MAR Pediatrics (2024) 5:6

Case Report

A Newborn with Spontaneous Intestinal Perforation and Congenital Cytomegalovirus Infection

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Received: 21 Sep 2024

Published: 01 Oct 2024

Abstract

Cytomegalovirus (CMV) is the most common etiology of congenital infections. Gastro-intestinal manifestations are recognized as a manifestation of congenital CMV infection unlike spontaneous intestinal perforation (SIP) which is exceptionally associated with this infection. This case study presents a newborn born at 33 weeks of gestational age, diagnosed with a congenital symptomatic CMV and who developed SIP. The newborn presented with persistent abdominal distension since day 2 of her life and no passage of meconium. Based on abdominal radiography, the patient underwent emergency surgery that showed an ileal perforation five centimeters distal to the ileocecal valve. Distal ileostomy was done. No intestinal resection and thus, no anatomopathological examination was performed.

Because of low birth weight, microcephaly, and thrombocytopenia, CMV PCR screen was done, and were positive in both saliva and blood. Cystic fibrosis (CF) was excluded as CF screen test was negative. Hirschsprung disease was excluded by rectal biopsy. No other abnormality was detected.

A course of valganciclovir was started with resolving of the symptoms and without complications. Restoration of bowel continuity was performed at two months of age without complications and the infant was discharged five days after surgery.

There are many case reports over the past two decades described newborns with severe intestinal diseases including SIP, some cases required abdominal surgery, that associated with positive CMV infection. Preterm infants, low birth weight, extremely low birth weight, and thrombocytopenia are common association in positive CMV newborns who experienced necrotizing enterocolitis (NEC) or SIP.

Based on observations of this case study and the other related case reports, we suggest that a pilot study for screening congenital cytomegalovirus infection be performed for newborns with SIP and focusing on how to prevent severe gastrointestinal diseases especially in premature infants.

Introduction

Congenital Cytomegalovirus (CMV), a member of the herpes DNA virus group, is the leading infectious cause of congenital malformation in children causing a wide spectrum of intrauterine and postnatal abnormalities. Around 5 to 10 % of CMV cases are symptomatic in the neonatal period (1). Neonatal intestinal involvement is widely recognized as a manifestation of congenital CMV infection unlike spontaneous intestinal perforation (SIP) which has only been exceptionally associated with this infection. Other neonatal intestinal diseases that associated to with CMV infection include experienced necrotizing enterocolitis, meconium peritonitis, abdominal compartmental syndrome, Meckel's diverticulum, volvulus, colonic stricture, and ulceration (2,3). Spontaneous intestinal perforation (SIP) is defined by isolated perforation of the intestine, while the surrounding tissues are normal. Usually, it affects the antimesenteric border of the terminal ileum, and presents during the first week of life. Few reports showed the incidence of SIP among newborns. Meyer et al. 1991 revealed that 1-2 % of newborns who born less 32 weeks gestation or less 1500 grams had SIP (4), while Attridge et al, 2006 mentioned the rate of SIP among extremely low birth weight infants were 3-8% (5).

Because of its rarity, spontaneous idiopathic intestinal perforation is typically diagnosed during surgery. 81% of a histopathologic analysis of autopsy or intestinal samples taken from infants with NEC, SIP and other surgical complication of bowel diseases, showed CMV infection (6).

Another study determines CMV infection in 3% of patients with spontaneous intestinal perforation and in 4% necrotizing enterocolitis stage 2B or above (7).

SIP is associated with increase the mortality rate up to 53% in ELBW infants (5,8,9), and increase the rate morbidities, such as increase rate of chronic lung disease to be 77%, and neurodevelopmental complication to reach 67% at age 18-22 months corrected age (9,10).

These facts about SIP association with CMV, attract the interest to know about diagnosis, management and progress or outcome of such cases. In current case report, we will present a newborn diagnosed with a symptomatic congenital CMV who developed a SIP.

Case Report

A female infant was born at 33 weeks of gestational age (GA), with a birth weighing 1400 g (6th percentile) with a head circumference of 27.5 cm (3rd percentile). Apgar score was 3 at one minute and 8 at five minutes. The infant was born to a 33-year-old mother, gravida 1, para 1 with irrelevant medical history. Pregnancy was complicated by intrauterine growth restriction (IUGR); diagnosed at the third trimester by abdominal scan.

