Gastrointestinal Mucormycosis in Extremely Low Birth Weight Infants Mimicking Atypical Necrotizing Enterocolitis and Intussusception

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ABSTRACT

Neonatal gastrointestinal mucormycosis, a rare disease with a high mortality rate, shows a rapid progressive course in premature infants with an immature immune system. We report the case of a male neonate weighing 970 g, delivered via cesarean section at 27 weeks, as one of a pair of dizygotic twins. From the 7th day after birth, bile was seen to drain through the orogastric tube, and paralytic ileus was noted on performing an abdominal X-ray. Thus, oral feeding was discontinued because necrotizing enterocolitis (NEC) was highly suspected. On the 9th day after birth, a firm mass was palpable in left upper abdominal quadrant, but no pneumatosis intestinalis was observed on performing abdominal X-ray. Small bowel intussusception was suspected on performing abdominal ultrasonography. Based on these findings, an exploratory laparotomy was performed, and although no intussusception was found intraoperatively, we performed a partial gastrectomy and hemicolectomy due to the presence of necrotic changes and perforations of the stomach and colon. Postoperatively, he was observed to have hypotension with persistence of hemorrhage at the surgical site. He died on the 11th day after birth. Intraoperative histopathological examination of stomach and colon showed fungal aseptate hyphae with broad branching. Gastrointestinal mucormycosis was confirmed based on findings of vascular involvement in the form of fungal hyphae and thrombosis in the transmural blood vessels. We report a case of an extremely low birth weight infant with neonatal gastrointestinal mucormycosis with an initial clinical presentation suggestive of intussusception and atypical NEC.

Key Words: Mucormycosis, Necrotizing enterocolitis, Intussusception, Low birth weight infant, Candida, Fungi

INTRODUCTION

Mucormycosis is a rare and fatal opportunistic fungal infection, with gastrointestinal mucormycosis affecting approximately 7% of all patients with this condition. The gastro-

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intestinal tract is the most common site of involvement of the fungal infection in neonates, and the condition is characterized by rapid progression due to an immature immune system in these patients, particularly in premature neonates. In neonates, the most frequent site of infection is the large bowel (74%), followed by the stomach and small bowel (37%)\(^2\). Most cases clinically are misdiagnosed as necrotizing enterocolitis (NEC) or intussusception and the diagnosis is only confirmed by performing histopathological examination after surgery, or death. Although a few cases have been reported globally, cases of gastrointestinal mucormycosis in premature Korean infants have not yet been reported. Therefore, it is difficult to identify and establish a clinical diagnosis for this disease. About 26% of cases are diagnosed before death, but most cases are diagnosed postmortem, and their mortality rate ranges between 38% and 80%\(^3\). After investigating the clinical features of gastrointestinal mucormycosis and its differential diagnosis, we concluded that it mimics the clinical presentation of other similar diseases. We wish to report this case as one that can help clinicians diagnose and treat this rare condition.

**CASE REPORT**

A male neonate, one of a pair of dizygotic twins, was delivered via cesarean section at 27 weeks’ gestation. He weighed 970 g, and Apgar scores were 1 and 4 at 1 and 5 minutes, respectively. He was admitted to the neonatal intensive care unit (NICU) with respiratory distress. His mother had been treated for candida vaginitis at 25 weeks of gestation. Also *Ureaplasma urealyticum* were identified in the mother’s vaginal culture at 26 weeks of gestation, and chlamydia was found to be weakly positive on performing polymerase chain reactions at 27 weeks of gestation right before childbirth. Later during pregnancy, she had developed hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, which had led to the emergency cesarean section. On the date of delivery, the mother’s white blood cell (WBC) was 13,800/µL, the number of platelets (PLT) was 16,000/µL, and her C-reactive protein (CRP) level was 8.8 mg/dL.

