Kobe J. Med. Sci., Vol. 70, No. 2, pp. E66-E69, 2024

A Case of an Extremely Preterm Infant with Intussusception Triggered by Acquired Cytomegalovirus Infection

SANAE NAITO[1], SACHIYO FUKUSHIMA[2,*], TOMOAKI IOROI[2], CHIE SAKATA[2], DAISUKE KUROKAWA[2], TSUYOSHI EGAWA[2], YUDAI TSURUNO[3], MITSUMASA OKAMOTO[3], HIROAKI FUKUZAWA[3], and MASAAKI KUGO[2]

[1]*Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Japan;*
[2]*Department of Pediatrics, Japanese Red Cross Society Himeji Hospital, Himeji, Japan;*
[3]*Department of Pediatric Surgery, Japanese Red Cross Society Himeji Hospital, Himeji, Japan*
**Corresponding author*

Received March 8, 2024/Accepted April 22, 2024

Keywords: Intussusception in preterm neonates (IPN), Necrotizing enterocolitis (NEC), Acquired cytomegalovirus (aCMV) infection

Intussusception is a common cause of intestinal obstruction in infants aged 6–18 months. However, intussusception in preterm neonates (IPN) is an exceedingly rare disorder. The etiology of IPN remains unclear, but common prenatal injuries, such as those causing intestinal hypoxia/hypoperfusion, dysmotility, and strictures, have been proposed as possible contributing factors. Diagnosis is often delayed because the symptoms closely resemble those of necrotizing enterocolitis (NEC). Given the divergent treatments for IPN and NEC, establishing an early and accurate diagnosis is crucial. IPN is predominantly located in the small intestine (91.6%), and ultrasonography proves useful in its diagnosis. We present a case of a very preterm infant who developed intussusception triggered by acquired cytomegalovirus (aCMV) infection, necessitating surgical treatment. The cause of intussusception in this case was diagnosed as aCMV enteritis because no organic lesions were observed in the advanced part of the intussusception. The presence of CMV was confirmed by CMV-DNA-PCR examination of the resected intestinal tract. Intestinal edema and decreased intestinal peristalsis due to aCMV enteritis are likely the primary causes of the intussusception.

INTRODUCTION

Intussusception is a common cause of intestinal obstruction in infants aged 6–18 months; however, IPN is an exceedingly rare disorder [1]. Distinguishing IPN from necrotizing enterocolitis (NEC) is challenging, as classical presentations of intussusception, such as an abdominal mass, vomiting, and bloody stools, are not commonly observed in IPN [1–4]. In most reported cases, diagnosis was achieved after an average of 9.8 ± 7.5 days from the onset of symptoms [1, 3]. Given the differences in the treatment of IPN and NEC, establishing an early and accurate diagnosis is imperative.

In this report, we present a case of a very preterm infant who developed intussusception triggered by acquired cytomegalovirus (aCMV) infection, necessitating surgical treatment.

CLINICAL CASE

A male infant weighing 673 g was delivered by emergency cesarean section at 24 weeks and 3 days of gestation due to fetal membrane rupture in the first trimester and difficulty in controlling uterine contractions. The mother had previously experienced four pregnancies with no births, and cytomegalovirus (CMV) serological testing was not conducted prenatally. Following birth, the infant developed respiratory distress syndrome and required intubation and ventilation. Enteral feeding with expressed breast milk commenced on day of life (DOL) 1 and increased steadily thereafter.

On DOL 53, the infant exhibited abdominal distention and worsening apnea, accompanied by sepsis-like symptoms. Treatment with meropenem (MEPM) and teicoplanin (TEIC) was initiated, and thrombocytopenia progressed, necessitating platelet transfusion. Urinary CMV-DNA-PCR performed at DOL 55 was positive and CMV-DNA-PCR of the dried umbilical cord at birth was negative, leading to a diagnosis of aCMV infection. We used the dried umbilical cord at birth as a surrogate test because we had no urine remaining from the first

Phone: +81-79-294-2251 Fax: +81-79-296-4050 E-mail: sachiyo425@gmail.com

three weeks of life. Although the possibility of false negative results cannot be ruled out with dried umbilical cord, the clinical manifestations suggestive of congenital CMV (cCMV) infection, such as intracranial calcification, enlarged ventricles, microcephaly, thrombocytopenia, liver dysfunction, and deafness, were not present from birth, and the possibility of cCMV infection was considered unlikely. The presence of sepsis-like symptoms, thrombocytopenia, and hepatic dysfunction, which were consistent with aCMV infection, led us to believe that the patient had aCMV infection overall. On DOL 62, white stools appeared, and ursodeoxycholic acid was initiated to treat biliary stasis and slow the progression of liver damage caused by the CMV infection.