Abdominal scan showed a fetal weight estimation in the third percentile for the gestational age associated with oligohydramnios and umbilical artery waveform notch. The mother was addressed for fetal monitoring which revealed an abnormal fetal rhythm. She received an incomplete course of antenatal corticosteroids and an emergency cesarean section was performed at 33 gestation weeks. Shortly after delivery, the newborn was admitted to the neonatal intensive care unit due to prematurity, low birth weight and respiratory distress syndrome that necessitated nasal CPAP during 24 hours. Initial routine examination after birth showed no abnormalities detected in the abdomen. She was enterally trophic fed from day one of life with formula for preterm infants. On day two of life, the newborn presented abdominal distention with gastric residuals. No passage of meconium since birth. Abdominal radiological investigations were performed because of the persistence of the abdominal distention showed presence of free air under diaphragm, which called a pneumoperitoneum.

The patient underwent emergency surgery that showed an ileal perforation five centimeters distal to the ileocecal valve. Macroscopic examination showed no signs of necrotizing enterocolitis. A distal ileostomy without intestinal resection was performed. No anatomopathological examination was done accordingly.

Laboratory studies showed a C-reactive protein of 22.6 mg/dL, a creatinine of 72 µmol/L, a normal hepatic function and a thrombocytopenia of 44,000/ mm3. No other laboratory abnormality was noted. Screening for mutations for cystic fibrosis was negative.

Echocardiograph was done and showed a small ductus arteriosus without hemodynamic significance, that needs no medical intervention except follow up.

Post-surgical evolution was unremarkable: After sustained clinical improvement, enteral feeding was reestablished two days after surgery without any complications.

Furthermore, the newborn was screened for CMV infection because of low birth weight, microcephaly, and thrombocytopenia. The results of CMV PCR were positive in both saliva and blood (3.5 log) on day 10 of life. No other malformation was detected. Cranial ultrasound and cerebral magnetic resonance did not show any abnormality. Ophthalmological examination and auditory evoked potentials were normal. Hirschsprung disease was excluded by rectal biopsy.

The newborn was treated with oral valganciclovir during six months. Restoration of bowel continuity was performed at age of two months without documented complications, and the infant was discharged five days after surgery as she is tolerating oral intake.

Discussion

This case report described spontaneous intestinal perforation occurred in a CMV infected premature infant. CMV is the leading infectious cause of congenital infectious disease in children affecting about 2 per 1000 live births. As only 20% of adults with a primary infection are symptomatic with nonspecific symptoms such as fever, rhinitis, pharyngitis, headaches, arthralgia and myalgia, the diagnosis of maternal CMV infection is often retrospectively based on fetal ultrasound signs of the infection. These signs are either cerebral manifestation, such as ventriculomegaly, microcephaly, or hydrocephalus, and extracerebral manifestation, such as IUGR, hyperechogenic fetal bowel, or hepatomegaly (11).

Most newborns affected with congenital CMV infection are asymptomatic at birth. Only around 10 % are symptomatic and may present at birth with sepsis-like symptoms, prematurity, IUGR, petechiae or purpuric rash, hepatosplenomegaly, hepatitis, pneumonitis, microcephaly, brain abnormalities, seizures, chorioretinitis with or without optic atrophy, cataracts, hydrops or jaundice. Laboratory abnormalities associated with CMV, especially in preterm babies, may include elevated C-reactive protein (CRP) levels, neutropenia, thrombocytopenia, hemolysis, elevated alanine aminotransferase and conjugated bilirubinemia, and high protein in cerebrospinal fluid (11).

Ten to fifteen percent of asymptomatic neonates and 40-60 % of symptomatic neonates are at risk of long-term sequelae with sensorineural hearing loss (SNHL) being the most common sequelae, followed by cognitive impairment, retinitis and cerebral palsy (12).

Gastrointestinal manifestations of congenital or perinatal CMV infection are also described. Multiple case reports suggest an association between CMV infection and enteric ulceration, colonic strictures, ileal atresia, abdominal compartment syndrome, necrotizing enterocolitis (NEC), ileal and colonic perforations. The perforations described occurred either in the presence of an underlying pathology; for example, Meckel diverticulum, or NEC occurring prior to perforation, or in immunocompromised patients (13,14,15).

