Neonatal gastrointestinal mucormycosis in an asphyxiated premature newborn

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Mucormycosis of the intestine is a rare fungal infection of childhood and is mostly encountered in neonates. It is a potentially lethal opportunistic fungal infection with rapid progression and high mortality in immunocompromised patients. The number of reported cases with intestinal mucormycosis is 19 to date. We herein report an asphyxiated preterm infant with intestinal mucormycosis who was presented with an atypical necrotizing enterocolitis (NEC), with findings similar to an intraabdominal mass. The diagnosis was made in the postmortem examination of the surgically removed bowel segment. Prematurity and asphyxia are important risk factors for mucormycosis. We suggest that the diagnosis of gastrointestinal mucormycosis should be considered in the differential diagnosis of atypical NEC cases.

Key words: premature, asphyxia, gastrointestinal system, mucormycosis.

Mucormycosis, or zygomycosis, is an opportunistic infection caused by a filamentous fungus of the group Mucorales[1-3]. Pathogens mostly involve the sinuses, oral cavity, brain, gastrointestinal tract (GIT), skin, or lungs in immunocompromised patients[1,3]. Mucormycosis of the intestine is rare and difficult to recognize. Thus, it is usually fatal in neonates, especially in prematures. Clinical presentation of intestinal mucormycosis usually mimics an atypical necrotizing enterocolitis (NEC) in neonates[4-6]. Therefore, definitive diagnosis is generally made in autopsies[7].

Here, we describe a neonatal intestinal mucormycosis in a 15-day-old premature newborn with the presumptive diagnosis of NEC; the definitive diagnosis was made upon histopathological examination of the resected intestine.

Case Report

An eight-hour-old male newborn, born by cesarean section at the 27th week of gestation with a birth weight of 900 g, was admitted to our neonatal intensive care unit with respiratory distress after surfactant replacement therapy. Apgar scores were 1 and 6 at the first and fifth minutes, respectively. The mother's medical history revealed neither an eventful pregnancy nor premature rupture of membranes. On examination, he had respiratory distress with tachypnea and intercostal retractions. He required a second dose of surfactant and assisted ventilation with a conventional mode. Minimal enteral nutrition was started on the third day with a gradual increase and without any intolerance. On the 11th day, a mass in the right lower quadrant was palpated and an erythema on the abdominal skin on the same side was observed. Occult rectal bleeding test was negative, there was no abdominal tenderness or distention, and the baby was stable. Complete blood count and C-reactive protein levels were normal. Abdominal radiographs showed a paucity of bowel gas, which was localized to the right lower quadrant (Fig. 1). Systemic antibiotics (ampicillin-sulbactam, cefotaxime sodium and metronidazole intravenous [i.v.]) were commenced on suspicion of NEC after obtaining a blood culture. Nothing was given orally to the baby and orogastric drainage was provided. During the subsequent four-day period, the patient had no vomiting. There were

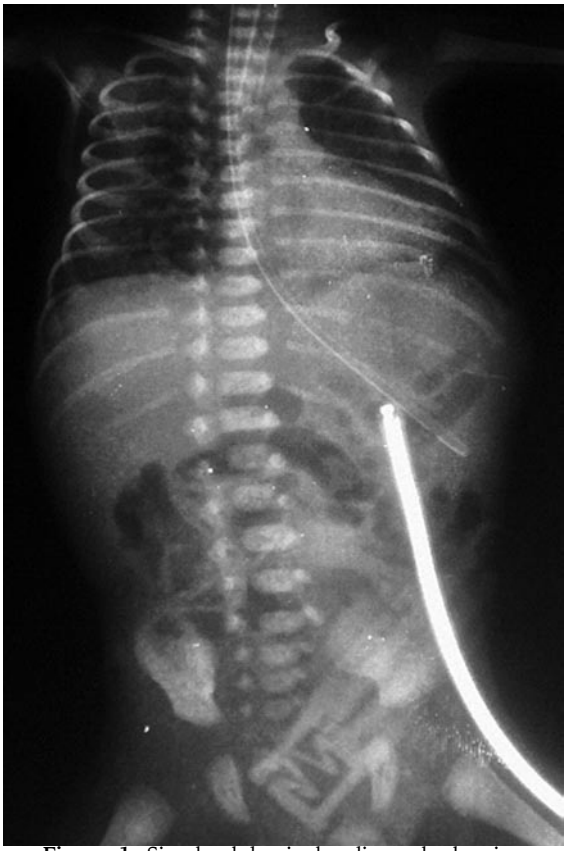

Figure 1. Simple abdominal radiograph showing a paucity of intestinal gas with no pneumatosis intestinalis or free intra-abdominal air.

