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Cytomegalovirus-associated colitis mimicking necrotizing enterocolitis – A near miss diagnosis of neonatal colonic stricture☆

Fanny Yeung*, Patrick Ho Yu Chung, Kenneth Kak Yuen Wong, Paul Kwong Hang Tam

Division of Paediatric Surgery, Department of Surgery, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

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ABSTRACT

Although cytomegalovirus (CMV) is a common congenital infection in neonates, most patients are asymptomatic. Gastrointestinal manifestation is unusual. In this report, we described a newborn with perinatal CMV infection presented with symptoms mimicking necrotizing enterocolitis. We hope to alert clinicians about this possible diagnosis when managing newborn gastrointestinal diseases.

Cytomegalovirus (CMV) infection may be acquired prenatally or perinatally and is the most common congenital viral infection, which occurs in 0.2–2.2% of live births worldwide [1,2]. CMV is frequently isolated from neonates. Although most infants shedding this virus are asymptomatic, others may have life-threatening illness or debilitating long-term sequelae. In neonates, viral culture of urine, saliva or tissue sample is the primary diagnostic tool. Congenital CMV is diagnosed if the virus is isolated from urine or other body fluids taken within the first 3 week of life. Beyond 3 week, positive cultures may indicate either perinatal or congenital CMV infection.

CMV infection of the gastrointestinal tract in infants is an unusual manifestation and had only been reported infrequently [3–5]. Clinical presentations may mimic other neonatal diseases, such as neonatal necrotizing enterocolitis [6,7] or Hirschsprung's disease [8], leading to delayed diagnosis and treatment. In this report, we describe a neonate with perinatal CMV infection who developed neonatal enterocolitis-like condition. Clinical features as well as histology will be discussed.

1. Case presentation

A male neonate weighing 3.09 kg was born at 36 + 6 weeks of gestation on 9 June 2014 to a 34-year-old primigravida seronegative for CMV. The labor was complicated by prolonged rupture of membrane for 28 hours, and was covered prophylactically with intravenous penicillin. The neonate was born by vaginal delivery with vacuum extraction due to prolonged second stage of labor. The Apgar scores were both 9 at 1 and 5 min.

Enteral feeding was started on the day 1 with formula milk. On the next day, blood streaked stools were noted. Abdominal X-rays showed prominent bowel loops with foamy appearance over the left side (Fig. 1a). There was no acidosis or thrombocytopenia. However C-reactive protein (CRP) increased from 16.9 mg/L to 21.6 mg/L. Blood and stool cultures were negative for pathogenic bacteria. He was managed clinically as necrotizing enterocolitis (NEC). Non-surgical treatment including bowel rest and antibiotics with ampicillin, gentamicin and metronidazole were started.

Enteral formula feeds were restarted on day 9 and was well tolerated. He was afebrile all along but elevated white blood cell count (WCC) (19.1 × 10⁹/L) and CRP (24.3 mg/L) were noted on the same day. Antibiotic regimen was switched to vancomycin and ceftazidime. However, his general condition deteriorated on day 22 when he developed fever and mild abdominal distension. Abdominal X-ray showed haziness over left side of bowels. CRP was elevated to 51.3 mg/

* Corresponding author. Department of Surgery, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong. Tel.: +852 62523700; fax: +852 28173155.
E-mail address: fannyeungtw@gmail.com (F. Yeung).

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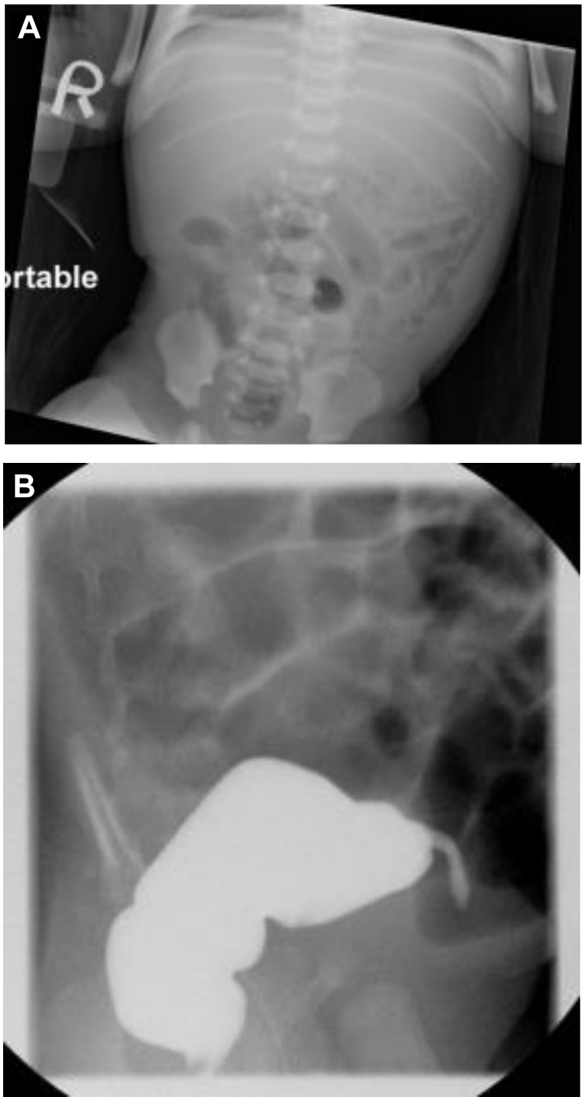

Fig. 1. A) Abdominal X-ray showing foamy appearance on left side of the abdomen. B) Contrast enema showing high grade narrowing at distal sigmoid.