On DOL 84, sudden worsening of abdominal distention (Fig.1a) and white watery stools were observed again. The gastrointestinal series showed no intestinal transit disorder, and the patient was diagnosed with aCMV enteritis and managed with fasting. After fasting, abdominal distention improved; however, it recurred when enteral feeding resumed. On DOL 93, apnea, severe abdominal distention, poor general color, and poor vitality were observed.

The patient was diagnosed with septic shock, reintubated, and treated with immunoglobulins, MEPM, and TEIC. On DOL 94, exchange transfusion was performed, and daily platelet transfusions were required thereafter. On DOL 95, rapid progression of anemia and bloody stools occurred, with abdominal ultrasonography revealing a target sign (Fig. 1b). Contrast-enhanced computed tomography (CT) of the abdomen confirmed ileo-ileal intussusception, prompting an emergency laparotomy on the same day. Approximately 30 cm of ileo-ileal intussusception was observed near the distal end of the ileum (Fig. 2). No intestinal perforation occurred, and ascitic fluid appeared clear and yellow without turbidity or hematogenous discharge. Manual repair proved challenging, leading to intestinal resection and enterostomy. Resected intestinal tissue showed no mass lesions causing intussusception, and most of the glandular epithelium was necrotic and desquamated. No nuclear viral inclusion bodies characteristic of CMV infection were detected, although there was evidence of lymphocytic infiltration in some remaining mucosal areas. CMV immunostaining was also negative, but CMV-DNA-PCR testing on both the intestinal tissue and ascitic fluid was positive, resulting in a histological diagnosis of aCMV enteritis.

Postoperatively, the patient had good drainage from the enterostomy and enteral feeding was resumed at DOL 109 (postoperative day 13). The platelet count was low (10,000–30,000/μL), requiring daily blood transfusions, and cholestatic liver damage had progressed. Since the intussusception was caused by CMV infection, ganciclovir (GCV) (12 mg/kg/day) administration was initiated on DOL 100, with the consent of the guardian. After the start of GCV administration, the platelet count improved, and at approximately one week from the start of treatment, blood transfusions were no longer required. On DOL 122, GCV treatment was switched to oral valganciclovir (VGCV) (32 mg/kg/day) for a total of eight weeks, and the liver injury showed an improving trend over time. After completion of the GCV/VGCV treatments, urinary CMV-DNA-PCR results remained negative, demonstrating no recurrence of CMV infection. The enterocutaneous fistula was closed on DOL 128.

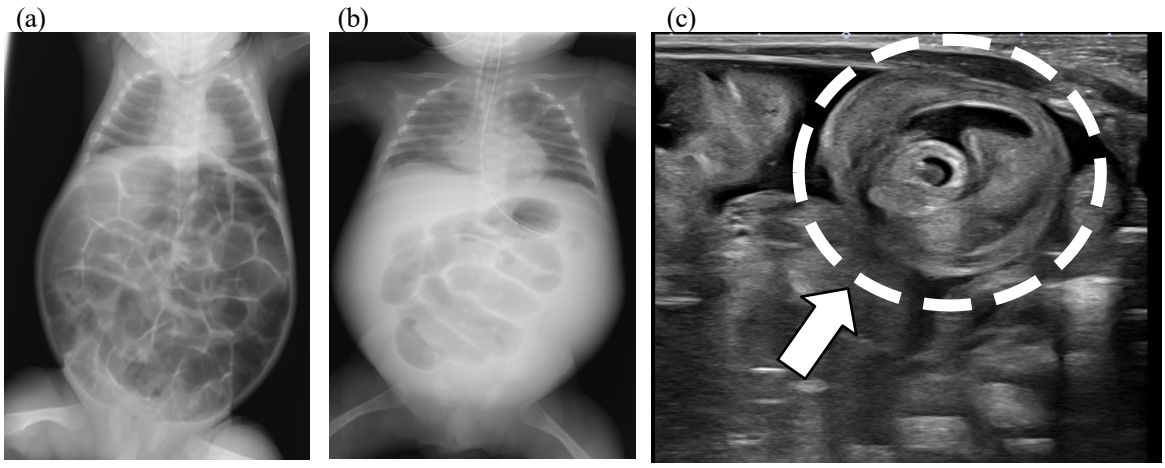

Fig. 1. (a) Simple x-ray at DOL 84. During sudden worsening of abdominal distention
(b) Simple x-ray at DOL 96. Diagnosis of intussusception
(c) Abdominal ultrasonography at DOL 96. The white arrow indicates a target sign.