Spontaneous intestinal perforation is defined as a perforation occurring spontaneously without an underlying pathology (idiopathic type) (16), unlike secondary perforations where underlying cause is identified. The leading cause of secondary intestinal perforations is NEC. Other common causes of secondary perforation include trauma, drugs, meconium ileus, meconium plug syndrome, volvulus, congenital anomalies obstructing the GIT, hernias and peptic ulceration (16).

The most important risk factor for SIP is extremely low birth weight (17). Other possible risk factors for SIP include: prior exposition to inotropic agents, intraventricular hemorrhage ≥ grade III, not being fed (18), early

exposure to postnatal steroids and/or indomethacin, congenital absence of the muscularis externa (19) and meconium ileus (18).

SIP presents with abdominal distention, discoloration of the abdominal skin, either a gasless abdomen or pneumoperitoneum on abdominal X-ray, and without prior signs of systemic illness. It usually occurs in the first 1 to 2 weeks of life. Diagnosis is usually an intraoperative diagnosis. Anatomopathological exam reveals isolated perforation without surrounding necrosis or neutrophil infiltrate, often accompanied by a focal thinning or the absence of intestinal muscularis propria. The most frequent site of SIP is the terminal ileum at the antimesenteric border (17).

In the current case study, we believe that SIP in this case was most probably associated with CMV, but we could not confirm this probability because we did not have any anatomopathological proof as no intestinal resection occurred. There are clinical considerations support our probability. First; the patient developed SIP at day 2 of her life with no evidence of presence of NEC clinically, radiologically plus macroscopic examination during surgery.

Second, the patient was a premature infant with low birth weight. Both are risk factors of SIP that mentioned previously in many studies. Compared to the CMV-negative group, infants with intestinal tissue containing CMV had lower birth weights and gestational ages. It is because the intestinal mucosal barrier in the preterm infants is at higher risk to be invaded by a pathogen such as CMV causing NEC or SIP (20)

Third, the patient had a symptomatic congenital CMV infection, including thrombocytopenia, that confirmed with PCR CMV in blood at day 10 of life. Study of Maheshwari, 2015 revealed that thrombocytopenia could serve as an indication for CMV testing in patients with NEC or SIP as Platelet counts were significantly lower among infants whose intestinal tissue contained CMV(21).

Despite the fact that CMV is an uncommon cause of severe gastrointestinal problems in preterm newborns, it was not previously considered in the differential diagnosis of gastrointestinal illness in preterm infants. However, numerous reports have demonstrated the involvement of CMV infection in the gastrointestinal symptoms experienced by SIP newborns.

However, CMV was detected in the intestinal tissue of infants with SIP and necrotizing enterocolitis (NEC) with a high prevalence compared to specimens from surgical or autopsied infants without bowel disease suggesting a significant association of CMV in SIP or NEC. In two retrospective studies that focused on the analysis of surgical specimens, maternal CMV serostatus was lacking as well as patients' urine or saliva CMV PCR. Thus, authors could not conclude whether patients who presented NEC or SIP had congenital or perinatal

CMV infection (6,13). In the second study, there were only one patient who had SIP and a positive intestinal tissue CMV PCR. This patient presented at day ten of life direct hyperbilirubinemia, thrombocytopenia, grade 1 intraventricular hemorrhage and ventriculomegaly. No additional testing for congenital CMV infection such as urine CMV PCR was performed. On follow-up, this infant developed cerebral palsy and hydrocephalus with placement of a ventriculoperitoneal shunt. The SIP in this study was most probably caused by CMV infection but this was not proved.

Bonnard et al. reported that CMV may cause intestinal atresia and perforation when associated with other local factors such as tissue ischemia (14). Also, the study showed CMV infection may increase secondary bacterial invasion, proinflammatory and inflammatory mediators such as 5- lipoxygenase that led to bowel inflammation and NEC (14), which is the leading cause of secondary perforations in newborns.

The gastrointestinal tissues contained CMV infection had signs of segmental vasculitis, that may cause perforation in preterm babies, newborns with low birth weight, as well as immunocompromised patients (22). Because of the conclusive diagnosis of CMV infection in the intestine have need of getting the patient's bowel sample, there may be an underdiagnosis of CMV associated gastro intestinal illness in preterm newborns (23). Based on observations of this case study and the other related case reports, we suggest that a pilot study for screening congenital cytomegalovirus infection be performed for newborns with SIP and focusing on how to prevent severe gastrointestinal diseases especially in premature infants.

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