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Case Report

CASE REPORT

An unusual cause of massive upper gastrointestinal bleeding—gastric mucormycosis

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Abstract

Mucormycosis of the gastrointestinal tract is a life threatening infection most commonly seen in patients with severe immunosuppression. A 42-year-old male with history of choriocarcinoma was admitted to the intensive care unit with septic shock. He developed massive hematemesis requiring upper endoscopy which showed multiple deep gastric ulcers. Due to uncontrollable bleeding he underwent an emergent gastrectomy which revealed necrotic ulcers with evidence of angioinvasion in the ulcer bed with mucor organisms. The PCR revealed the mucor to be *Mycotypha microspora* which is extremely rare. We discuss the challenges involved in the diagnosis and treatment of gastric mucormycosis.

INTRODUCTION

Mucormycosis is a fungal infection that produces varying symptoms depending on the organs involved. Within the gastrointestinal tract it causes ischemia, bowel infarction and deep ulcers which can lead to massive bleeding due to angioinvasion. It is ubiquitous in the environment.

Angioinvasive infection develops in patients with risk factors such as hematological malignancy, diabetic ketoacidosis and immunosuppressant use. Prompt recognition and treatment of gastric mucormycosis with surgical resection of the infected tissue alongside antifungal therapy is imperative for successful outcomes.

CASE REPORT

A 42-year-old male with stage 1 S germ cell tumor of the mediastinum, hemorrhagic pituitary prolactinoma which was diagnosed incidentally on computed tomography of the chest and brain after he had a left middle cerebral artery thrombotic stroke 7 months prior, presented to emergency room with complaints of lethargy and extreme weakness. He was being treated with Etoposide, Ifosfamide, Cisplatin regimen for his germ cell tumor with last dose a week before his emergency room visit. His prolactinoma was well controlled on Cabergoline. He was admitted to the intensive care unit with febrile neutropenia (absolute neutrophil count of 33 cells/μL) and septic shock from Escherichia Coli bacteremia. Initial labs revealed severe anemia with hemoglobin of 5.1 g/dL and platelet count of 2 k/uL. He required multiple units of blood and platelet transfusions. His hospital course was complicated by respiratory failure requiring mechanical ventilation and blood pressure support with four vasopressors (norepinephrine, dobutamine, vasopressin and phenylephrine). He was given multiple doses of intravenous methylprednisolone for additional blood pressure support. He

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was started on meropenem with gradual improvement in his clinical condition.

On Day 20 of admission, he developed hematemesis and drop in hemoglobin unresponsive to blood transfusions. A pantoprazole drip was started and emergent bedside upper endoscopy revealed blood clots in the fundus and upper body, ulcers in the gastric antrum and body, and a normal esophagus and duodenum (Fig. 1). Biopsy of an ulcer showed chronic active gastritis and foveolar hyperplasia suggestive of adjacent ulceration. Repeat endoscopy following IV erythromycin revealed multiple ulcers and a large blood clot in the fundus which could not be evacuated precluding endoscopic therapy. The patient underwent mesenteric angiography without an identifiable source of bleeding and empiric left gastric artery embolization was done in an attempt to stop the bleeding. Despite the procedure, he continued to have hematemesis and dropping hemoglobin. Emergent exploratory laparotomy was subsequently done which revealed a distended, blood filled stomach with multiple deep ulcerations. Total gastrectomy was performed with esophagojejunostomy and jejunostomy tube placement.

Gross pathology revealed multiple hemorrhagic, deep ulcerations in the stomach (Fig. 2). Within the necrotic tissue of two ulcers histopathology revealed broad aseptate fungi with variable angle branching concerning for mucormycosis. These organisms were noted to surround and invade into ghost outlines of vessels indicating angioinvasion (Figs 3 and 4). Warthin Starry stain and immunostaining were negative for *Helicobacter pylori* and Cytomegalovirus (CMV), respectively. Our patient remained hemodynamically stable without further blood transfusions; he was titrated off blood pressure support medications and eventually extubated. During the postoperative course his sputum cultures grew *Aspergillus fumigatus*. He was started on combination treatment with amphotericin B and voriconazole. Polymerase chain reaction (PCR) later revealed *Mycotypha microspora* as the fungus causing invasive gastric mucormycosis. In view of renal failure, amphotericin B and voriconazole were switched to isavuconazole. He was ultimately discharged to rehabilitation facility with a prolonged course of posaconazole and micafungin.

