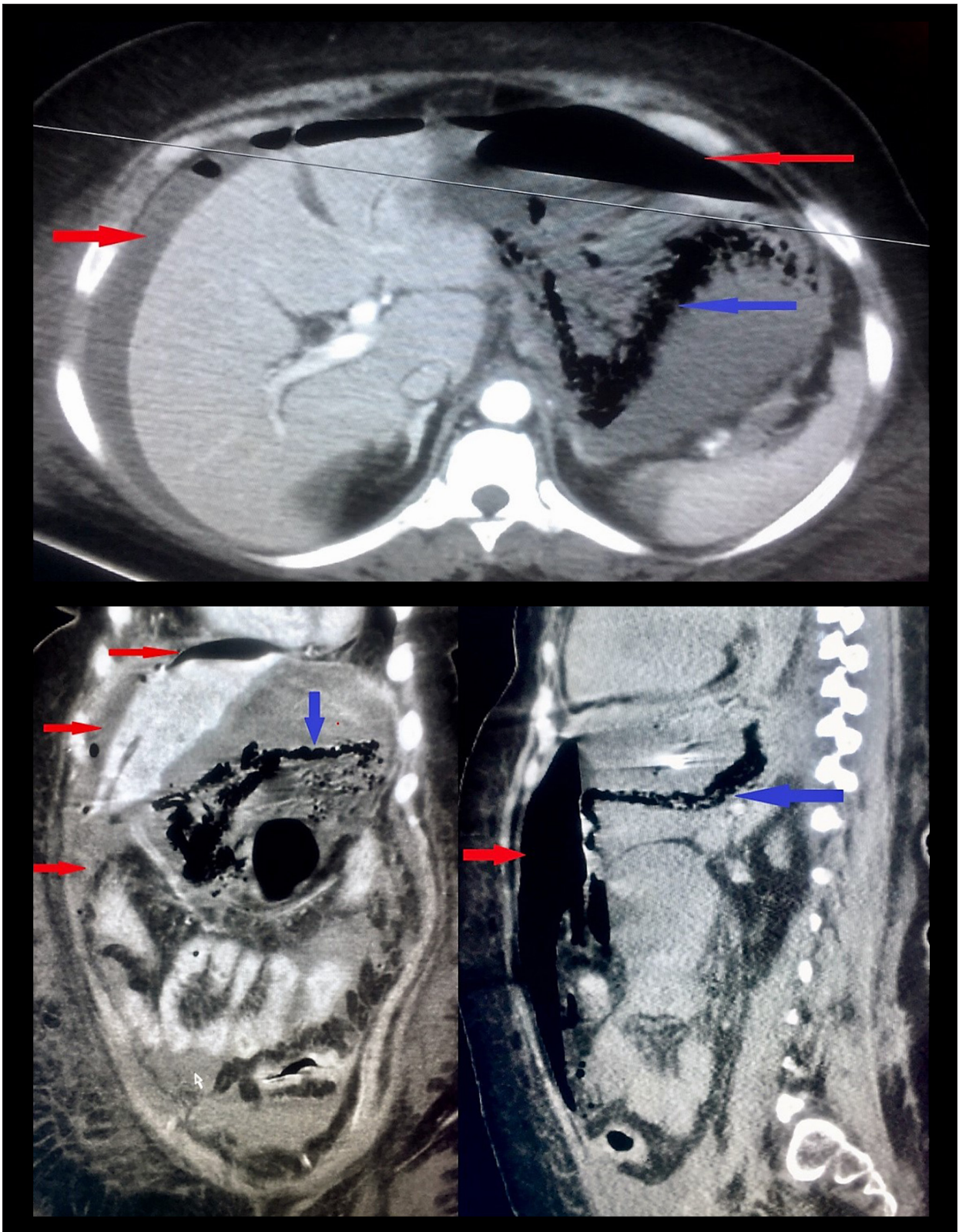


Figure 1. Enhanced abdominal computed tomography (CT) imaging. Enhanced abdominal computed tomography (CT) imaging shows free air and a large amount of free fluid in the abdominal cavity indicating the perforation of a hollow viscus perforation (red arrows), and gastric pneumatosis, or intramural gas in the gastric wall (blue arrows).