A surfactant was used on the 1\(^{st}\) day after birth after diagnosing respiratory distress syndrome in the newborn, and nasal continuous positive airway pressure (NCPAP) was instituted after extubation on the 3\(^{rd}\) postnatal day. Blood tests revealed a WBC count of 4,200/µL, PLT 232,000/µL, and CRP 0.2 mg/dL. Ampicillin-sulbactam, cefotaxime, fluconazole, and azithromycin were administered on the first day of birth for suspected early-onset sepsis and *Candida* infection. From the second day after birth, the patient was fed 2 mL of formula every 8 hours, and prophylactic ibuprofen was administered on the first day of birth for patent ductus arteriosus (PDA).

On the 4\(^{th}\) day after birth, transthoracic echocardiography confirmed closure of the PDA, and no intraventricular hemorrhage was observed on ultrasonography of brain. His vital signs remained stable until the 6\(^{th}\) day of birth, and feeding progressed smoothly and was increased by 4 mL every 3 hours.

On the 7\(^{th}\) day after birth, he showed good activity levels and stable vital signs. However, he was noted to have bile draining through the orogastric tube, and physical examination showed a soft abdomen with some distension. Because an abdominal X-ray showed air shadows primarily on the right side (Figure 1A), and blood tests revealed an elevation of CRP and a decrease in PLT, he was maintained on a nil per os (NPO) status for suspected NEC. Blood tests revealed WBC 6,900/µL, PLT 117,000/µL, and CRP 3.3 mg/dL. The antibiotics were changed to vancomycin and meropenem, and fluconazole was continued. On the 8\(^{th}\) day after birth, an abdominal X-ray showed intestinal air shadows that were localized predominantly to the right side (Figure 1B), and metabolic acidosis was evident on venous blood gas analysis (VBGA) at pH 7.191, pCO\(_2\) 43.3 mmHg, and HCO\(_3^−\) 16.7 mmol/L.

On the 9\(^{th}\) day after birth, a firm mass could be palpated in the left upper abdomen with a change of skin color observed. Blood tests revealed WBC 2,900/µL, PLT 40,000/µL, CRP 19.7 mg/dL, VBGA showing pH 7.029, pCO\(_2\) 74.1 mmHg, and HCO\(_3^−\) 19.7 mmol/L. Metronidazole was added to the antibiotic regimen, and fluconazole was replaced with amphotericin B liposome. Additionally, endotracheal intubation was performed and a ventilator was used because of the development of metabolic and respiratory acidosis. Abdominal X-ray and ultrasonography showed no pneumatosis intestinalis, free intra-abdominal air, and/or portal venous gas (Figure 1C), but a mass-like lesion, detected in the small intestine, suggestive of small bowel intussusception (Figure 2) necessitated an exploratory laparotomy. Intraoperatively, we noted adhesions of the stomach and colon due to perforations and multiple necrotic changes in the anterior and posterior walls of the stomach and the distal transverse to proximal descending colon. Therefore, a partial gastrectomy and hemicolectomy were performed. However, small bowel intussusception was not observed. Postoperatively, he...
demonstrated persistent hypotension, which failed to respond to inotropic agents. Despite repeated transfusions of packed red blood cells, platelet concentrates, and fresh frozen plasma, the patient died on the 11th day after birth (2nd postoperative day) because of persistent and worsening bleeding at the surgical site. Intraoperative histopathological examination of stomach and colon showed fungal aseptate hyphae with broad branching (Figure 3A). Gastrointestinal mucormycosis was confirmed based on findings of vascular involvement in the form of fungal hyphae and thrombosis (Figure 3B) in the transmural blood vessels. Blood cultures obtained on day 1, 7, and 9 after birth revealed no bacteria.