DISCUSSION

Mucormycosis, also known as zygomycosis, is an infection caused by a fungus of the Mucorales order prevalent throughout the environment. Common fungi causing mucormycosis include Rhizopus species, Mucor and Lichtheimia. In our case

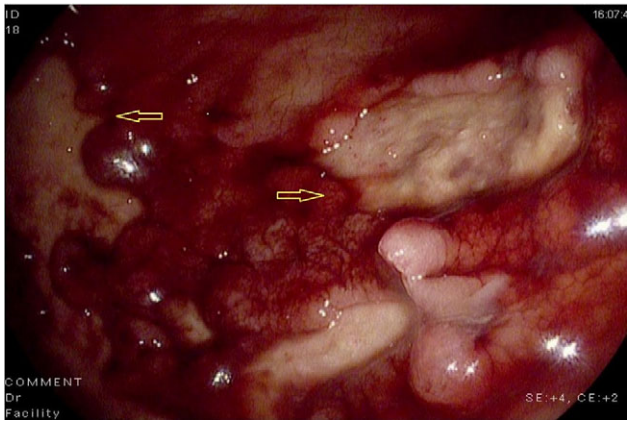

Figure 1: Upper gastrointestinal endoscopy revealing multiple deep ulcers in the body (yellow arrows) with fresh blood in the lumen of the stomach.

the gastric PCR showed *Microtypha microspora* subtype which is very rarely known to cause angioinvasive infection in humans [1]. These fungi have an enzyme called ketone reductase which helps to promote its growth in high glucose acidic conditions. The tendency for angioinvasion is due to high oxygen content in blood. Angioinvasion causes local ischemia, ulceration, infarction and necrosis [2]. Risk factors for angioinvasion include people with immunosuppression especially steroid use, prolonged antibiotic therapy, diabetic ketoacidosis, deferoxamine use and hematological malignancies. The mode of entry is either from inhalation or direct inoculation of sporangiospores into disrupted epithelium, such as skin or mucosa.

Mucor infection occurs anywhere in the body but the most common sites are pulmonary (24%), rhinocerebral (21%), cutaneous (19%), gastrointestinal (7%), CNS and disseminated forms. Within the GI tract, the stomach is most commonly involved (57.5%), followed by the colon (32.3%), then ileum (6.9%) [3, 4]. The most common presentation with GI mucormycosis is upper GI bleeding or gastric ulcers with abdominal pain. Potential complications also include intestinal obstruction, perforation and peritonitis.

Thompson *et al.* [5] classified gastric mucormycosis into three groups: colonization, infiltration and vascular invasion types. Colonization usually occurs in preexisting gastric ulcers and is of little clinical significance. Infiltrative type is where the fungus invades healthy adjacent tissue with no evidence of angioinvasion. The vascular invasive type is characterized by deep invasion into the stomach wall especially into the wall of blood vessels. Both infiltrative and invasive types are serious forms of infection with infiltrative disease having a lower risk of mortality than the angioinvasive type. In our patient above, the prolonged complicated hospital course requiring vasopressors and mechanical ventilation probably led to development of multiple ischemic ulcers in the stomach with neutropenia, germ cell tumor, intravenous steroid and broad spectrum antibiotic use promoting development of angioinvasive mucormycosis. Diagnosis requires a high level of clinical suspicion as it usually occurs in very ill patients admitted to the intensive care unit. Endoscopy usually shows multiple deep necrotic ulcerations in the stomach [6] with high risk for bleeding, infarction and perforation. As in our patient above, surgical resection of affected tissue is vital for diagnosis and treatment of mucormycosis as isolation of the causative organism can lead to therapy directed towards the specific fungus. Identification of the organism by histopathology followed by culture is used to confirm the diagnosis. The invasive type of mucormycosis requires microscopic evidence of aseptate, 10–20 μm hyphae branched at right angles in tissue that infiltrate into the blood vessels. As these organisms are ubiquitous in the environment culture results must be interpreted with caution. Culture often results in no growth, but more recently PCR is commonly being performed in the biopsy tissue with promising results [7]. Imprint cytology is another established tool for rapid diagnosis of mucormycosis [8]. The diagnosis is made on recognition of characteristic mucorales fungal hyphae. In some cases it may be difficult to demonstrate the fungus due to the fragile nature of the organism, but the sensitivity and specificity can be as high as 95% with proper technique [9]. This technique is useful for early institution of antifungal therapy for this potentially fatal disease while waiting for histopathological confirmation.