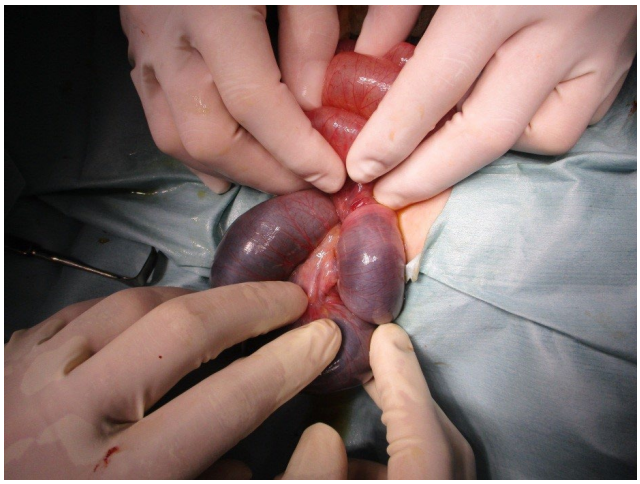

Fig. 2. An ileo-ileal intussusception, approximately 30 cm in length, was observed near the distal end of the ileum. The distance of the intestine was long, and the intussusception was very narrow, making it difficult to repair.

DISCUSSION

IPN is an extremely rare clinical entity, accounting for only 3% of all neonatal intussusception cases, and 0.3% of all intussusception cases [1]. There are no specific radiological findings of IPN [4]. Signs of ileus, such as dilated intestinal loops and occasionally air-fluid levels, are common but non-specific findings, whereas X-rays of patients with NEC typically show pneumatosis intestinalis or portal venous gas [1, 2, 4]. Diagnosis by gastrointestinal series is often difficult, carrying a non-negligible risk of perforation. Ultrasonography is useful in the diagnosis of IPN [1, 3, 4]. When performing ultrasonography, it is important to note that the presence of significant abdominal gas obscures visualization of the intussusception and that the small intestine is the most common site of IPN (91.6%) [3]. In cases of prolonged abdominal distention, such as in the present case, it is important to repeat ultrasonography with intussusception in mind, even if the patient's general condition is relatively good.

IPN is difficult to diagnose because the typical symptoms of intussusception are less likely to appear. IPN presents with abdominal distention (85%), bilious gastric residuae (77%), and hematochezia (43%) [1], but only approximately one third of cases present with all three symptoms. Furthermore, these symptoms are similar to those of NEC [1–5], making the diagnosis difficult. In most reported cases, it took 9.8 ± 7.5 days from the onset of symptoms to diagnosis [1, 3]. This delay in diagnosis increases the risk of developing intestinal disorders such as necrosis and perforation [1]. About 53% of cases had perforation at the time of diagnosis [1]. As in previous reports, our case was also difficult to diagnose, requiring 12 days to confirm IPN. The patient developed intussusception when he presented with abdominal distention at DOL 84 and could be diagnosed at DOL 96. The diagnosis was delayed because the patient's general condition was relatively good and even when he first showed abdominal distention, fasting relieved the symptom. In the case of NEC, the abdominal findings and deterioration of the general condition develop simultaneously. In many cases, especially in premature infants weighing less than 1000 g, a similar abdomen is diagnosed as NEC, and conservative treatment should be continued [5, 6]. As reported by Ruichong Ma et al. [6], in this case, the abdominal findings improved after fasting, but worsened after resuming nutrition. Since the most common site of accumulation is in the small intestine, it is assumed that the patient had repeated fits and releases. Worsening of his general condition, bloody stools and dilated intestinal gas may be considered as progression of intestinal ischemia and necrosis due to the fusion of the site of accumulation, and in such cases, surgery should be performed urgently.

aCMV infection is usually subclinical in term infants, but it may cause symptomatic disease in preterm infants [7]. Infants with low gestational weeks and low maternal transfer of anti-CMV IgG may be at risk for aCMV infection [8]. A gestational age of less than 32 weeks and a birth weight of less than 1500 g are considered risk factors, and Lanzieri reported that among approximately 300 very low birth weight infants, aCMV infection was present in 19% with symptoms in 4% [9].

Clinical manifestations of aCMV infection include liver dysfunction, myelosuppression, sepsis-like syndrome (bradycardia, respiratory distress, apnea), pneumonia, and gastrointestinal disease [10]. Jennifer reported that of 32 previously reported cases of gastrointestinal disease caused by CMV, 12 were accompanied by NEC and 20 were enterocolitis [11]. Patel reported that 18% (6/33) of children with aCMV infection developed NEC [12].