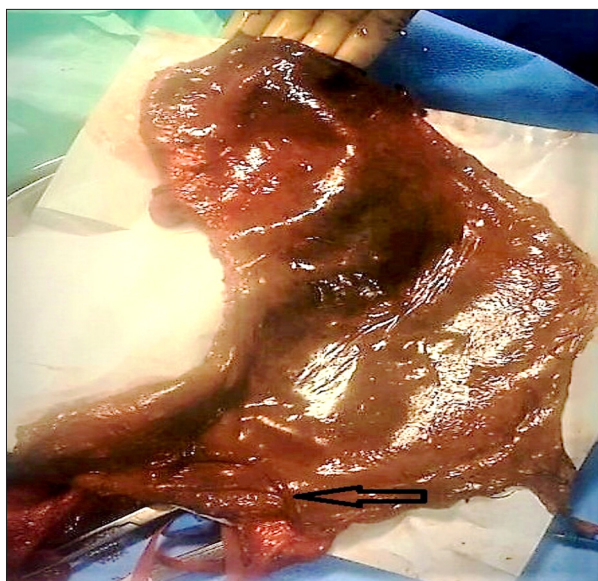


Figure 2. The macroscopic appearance of the transmural gastric necrosis showing a large perforation.

Risk factors for mucormycosis include diabetes mellitus, diabetic ketoacidosis, neutropenia, corticosteroid use, hematologic malignancies, bone marrow or solid organ transplantation, treatment with deferoxamine, iron overload, and human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) [7]. Predisposing factors for gastrointestinal mucormycosis have been reported to include kwashiorkor, malnutrition, pellagra, uremia, amebic colitis, and typhoid fever [8]. The patient presented in this report had a history of heroin abuse and presented with abscesses of both arms. She

also had long-standing hypertension and uncontrolled diabetes mellitus with associated vasculopathy, and with nephropathy that required dialysis. These clinical risk factors were likely to have made her susceptible to opportunistic fungal infection and fungal super-infection.

All parts of the alimentary tract are vulnerable to gastrointestinal mucormycosis infection, with the stomach being the most commonly affected, followed by the colon and ileum, and with the route of infection likely to be due to ingestion of infected sputum or secondary colonization of pre-existing ulcers [9]. The clinical features of gastrointestinal mucormycosis infection can range from nonspecific symptoms to fever, gastrointestinal bleeding, and perforation. In premature neonates, gastrointestinal mucormycosis infection may present as necrotizing enterocolitis [7,10]. Mucormycosis that affects only the stomach, or gastric mucormycosis, exists in one of three forms: colonization, infiltration, and vascular invasion. While there have been previously published case reports of gastric mucormycosis in premature neonates and malnourished children, primary gastric mucormycosis in adults, although rare, appears to be on the rise [11,12].

The pathophysiology of mucormycosis is strongly related to the evolution and progression of the fungi, as mucor molds in the environment develop their hyphal forms in the tissue, and once the spores begin to grow, fungal hyphae (angioinvasive hyphal forms) invade blood vessels, which explains the high risk of perforation and bleeding seen in gastrointestinal mucormycosis infection. Two major hallmarks of the histopathology of gastrointestinal mucormycosis infection are direct