The patient had a twin sister who weighed 900 g at birth, with Apgar scores of 3 and 6 at 1 and 5 minutes, respectively. She was admitted to the NICU because of respiratory distress, which resolved with oxygen treatment for 33 days. After 84 days of hospitalization, she was discharged with a weight of 2,780 g at the corrected age of 38 weeks and 6 days. She showed no complications other than requiring laser treatment for retinopathy. Prophylactic amphotericin B was prescribed for a month after her brother was diagnosed with mucormycosis, because we considered the possibilities of vertical mother to child transmission for both twins. At the beginning of the treatment, her blood tests showed WBC 15,600/µL, PLT 120,000/µL, and her PLT showed a decreasing trend. Moreover, she showed feeding intolerance and apnea, which required NCPAP.

**DISCUSSION**

Zygomycosis refers to opportunistic fungal infections caused by fungi belonging to the class Zygomycetes. They are found globally, primarily in the soil, in decayed plants and animals, aged cheese, rotten fruits, and stale bread. This Zygomycetes class is divided into two orders—Mucorales and Entomophthorales. Among these, infections caused by Mucorales, called mucormycosis, are characterized by rapid progression due to an immature immune
Any part of the gastrointestinal tract could be affected in this group, although the most common site of involvement is the gastric and colonic mucosa (50%), the small bowel (39%), and the esophagus (11%). However, in neonates, the colon (74%) is the most commonly involved site, followed by the gastric mucosa and small bowel (37%), the appendix (16%), and extraintestinal involvement (26%). Perforation of the stomach or bowel wall is likely to occur. In this patient, perforation was observed with necrotic changes and adhesions involving the gastric and colonic mucosa.

Clinically, patients with gastrointestinal mucormycosis usually present with abdominal pain and distension, hematemesis, hematochezia, and melena. Previously, it was considered a variant of NEC because nonspecific symptoms observed in this condition were not easily distinguishable from NEC. A comparison between the pathophysiology of NEC and gastrointestinal mucormycosis reveals that NEC is caused due to intestinal reperfusion injury following which the affected intestinal tract becomes moist and congested leading to its necrosis, while gastrointestinal mucormycosis is caused by vascular thrombosis of the affected mesenteric artery resulting in a dry, avascular bowel, and infarction. Additionally, the intestine affected by gastrointestinal mucormycosis becomes adherent to the surrounding healthy area in order to absorb oxygen. Moreover, in patients with gastrointestinal mucormycosis, symptoms such as a palpable abdominal mass and abdominal distension appear before the onset of features associated with NEC such as intestinal perforation, rectal bleeding, or pneumatosis intestinalis.

In this case, abdominal distension was noted in the neonate system in patients, such as premature infants. Siu and Lee reported that low birth weight infants are highly vulnerable to mucormycosis infection. Factors predisposing them to infection are as follows: (1) an immature immune system. (2) a fragile skin barrier. (3) the need for long-term treatment in the NICU. (4) nursing in a highly humid environment (approximately, 85%), which is suitable for the growth of Mucorales. (5) steroid administration to help weaning from the ventilator. (6) administration of a broad range of intravenous antibiotics that tend to affect healthy normal gastrointestinal flora. Additionally, intubation and indomethacin treatment increase the risk of gastrointestinal mucormycosis by causing mucosal damage. Lowe et al. have described prematurity as an independent risk factor and 74% of neonatal mucormycosis patients were preterm infants with a median gestational age of 28 weeks.

