

Case Report

Gastric wall perforation secondary to presumed aspergillosis in a pediatric patient with aplastic anemia: A case report

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Abstract

Aspergillosis is an opportunistic fungal infection that may develop in immunocompromised patients with conditions such as leukemia or aplastic anemia. A rare case of stomach perforation following acute fungal gastritis in a 13-year-old female patient with aplastic anemia is reported herein. The patient had developed aplastic anemia without bone marrow fibrosis secondary to acute lymphoblastic leukemia and chemotherapy. The pathological examination revealed a large ischemic transmural perforation (9.5 × 9 cm) associated with fungal septic emboli. Fungal hyphae characteristics were compatible with those of *Aspergillus* spp. There are few reports identifying fungi as agents associated with gastric perforation. There is a need for early identification of the infectious agent.

Key words: aspergillosis; gastric perforation; leukemia; aplastic anemia

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Introduction

Gastric wall perforation caused by fungal agents is very rare, even in adult patients. It is seen mostly in some immunocompromised patients, or in some healthy subjects with habitual use of strong antacids [1]. Although gastric perforation is uncommon in children and is usually associated with prematurity, foreign bodies, trauma, or even anorexia nervosa [2], there are few reports identifying fungi such as Mucormycetes and species of *Aspergillus* and *Candida* as causing agents. We report a case of a fungal infection, presumably due to *Aspergillus* spp., in a pediatric patient with aplastic anemia secondary to chemotherapy due to acute lymphoblastic leukemia (ALL) who was unsuccessfully treated, with a fatal outcome as a consequence.

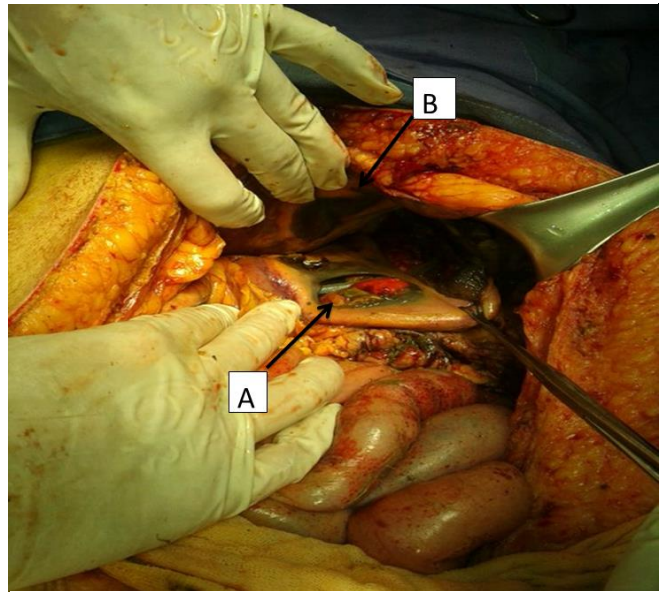
Case Report

The case of a 13-year-old female who presented with neutropenic fever, abdominal pain, mucositis, and constipation is presented. Previously, she had received chemotherapy (the Larson regimen) for a period of 30 months because she suffered from acute lymphoblastic

leukemia (ALL). Secondary to this condition, she presented aplastic anemia without bone marrow aplasia two months before admission to Central South Hospital from Petroleos Mexicanos. Upon admission, her blood examination results were as follows: hemoglobin, 7.7mg/dL; hematocrit, 21.2%; white blood cell count, 130 cells/μL; neutrophils, 31%; lymphocytes, 30%; and platelets, 35,000 cells/μL. Blood cultures were negative; serology tests for cytomegalovirus (CMV) and Epstein-Barr, as well as urine polymerase chain reaction (PCR) for herpes simplex virus 1 (HSV-1) and HSV-2, human herpesvirus 6 (HHV-6) and CMV were negative. A galactomannan test was not performed as it was not available in the hospital. Chest radiographs were unremarkable. The abdominal ultrasonography showed an intestinal wall thickening of 2.5 mm and intestinal distension, interpreted as colonic inflammation. The patient was treated with meropenem (20 mg/kg every eight hours for 10 days), with which fever remitted. After completion of the treatment with meropenem, ciprofloxacin (1 g per day for 4 days) and fluconazole (200 mg/day for 12 days)