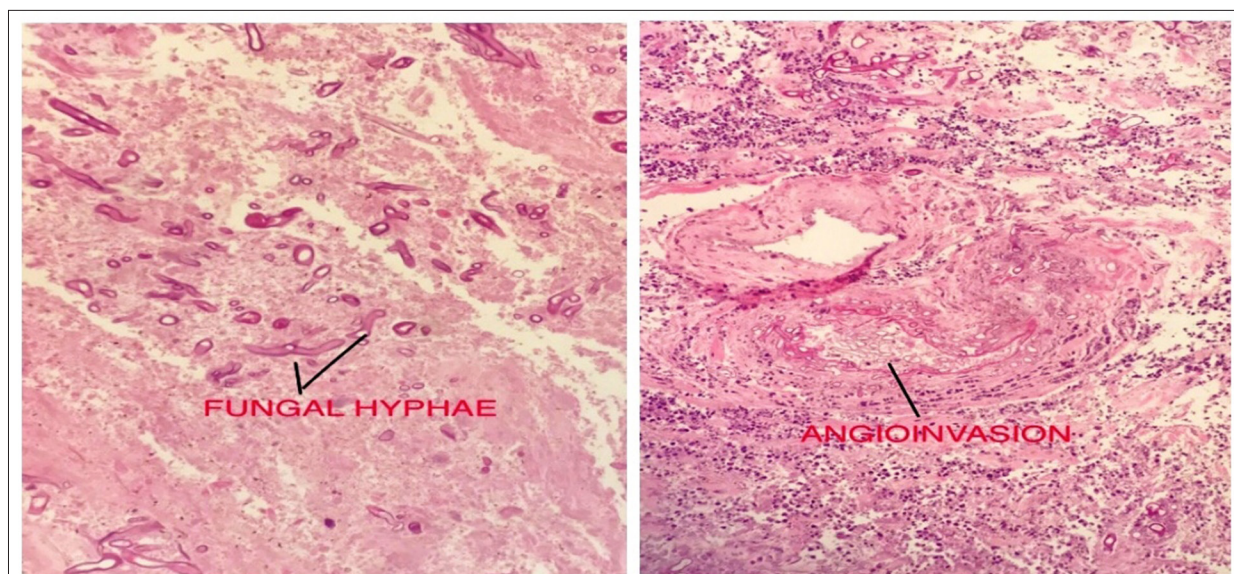


Figure 3. Photomicrograph of the histological appearance of mucormycosis. A gastric wall tissue section examined by light microscopy. The histology of the fungal form of mucormycosis shows large, non-septate hyphae with 90-degree angle hyphal branching and the property of angioinvasion that results in tissue necrosis.

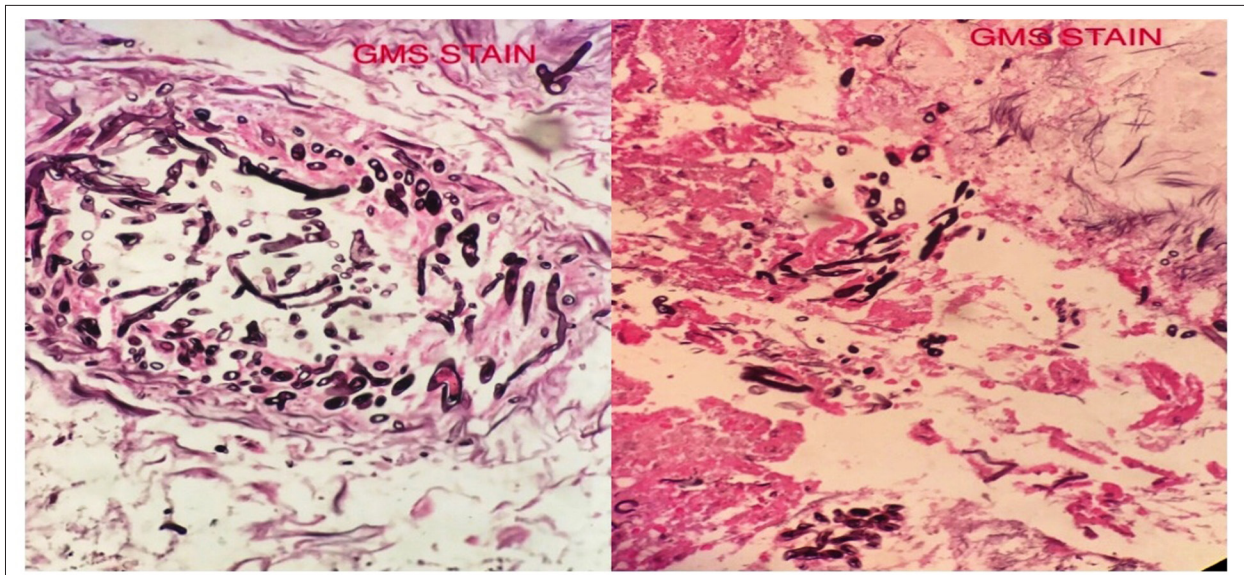


Figure 4. Photomicrographs showing the morphology of mucormycosis. Grocott-Gömöri methenamine silver stain (GMS) (black).