also no hematologic or electrolyte abnormality, hypotension or metabolic acidosis. The occult blood test was still negative. However, the clinical status of the patient did not improve. The signs of absent bowel gases continued without sub-diaphragmatic intraperitoneal free gas. Minimal free fluid was detected in the abdominal space on ultrasonographic examination. Meconium-stained fluid and leukocytes in large numbers were detected in the sample obtained via paracentesis, suggesting a closed intestinal perforation. An exploratory laparotomy was performed immediately. During the surgery, wide necrotic areas were observed, starting at about 10 cm proximal to the ileocecal valve and extending to the ascending colon segment. Additionally, a ball formed by the intestine was noticed. The ileocecal valve, located in the center, was surrounded by omentum. The abdominal cavity was not filled with meconium-stained fluid. Resection of the necrotic segment with ileostomy was performed. The child died within the postoperative 8th hour. The resected bowel specimen was a 10-cm long segment of the distal ileum with ileocecal valve and half of the ascending colon. The specimen was necrosed and grayish-brown in color macroscopically. Histopathologic sections from the involved segments showed areas of congestion, necrosis and transmural inflammation without any evidence of gas-filled vesicles in the intestinal wall (Fig. 2a). Twisted and collapsed broad hyphae of fungi in varying thicknesses with infrequent branching were predominantly within the lumen of the vessel and infiltrating the vessel wall, but could be seen in numerous places on the intestinal wall (Fig. 2b).

Discussion

Mucormycosis, which accounts for 10% of all mycotic infections, is a rare opportunistic and usually fatal infection caused by fungi of the order Mucorales. Mucorales, also called Mucor, are within the class Zygomycetes including the genera Absidia, Mucor, Rhizomucor, and Rhizopus[1,3]. These fungi are ubiquitous saprophytes of soil and decaying vegetable matter producing large numbers of airborne spores[3]. The most common genera causing disease in humans include Mucor, Rhizopus and Absidia[1,3].

The clinical entities caused by Mucor are named based on the involved part of the body, such as rhinocerebral (39%), pulmonary (22%), cutaneous (16%), GI (4%), and disseminated mucormycosis (16%)[8]. According to a review

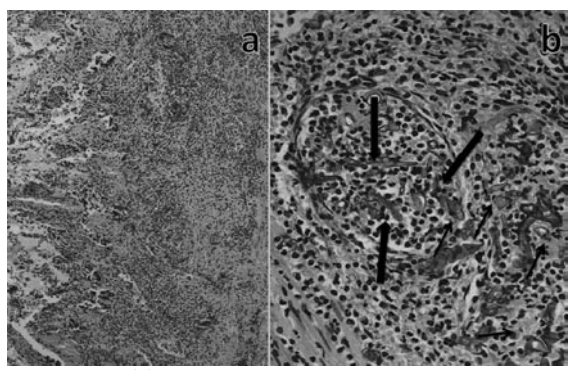

Figure 2: (a) Transmural ischemic intestinal necrosis and inflammation (hematoxylin & eosin [H&E] × 40). **(b)** A thrombus is seen in the intestinal vessel lumen with many hyphae of fungi (large arrows). Invasion and penetration of the vessel wall by broad hyphal filaments of Zygomycetes/mucor (large arrows) and tissue involvement (small arrows) are shown (H&E × 100).

of the literature, 19 cases of infants with GI mucormycosis have been reported to date[5,6]. Considering the overall low percentage of mucormycosis among fungal infections and the low percentage of the GIT type among the different types of mucormycosis, our case report highlights the rarity of mucormycosis of the GIT.