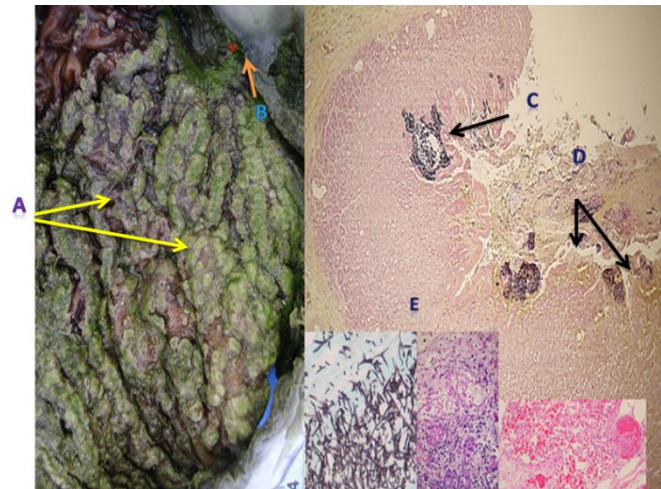
were administered as prophylaxis because of persistent neutropenia. As the alterations of the hematological parameters persisted, five doses of methylprednisolone and thymoglobulin pulses were administered, as indicated for this condition. Five days later, she reported hypogastric and left upper quadrant pain, radiating to the left shoulder and increasing with inspiration. The abdominal ultrasonography showed a 3.7 mm intestinal wall thickness. Based on the clinical and radiological data, a diagnosis of neutropenic colitis was set. Fasting with the support of calculated solutions, orogastric probe, and parenteral nutrition were applied, and meropenem (20 mg/kg every eight hours) was restarted. For a week, her condition evolved with a partial decrease of the symptoms until she presented fever, tachycardia, tegument pallor, hypo activity, nasal flutter, oliguria, abundant transvaginal bleeding, and hematuria. The abdominal pain increased, auscultation revealed no peristalsis, and the abdominal perimeter had increased 7 cm from baseline (93 cm). The computed tomography (CT) scan revealed intestinal perforation. An exploratory laparotomy and washing of the abdominal cavity were done. The laparotomy revealed 600 cc of liquid without biliary traits and with food remainders; there was also necrosis and an 80% perforation of the gastric anterior wall, in whose lumen appeared circular injuries with raised edges. In the small intestine, ecchymotic areas were observed. The descending colon did not show evidence of perforation, and in the liver, an approximately 5-cm necrotic lesion with an edge was found (Figure 1). The following procedures were performed: subtotal gastrectomy, decompressing gastrostomy, yeyunostomy, and placement of drainages. Because a fungal infection was possible according to the surgical findings despite fluconazole prophylaxis, caspofungin (50 mg per day, every 24 hours) was administered. The patient showed a poor postoperative course; she continued with pancytopenia, hydro-electrolytic imbalance, and metabolic acidosis. Three days after surgery, she presented signs of disseminated intravascular coagulation and liver failure. Five days after surgery, she presented severe hypotension, less than 70% desaturation, and bradycardia, and did not respond to advanced reanimation maneuvers. The pathological examination confirmed the presence of a large ischemic transmural perforation (9.5 × 9 cm), associated with septic emboli with fungal microorganisms morphologically compatible with *Aspergillus* spp. (Figure 2). Microbiological tissue cultures were not performed.

Figure 1. Exploratory laparotomy



Loss and necrosis in 80% of anterior stomach wall (A). Necrotic lesion of the inferior face in the gastric pit of the left lobe of the liver (B).

Figure 2. Pathology examination results



Left: Macroscopic appearance of the gastric mucosa with micronodules of necrosis, fibrin pseudo-membranes and ischemia wall (A), and perforation area on the top (B). Right: Histological picture of the gastric mucosa with abundant fungal microorganisms corresponding to *Aspergillus* sp. into the lumen alternating with mucosal ulceration (C). Bottom panels with black stained hyphae, compatible with those of hyaline molds, including *Aspergillus* (Grocott's methamine silver stain) (D), and intravascular pink-stained hyphae (PAS stain) (E).

Discussion

Fungi are a rare cause of gastric perforation, since stomach pH does not allow their development [3]. Thus, the pathogenesis of this condition implies the participation of multiple factors [4]. Patients on

chemotherapy have a high risk of infection by fungi due to neutropenia, and the risk is substantially increased in cases of absolute neutropenia [5].