Table 1. Histomorphological characteristics of *Aspergillus* sp. and Mucormycosis [17].

Characteristic	<i>Aspergillus</i>	Mucormycosis
Width	Narrow (3–6 µm)	Wide (5–20 µm)
Caliber	Uniform	Varying
Branching	Regular, acute angle	Random, right angle
Branching orientation	Parallel or radial	Random
Septum	Common finding	Uncommon finding

invasion through the blood vessel wall, causing an increased propensity for thrombosis and tissue necrosis with black eschar, which is a dark, dry scab, and a discharge that are pathognomonic of mucormycosis [4].

The diagnosis of mucormycosis can be made microscopically by biopsy of the suspected area at surgery or endoscopy and seldom made by microbiological culture [7]. However, polymerase chain reaction (PCR)-based techniques can now allow identification of mucormycosis infection, even in culture-negative cases, but this diagnostic method is time-consuming. Aspergillosis is considered the main histopathological differential diagnosis of mucormycosis. However, in aspergillosis, the fungal hyphae are thinner, septate, and branch at an acute angle rather than a 90-degree right angle (Table 1).

According to Chamilos et al., rapid diagnosis and initiation of antifungal therapy within six days of presentation are strongly associated with improved patient survival [13]. However, the patient described in this case report presented to the hospital with bilateral extensive upper limb cellulitis and abscesses, and no abdominal symptoms were initially noted. It was

only the sudden and later gastric perforation and tissue histological examination that resulted in the diagnosis of gastric mucormycosis. In this case, the delay of appropriate anti-fungal therapy, at day 10 after hospital admission and at postoperative day 4 were likely to explain her increased mortality risk, despite adequate surgical debridement. Although there is still there is no consensus to define optimal antifungal therapy for mucormycosis, recent expert opinion has advised the use of adjunctive liposomal amphotericin B as it can be used at higher doses and with less toxicity than amphotericin. Liposomal amphotericin B can be given at 5–15 mg/kg/day and the successful therapy course usually lasts for a period of between 4–6 weeks [14]. Posaconazole is a new triazole antifungal agent that has recently been approved by the US Food and Drug Administration (FDA) and is typically prescribed at a dose of 400 mg, twice daily. Combination therapy can be used, as has been previously reported in 2006 by Rickerts et al. as a successful treatment option in patients with disseminated mucormycosis who were unable to undergo surgery [15,16].

Antifungal therapy alone is still inadequate to control mucormycosis. Surgical debridement and removing the infected

Table 2. Recent case studies of invasive gastric mucormycosis, clinical presentation and outcome.

