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 Myco typha 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/µL. 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
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 pan-
toprazole drip was started and emergent bedside upper endos-
copy 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 under-
went 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 esophagoje-
junostomy and jejunostomy tube placement.

Gross pathology revealed multiple hemorrhagic, deep ulcera-
tions 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 hemo-
dynamically stable without further blood transfusions; he was

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dynamically stable without further blood transfusions; he was
directed off blood pressure support medications and eventually extrubated. During the postoperative course his sputum cultures grew *Aspergillus fumigatus*. He was started on combination treat-
ment with amphotericin B and voriconazole. Polymerase chain reaction (PCR) later revealed *Mucorpa 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 pro-
longed course of posaconazole and micafungin.

DISCUSSION

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

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, deferoxama-
ine use and hematological malignancies. The mode of entry is either from inhalation or direct inoculation of sporangios-
pores 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%), cuta-
eous (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 mucormyc-

osis is upper GI bleeding or gastric ulcers with abdominal pain. Potential complications also include intestinal obstruc-
tion, 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 angioinva-
sion. 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 compli-
cated hospital course requiring vasopressors and mechanical ventilation probably led to development of multiple ischemic ulcers in the stomach with neutropenia, germ cell tumor, intra-

venous 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 diag-

nosis and treatment of mucormycosis as isolation of the causa-
tive 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, 10–20µm 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 com-

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

REFERENCES
1. Lacroix C, Leblanc T, Feuilhade de Chauvin M. Isolation of Mycotypha microspora from stool samples of a leukemic child. J Mycol Med 2007;17:188–90.
2. Chow KL, McElmeel DP, Brown HG, Tabriz MS, Omi EC. Invasive gastric mucormycosis: a case report of a deadly complication in an immunocompromised patient after penetrating trauma. Int J Surg Case Rep 2017;40:90–3.
3. Spellberg B. Gastrointestinal mucormycosis: an evolving disease. Gastroenterol Hepatol 2012;8:140–2.
4. Roden MM, Zaoutis TE, Buchanan WL. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 2005;41:634–53.
5. Thomson SR, Bade PG, Taams M, Chrystal V. Gastric mucormycosis. Br J Surg 1991;78:952–4.
6. Ismail MH, Hodkinson HJ, Setzen G, Sofanos C, Hale MJ. Gastric mucormycosis. Trop Gastroenterol 1990;11:103.
7. Hammond SP, Bialek R, Milner DA, Petschnigg EM, Baden LR, Marty FM. Molecular methods to improve diagnosis and identification of mucormycosis. J Clin Microbiol 2011;49:2151. Epub 2011 Apr 20.
8. Kamatchi V, Aravindha Babu N, Leena Sankari S, Rajesh E. Imprint cytology. J Pharm Bioallied Sci 2015;7:S207–8.
9. Shilpa P, Tathe MD, Aarti A, Dani MD, Sanjay M, Chawhan MD, et al. Gastric mucormycosis: diagnosis by imprint cytology. Diagn Cytopathol 2016;Vol 44:820–2.
10. Arendrup MC, Jensen RH, Meletiadis J. In vitro activity of isavuconazole and comparators against clinical isolates of the mucorales order. Antimicrob Agents Chemother 2015;59:7735–42. Epub 2015 Oct 5.
11. Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. Clin Infect Dis 2008;47:503.