Mucormycosis is classified into sinus/rhinocerebral, pulmonary, cutaneous, gastrointestinal, and disseminated types, based on clinical features and anatomical sites of involvement. Gastrointestinal mucormycosis is the rarest form, accounting for only 7% of all types of mucormycosis. However, in neonates, the gastrointestinal type (51%) is the most common variety, followed by cutaneous involvement (36%). Gastrointestinal mucormycosis is known to occur following the ingestion of fomites contaminated with fungal spores, swallowing infected sputum, or through hematogenous dissemination from the primary site of infection. Use of adhesive tape, monitor leads, or sites of insertion of central venous catheters are the most common modes of transmission in newborns. One-third of all patients with gastrointestinal mucormycosis are diagnosed early in childhood, among which 50% are infants. Any part of the gastrointestinal tract could be affected in this group, although the most common site of involvement is the gastric and colonic mucosa (50%), the small bowel (39%), and the esophagus (11%). However, in neonates, the colon (74%) is the most commonly involved site, followed by the gastric mucosa and small bowel (37%), the appendix (16%), and extraintestinal involvement (26%). Perforation of the stomach or bowel wall is likely to occur. In this patient, perforation was observed with necrotic changes and adhesions involving the gastric and colonic mucosa.
on the 7th day of birth, and a firm mass was palpable in the left upper quadrant of the abdomen on the 9th day of birth. Inoue et al. have reported that a palpable abdominal mass is not one of the first symptoms to present in patients with NEC, but is one of the early symptoms in cases of gastrointestinal mucormycosis. Additionally, Sarin has reported that gastrointestinal mucormycosis should be suspected in low birth weight infants with clinical features suggestive of NEC in the presence of persistent neutropenia or if they show a slowly progressive need for enteral nutrition despite treatment with various antibiotics. In addition to NEC, intussusception is also difficult to differentiate from gastrointestinal mucormycosis.

Agrawal et al. have reported a case of a newborn who was clinically diagnosed with intussusception and underwent exploratory laparotomy, but no intussusception was found intraoperatively. Gastrointestinal mucormycosis was later confirmed in this patient with histopathological examination. In our case, intussusception was suspected based on findings of abdominal ultrasonography; however, intraoperative histopathological examination confirmed gastrointestinal mucormycosis.

Diagnosis of gastrointestinal mucormycosis is based on identification of causative organisms in a culture or through biopsies performed on specimens obtained from suspected sites of involvement. On histological examination, Mucorales show broad, irregularly branching, and aseptate hyphae. Moreover, vascular thrombosis and infarction are hallmarks of mucormycosis infection. However, Patra et al. have proposed that a conclusive diagnosis of invasive mucormycosis is possible only through histopathological examination of specimens based on the fact that a blood culture can only prove the presence of the causative organism, but fails to demonstrate its invasion into blood vessels or mucous membranes.

The timing of the symptom occurrence could also help in the diagnosis of mucormycosis. NEC usually occurs within 2 or 3 weeks after birth, and most case of fungal colonization also occur between 2 to 3 weeks after birth. On the other hand, when we analyzed 13 cases of neonatal gastrointestinal mucormycosis, the symptoms occurred 8 days (3–15 days) after birth on average, and the first symptom occurred 7 days after birth in our case. Accordingly, it can be concluded that gastrointestinal mucormycosis occurs earlier than NEC or other fungus infections.

Drug therapy consists of long-term use of amphotericin B. Kliegman et al. have reported that amphotericin B deoxycholate (1–1.5 mg/kg/day to a total dose of 70 mg/kg) or amphotericin B lipid complex (3–5 mg/kg/day) can be successful in treating mucormycosis. Although fluconazole, which is generally used as a prophylactic antifungal drug, is useful, newer agents such as voriconazole and caspofungin are not effective for treatment of mucormycosis. Fluconazole was administered to our patient at birth but was not effective. Early diagnosis, prompt administration of IV amphotericin B treatment, and extensive surgical removal of the devitalized tissue are essential for optimal management of the condition.

In conclusion, as was demonstrated in this case, gastrointestinal mucormycosis should be considered in the differential diagnosis of premature or low birth weight infants with a clinical presentation suggestive of NEC. Additionally, this diagnosis should be considered in those showing a good systemic condition and activity, a palpable abdominal mass on physical examination, no evidence of pneumatosis intestinalis and air shadows localized predominantly to the right side on radiologic examination, a decreased WBC count on blood tests, and no response to conventional antibiotics. If gastrointestinal mucormycosis is suspected based on the clinical features of atypical NEC, as described above, conventional antimicrobial therapy with early amphotericin B should be considered, which may lead to more favorable prognoses.

REFERENCES