The etiology of IPN remains unclear, but common prenatal injuries causing intestinal hypoxia/hypoperfusion, dysmotility, and strictures have been proposed as a possible lead [1]. Mostafa reported that only 7 of 52 cases (four Meckel's diverticulum, two meconium plugs, and one abdominal lymphangioma) were able to identify the

lead point of IPN [1]. An association between intussusception and viral infection has also been proposed in full-term infants. Studies utilizing serolo gyandvirus isolation from fecal and pharyngeal swabs indicate that adenovirus is found in 41% of children with intussusception, rotavirus in up to 10%, and enterovirus in 6% [6]. In our case, considering that the baby had been managed in the NICU since birth, had no sick contact, and had developed aCMV infection, CMV infection was considered the most suspicious, so tests to exclude viral infections other than CMV infection were not performed. The cause of the intussusception in this case was diagnosed as aCMV enteritis because no organic lesions were observed in the advanced part of the intussusception, and the presence of CMV was confirmed by CMV-DNA-PCR examination of the resected intestinal tract. Intestinal edema and decreased intestinal peristalsis due to aCMV enteritis may be the main causes of the intussusception. In the preceding case [6], as in the present case, the postoperative course was excellent. However, in our case, the systemic symptoms of CMV infection became apparent with liver dysfunction, thrombocytopenia, and sepsis-like symptoms before the gastrointestinal symptoms became symptomatic. In this case, postoperative abdominal findings of intestinal polyposis improved quickly, but the thrombocytopenia and liver dysfunction caused by CMV infection did not improve, requiring antiviral medication. Antiviral therapy may be necessary when symptoms of CMV infection are severe.

We report the case of a very preterm infant with intussusception triggered by aCMV infection. In cases of symptomatic aCMV infection in preterm infants, it is important to list intussusception as a differential diagnosis in cases of abdominal distention that responds poorly to medical treatment.

ACKNOWLEDGEMENTS

We extend our sincere gratitude to the parents of the patients for their generous cooperation and for granting us permission to publish this report. Additionally, our appreciation goes to Dr. Takumi Kido of Kobe University Hospital for his invaluable contribution in analyzing the CMV-DNA.

REFERENCES

1. Kotb M, Abdelatty M, Rashwan H, AbdelMeguid Y, Elrouby A. Intussusception in preterm neonates: A systematic review of a rare condition. BMC Pediatr. 2021;21(1):587.
2. Raza HA, Basamad MS, El Komy MS, Al Maghrabi A, Habbach H, Abokrecha AY. Diagnosing Intussusception in Preterm Neonates: Case Report and Overview. J Clin Neonatol. 2014;3(2):103–105.
3. Martínez Biarge M, García-Alix A, Luisa del Hoyo M, Alarcón A, Sáenz de Pipaón M, Hernández F, et al. Intussusception in a preterm neonate; a very rare, major intestinal problem – systematic review of cases. J Perinat Med. 2004;32(2):190–194.
4. Jung JH, Park JY, Park SH. Small Bowel Intussusception in a Preterm Infant. Perinatology. 2021;32(2):90–94
5. Avansino JR, Bjerke S, Hendrickson M, Stelzner M, Sawin R. Clinical Features and Treatment Outcome of Intussusception in Premature Neonates. J Pediatr Surg. 2003;38(12):1818–1821.
6. Ma R, Alam M, Pacilli M, Hook E, Nagy A, Carroll D. A Rare Case of Neonatal Intussusception Caused by Cytomegalovirus. Eur J Pediatr Surg. 2014;24(2):184–186.
7. Kadambari S, Whittaker E, Lyall H. Postnatally acquired cytomegalovirus infection in extremely premature infants: how best to manage? Arch Dis Child Fetal Neonatal Ed. 2019;F1–6.
8. Nijman J, van Loon AM, Krediet TG, Verboon-Maciolek MA. Maternal and neonatal anti-cytomegalovirus IgG level and risk of postnatal cytomegalovirus transmission in preterm infants. J Med Virol. 2013;85(4):689–695.
9. Lanzieri TM, Dollard SC, Josephson CD, Schmid DS, Bialek SR. Breast Milk-Acquired Cytomegalovirus Infection and Disease in Very Low Birth Weight and Premature Infants. Pediatrics. 2013;131(6):e1937–1945.
10. Garofoli F, Civardi E, Zanette S, Angelini M, Perotti G, Zecca M, et al. Literature Review and an Italian Hospital Experience about Post-Natal CMV Infection Acquired by Breast-Feeding in Very Low and/or Extremely Low Birth Weight Infants. Nutrients. 2021;13(2):660.
11. Pham JT, Dahlgren AF, Rasamimari P. Recommendations for Diagnosis and Prevention of Cytomegalovirus-Associated Necrotizing Enterocolitis in Breast-Fed Preterm Infants. J Pediatr Pharmacol Ther. 2022;27(2):180–191.
12. Patel RM, Shenvi N, Knezevic A, Hinkes M, Bugg GW, Stowell SR, et al. Observational study of cytomegalovirus from breast milk and necrotising enterocolitis. Arch Dis Child Fetal Neonatal Ed. 2020;105(3):259–265.