Treatment usually involves the combination of surgical resection of infected tissue, antifungal medications and control of the predisposing conditions. The aim of surgery is to resect all infected necrotic tissue. The antifungal of choice is amphotericin B given the favorable profile against many of the organisms

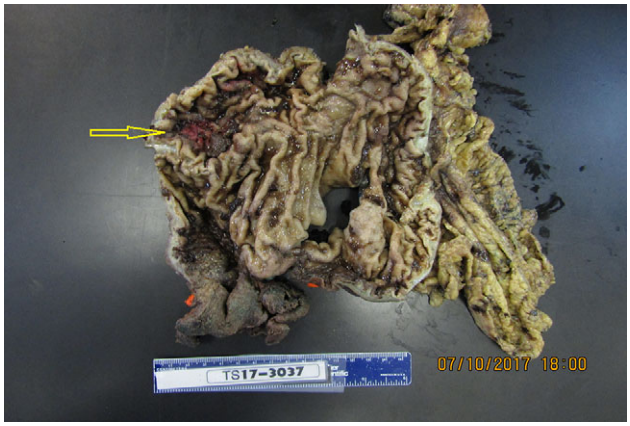

Figure 2: Gross examination of gastrectomy specimen revealing multiple deep ulcers with necrotic base (yellow arrow).

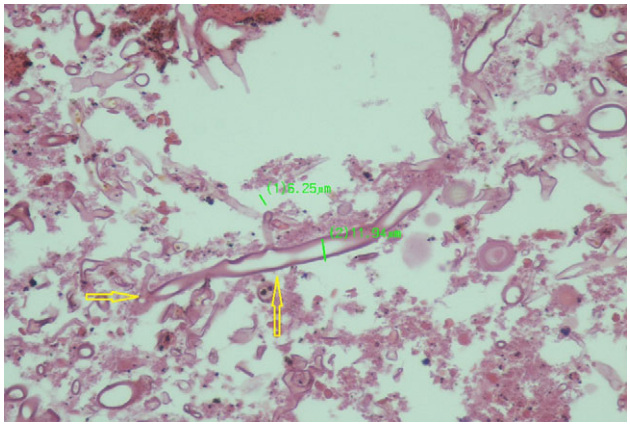

Figure 3: Hematoxylin and eosin staining at ×400 magnification showing a broad aseptate fungus with variable angle branching (yellow arrows) consistent with mucormycosis in a background of cell debris.

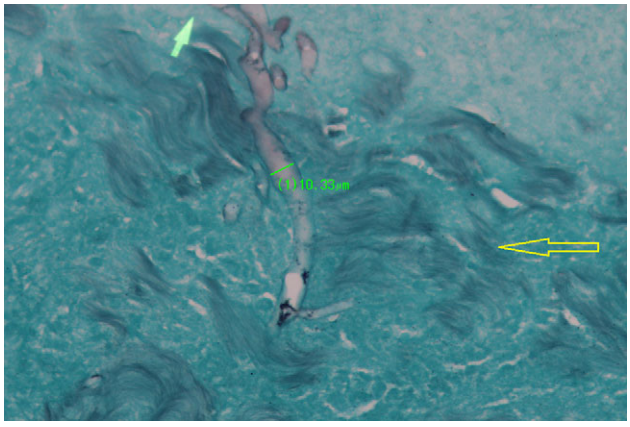

Figure 4: Broad aseptate fungus (green arrow) consistent with mucormycosis surrounding and invading into ghost outline of blood vessel (yellow arrow) consistent with angioinvasion. Grocott's methenamine silver stain (GMC stain) at ×400 magnification.

within the Mucorales order. Posaconazole or isavuconazole is used as step-down therapy once adequate response is achieved with amphotericin B [10]. For patients who do not respond to amphotericin B, literature supports the use of posaconazole or isavuconazole as salvage therapy. Antifungal therapy is usually continued for several weeks until adequate control of infection is achieved. Early initiation of therapy is important, one retrospective study demonstrated delaying treatment (more than 6 days) resulted in an almost 2-fold increase in mortality at 12 weeks [11]. In summary, gastric mucormycosis is a potentially fatal disease that develops in critically ill patients with multiple challenges in diagnosis and management. Successful outcomes are achieved with early diagnosis, prompt resection of infected tissue and a prolonged course of antifungal therapy.

CONFLICT OF INTEREST STATEMENT

None.

AUTHOR CONTRIBUTIONS

Harish Guddati, MD—Author of the case (third year Gastroenterology fellow in the Division of Gastroenterology, Montefiore Medical Center, Wakefield Campus). Christopher Andrade, MD—Coauthor of the case (Internist at Andrade Medical Center, Bronx, NY). Peter Muscarella, MD—Reviewer of the case (General Surgery Site Director, Montefiore Medical Center, Weiler Hospital). Hilary Hertan MD, FACG—Reviewer of the case (Chief of Gastroenterology, Montefiore Medical Center, Wakefield Campus).

GUARANTOR OF THE ARTICLE

Harish Guddati, MD.

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STATEMENT OF INFORMED CONSENT

Informed consent was obtained for this case report from the deceased patient's next of kin.

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