To find previously published cases of gastric wall perforation by aspergillosis in children, a literature search was conducted using Pubmed. The search strategy used combinations of the terms gastric perforation and mycotic infection. The reference lists of the retrieved articles were searched to identify additional publications. A total of 42 articles were found in Pubmed; only 10 involved children with gastro-intestinal perforation by fungal agents. Mucormycosis is the fungal infection with the highest number of reported cases of gastric perforation, most of them in premature or malnourished children. [6-9]. A case of *Candida tropicalis* cells infiltrating the submucosal margins of an acutely perforated gastric ulceration in an immunocompetent 3-year-old girl was also reported [10].

There were two reports identifying *Aspergillus* as an agent associated with gastric perforation in children. In 2013, Karaman *et al.* reported a case of invasive aspergillosis in a 13-year-old girl with multiple congenital arthrogriposis and stomach necrosis. Their review included four more cases in adults found in the medical literature: three on steroid treatment and one on chemotherapy. All of them had necrosis, ulceration, and the presence of hyphae invading or surrounding the ulcer area [11]. Franciosi *et al.* (2002) reported the case of a 2-year-old child, the son of consanguineous parents and heterozygous for Di George's syndrome [12]. Epstein-Barr infection was suspected and was treated with steroids. Posteriorly, the patient developed melena and peritonitis; six perforations on the anterior and three perforations on the posterior gastric wall by *Aspergillus* spp. were documented. Both children recovered with treatment. As aspergillosis and mucormycosis share similar clinical presentations and radiological findings, histopathological distinction between mucormycosis and aspergillosis is important. In aspergillosis, hyaline and septate, dichotomously branched fungal hyphae of uniform diameter, are observed; conidial heads are occasionally observed. In mucormycosis (infection caused by zygomycetes of the order Mucorales such as *Rhizopus*, *Mucor*, and others), broad, thin-walled, hyaline, aseptate or sparsely septate hyphae with right-angle branching are observed instead. Necrotizing inflammation is present in both infections [13].

The present case describes the progress towards severity of a girl with aplastic anemia, treated with

broad-spectrum antibiotics in order to decrease the risk of serious infection. The developed fungal infection was presumed to be aspergillosis based only on histopathologic characteristics, as the fungus was not grown in culture. Although an antifungal agent was used, deterioration was evident; fluconazole is usually effective against *Candida* but not against *Aspergillus*. Due to the negative blood cultures, a more appropriate antifungal was introduced only at a late stage. In cases of aspergillosis, blood cultures are not a useful tool, as they almost invariably yield a negative result [14].

Data to guide management of children with invasive fungal infections are limited, but it appears that treatment recommendations are similar for pediatric and adult patients. [15]. According to the guidelines of the Infectious Diseases Society of America [16], empirical or preemptive antifungal therapy with amphotericin B (AMB), a lipid formulation of AMB, itraconazole, voriconazole, or caspofungin is strongly recommended for high-risk patients with prolonged neutropenia who remain persistently febrile despite broad-spectrum antibiotic therapy. The frequency of aspergillosis among children with neutropenic colitis in our hospital however, is low [17], which explains why antifungals were not included in the primary treatment of our patient. Caspofungin was started when the surgical evidence was found and was used briefly. Voriconazole is the recommended primary antifungal therapy of invasive aspergillosis [16]; in our case, it was not used because it was not available in our hospital.

The child with cancer is the most predisposed host to aspergillosis due to neutropenia caused by the use of chemotherapy. The most common forms of the infections among these children involve the lungs, the paranasal sinuses, and the brain [18]. Infection with *Aspergillus* spp. is initiated following inhalation of airborne spores of this ubiquitous fungus. *Aspergillus* hyphae are angiotropic and adhere to and invade the abluminal surface of vascular endothelial cells to gain access to the vascular compartment; hyphal fragments can disseminate to distal sites where they adhere to the luminal surface of endothelial cells before traversing them and invading into deep tissues [19]. *Aspergillus* spp. that invade the gastric mucosa require a lesion in that area due to ischemia, which is a predisposing factor for the development of the infection originated in distant tissues and spreading through the bloodstream as septic emboli, including to the intestines and the liver [20].

Conclusions

Our case emphasizes the fungal etiology of gastric perforation, a rare and serious medical condition that requires immediate medical attention. In our case, an inflammatory infiltration of the stomach wall by a filamentous, non-mucoralean fungus, presumably *Aspergillus*, leading to perforation was confirmed. To our knowledge, only two cases of gastric perforation by *Aspergillus* spp. have been previously reported in pediatric patients.

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