Study group	Age & sex	Co-morbidities	Presentation	Findings	Treatment	Outcome
Our patient	52 F	DM, HTN, CKD, Cocaine drug abuse	– Refractory sepsis – CT: Perforated Hollow viscus gastric pneumatosis	Complete stomach necrosis with prepyloric perforation	– Total gastrectomy without reconstruction due to instability – Liposomal amphotericine	Died
Sánchez-Velázquez P. et al. 2017 [18]	53 F	– Prolonged ICU admission – Aspiration pneumonia	– Massive Upper GI bleeding – Hypovolemic shock	Perforated gastric ulcer at GE junction & fundus	– Total gastrectomy without reconstruction due to coagulopathy	Died
Enani M.A. et al. 2014 [19]	54 M	DM, HTN, IHD CKD & Anasarca	– Abdominal pain – Distension – Melena & hematemesis	Perforated gastric ulcer posterior wall & abscess formation splenic infarction, DIC	– Closure of the perforation – Splenectomy	Died
Kulkarni R.V. et al. 2014 [20]	50 M	Alcoholic & DM	Acute surgical abdomen	4x4 cm perforated ulcer in the gastric body	Wedge resection of the ulcer	Died
Alvarado-Lezama J. et al. 2014 [21]	32 M	– DM – ICU admission due to head trauma	– Diabetic ketoacidosis – Upper GI bleeding	– CT showed emphysematous stomach erosive esophagitis necrotizing gastritis	Total gastrectomy	Died
Bäcker H. et al. 2017 [22]	71 M	– DM, HTN – Duodenal carcinoma	Post whipple leakage	– Leak from pancreatic anastomosis – Endoscopy revealed large gastric ulcer	– Completion total pancreatectomy – Laparotomy and wash – Conservative drainage – Liposomal amphotericin	Survived
Lee S.H. et al. 2014 [23]	55 M	– Alcoholic & liver cirrhosis – History of gastric ulcer	– Severe abdominal pain, distention and sepsis	Ct scan showed pneumoperitoneum due to gastric ulcer perforation at the antrum & ascitic fluid	– Subtotal gastrectomy & gastrojejunostomy – Liposomal amphotericin	Survived
Irtan S. et al. 2013 [24]	4 F	– Multivisceral transplant for chronic intestinal pseudo-obstruction syndrome – Immunotherapy	– Day 6 after transplantation – Massive upper GI bleeding	2 small ulcers at the transplanted stomach	– 1 st laparotomy wash & drainage – 2 nd laparotomy partial gastrectomy – Liposomal amphotericine	Survived
Azhar A. et al. 2009 [25]	43 M	DM, acoholic	Abdominal pain	Gastric ulcer perforation, pancreatic necrosis	– Total gastrectomy – Liposomal amphotericine	Survived
Song K. et al. 2006 [26]	60 M	History of AML	– Sepsis – CT showed discontinuity of post. wall of the stomach	– Laparotomy showed massive gastric bleeding & multiple perforations	– Total gastrectomy & splenectomy – Liposomal amphotericine	Survived

and devitalized tissue is usually required to improve the outcome as some strains of mucormycosis can be resistant to antifungal therapy. Also, because mucormycosis is angioinvasive and can induce vascular thrombosis, the tissue necrosis that results from mucormycosis infection also results in poor penetration of pharmacotherapy to the targeted tissue [7]. In multiple case series, patients who did not undergo surgical

debridement of mucormycosis infected tissue had significantly increased mortality when compared with those who underwent surgical debridement [17].

Roden et al. reviewed more than 900 cases of mucormycosis and concluded that the prognosis was usually poor with a mortality of between 70–100% [7]. The outcome is further

dependent on the burden of associated comorbidities, as well as the timing of the initiation of antifungal therapy. According to a review of the medical literature written in the English language, only a few cases of gastric mucormycosis have been reported, and the outcomes have been varied, but only this case was associated with IV heroin abuse (Table 2). Table 2 summarizes the ten recent cases (from 2006–2017) that show 50% mortality from this infection. The medical literature also supports that uncontrolled diabetes mellitus and chronic kidney disease are considered to be poor prognostic factors in mucormycosis infection. The review of cases of gastric mucormycosis infection, as shown in Table 2, has shown that early surgical management and the introduction of an antifungal agent was very significantly associated with clinical outcome, and that the patients who had complications during admission for other causes, had improved survival rates due to more rapid diagnosis and management (three cases out of the five patients who survived). Also, more necrosis of the stomach was associated with worse clinical outcome. The case presented in this report had several poor prognostic clinical factors and was detected incidentally and late due to refractory sepsis despite initial treatment broad-spectrum antimicrobial therapy.

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Conclusions

Gastric perforation due to transmural gastric necrosis secondary to invasive mucormycosis is a rare occurrence. Knowledge of the invasive properties of this fungal pathogen and awareness of its clinical presentation and the patient risk factors for mucormycosis infection may benefit the early diagnosis and management of this disease. A high index of suspicion is required to make the diagnosis of mucormycosis, and prompt and aggressive surgical debridement with initial adjunctive treatment with liposomal amphotericin B therapy is recommended to improve patient prognosis.

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Conflict of interest

None