Children account for one-third of all patients with mucormycosis of the GIT, and additionally, 50% of children with mucormycosis of the GIT are infants[9,10]. The most commonly invaded GIT sites are as follows: gastric and colonic mucosa (50%), small intestine (39%) and esophagus (11%). Furthermore, multiple GIT sites with spread of infection to adjacent organs occurred in 39% of infants, with disseminated disease beyond the abdominal cavity in 17%[6]. Reported mortality rates range from 38% to 80%, with the higher rates being associated with delay in recognizing the infection[1,3,11]. Survival depends upon multiple factors, such as the extent of disease, whether it is localized or systemic, the immunological status of patient, and the virulence of the organism. Among the reported 19 patients with mucormycosis of the GIT (13 premature, 6 term), only seven cases survived, three of whom did not receive amphotericin B treatment. A pre-mortem diagnosis was made in only five (26%) cases[5,6].

The major risk factors for mucormycosis are diabetes and diabetic ketoacidosis, neutropenia, severe malnutrition, sustained immunosuppressive therapy, prolonged treatment with corticosteroids, prematurity, and iron overload with or without the concomitant chelation therapy[1,12]. The fungus gains entry to the GIT by the ingestion of fomites contaminated with fungal spores or by swallowing infected sputum, or by hematological dissemination from other primary sites of infection[5,13]. Breakdown in the integrity of the intestinal mucosal barrier or local damage caused by medical/surgical procedures or diseases facilitates the establishment of infection[5,13]. In the macroscopic examination, the lesion of the mucormycosis of the GIT resembles a crater, ulcerating and necrotic with clear demarcated edges. Microscopically, the most characteristic feature of mucormycosis is the perivascular and blood vessel invasion. Invasion by Mucorales results in more arterial than venous thrombosis. Eventually, an ischemic and hemorrhagic necrosis occurs[5,7].

Necrotizing enterocolitis (NEC), which is the most common GI surgical emergency, is a multifactorial illness in which perinatal and postnatal factors reducing GIT blood flow have been implicated. Although the exact etiology remains unknown, ischemia and/or reperfusion injury with activation of pro-inflammatory cascades and intestinal mucosal immaturity or dysfunction may play a significant role[14,15]. Moreover, perinatal asphyxia has a major detrimental effect on bowel perfusion as in the whole body. Intestinal ischemia results in intestinal necrosis and breach of the mucosal barrier[14,15]. Additionally, invasion of fungi as well as bacteria could be secondary to the combination of lack of vascular support of the GIT in premature neonates, who suffered asphyxia due to impaired mucosal barrier functions, as in our patient. Hence, one could infer that mucormycosis of the GIT may be a variant of NEC, but pneumatosis intestinalis is not seen and it does not respond to antibiotic treatment during the course[5-7]. Treatment of the suspected NEC cases included orogastric drainage and antimicrobial treatment. Choices of empirical antimicrobial treatment in suspected NEC cases tend to be multiple antibacterial agents including Gram-negative, Gram-positive and anaerobes[16]. In our case, we started broad-spectrum antibiotic treatment empirically.

Early diagnosis of such a fatal disease is very important, but it is also very difficult. Blood cultures are rarely useful[1,11]. Although it is not possible in closed organ systems, a tissue biopsy should be obtained to identify hyphae on the microscopic examination. The different genera and species of Mucorales cannot be distinguished morphologically in tissue sections. Therefore, microbiological study of the biopsy samples of the lesion is important to establish the class, order and genus of the causative agent in involved organs that are easily accessible, such as skin, oral cavity and sinuses[17]. All cases reported thus far, with the exception of two, had been infected with Rhizopus spp.[6]. More importantly, most of these fungi are resistant to the currently available azole and echinocandin antifungals[1]. In vitro synergistic activity between amphotericin B and rifampicin has been reported[18]. Aggressive

treatment needs to be instituted without waiting for culture results. Unfortunately, in the present case, the definitive diagnosis of the GI mucormycosis was made in the resected bowel segment postmortem. Therefore, systemic antifungal medication such as amphotericin B was not included in the empirical antibiotic treatment.

In conclusion, we present a case, known to be rare, with mucormycosis of the GIT in a preterm newborn. Our patient showed an atypical course of the NEC features like other cases in the literature. We argue that premature infants, especially those undergoing asphyxia, should be evaluated as individuals at risk for invasive zygomycotic disease. We conclude that establishment of mucormycosis of the GIT can be facilitated in premature infants having varying immune deficiencies[19], immature intestine[14,15] and intestinal hypoxia[15] caused by perinatal asphyxia. Additionally, adding amphotericin B to the empirical broad-spectrum antibiotic treatment may be useful for such asphyxiated premature infants demonstrating an atypical course of NEC.

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