L. Computed tomography of abdomen revealed only prominent sigmoid and rectum and no intra-abdominal collection. He was managed as recurrent NEC and treated again with bowel resting and antibiotics (vancomycin with meropenem). The fever initially responded and CRP level progressively decreased to 17.1 mg/L.

However, there was worsening of condition again on day 34. Abdominal distension was noted. Microbiology investigations revealed the presence of CMV pp65 antigen in urine and blood. Screening for CMV systemic disease in brain and eyes was negative. Water-soluble contrast enema was performed for persistent abdominal distension, which showed an irregular focal segment of narrowing at distal sigmoid (Fig. 1b).

Laparotomy was performed in view of intestinal obstruction. Two centimeter sigmoid colonic stricture was excised followed by a double barrel colostomy due to marked discrepancy between proximal and distal loops. The histopathology of the stricture revealed ulceration, mixed inflammation and presence of cytomegalic intranuclear inclusion bodies within the stromal and endothelial cells, suggestive of CMV colitis. The presence of CMV inclusions was confirmed using immunostaining (Fig. 2).

Post-operative recovery was satisfactory. A course of intravenous ganciclovir was completed with CMV pp65 serial monitoring

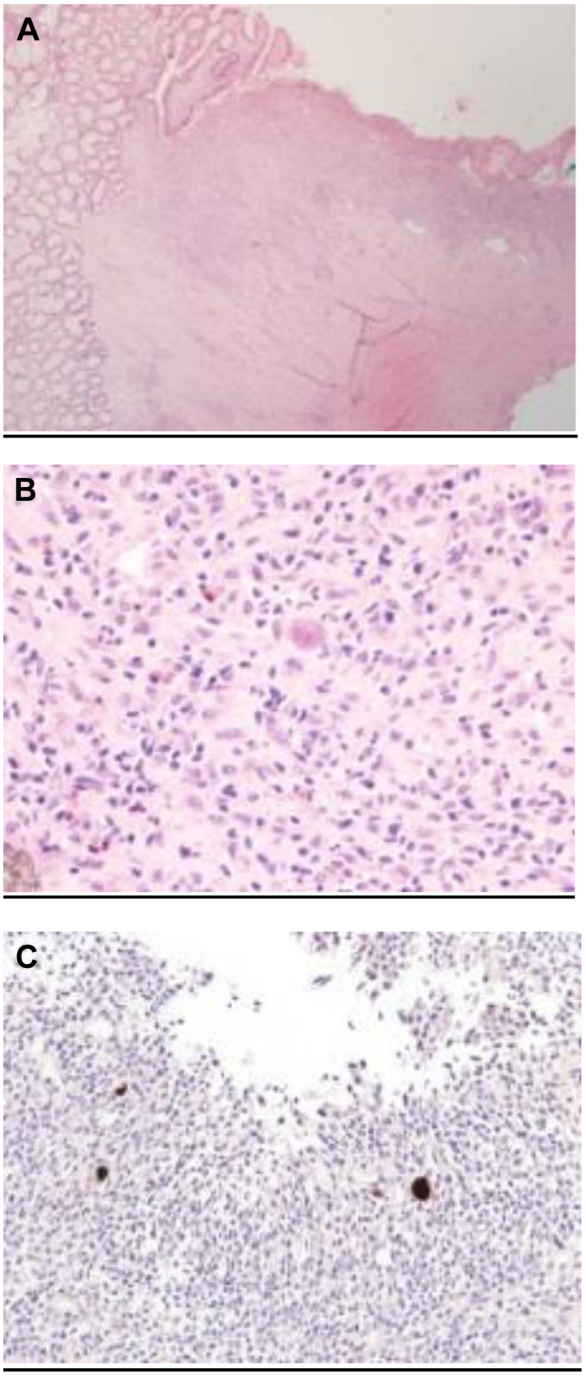

Fig. 2. A) Hematoxylin & eosin stain ×2: The large intestine shows an area of ulceration with fibrotic base. B) Hematoxylin & eosin stain ×40: Isolated large size stromal cells with eosinophilic viral inclusion are found at the ulcer base. C) Immunohistochemical stain for cytomegalovirus ×20: confirms the viral inclusions are CMV infected cells.

tested negative. Closure of colostomy was done five weeks later after instigating a regime of daily distal loop instillation with normal saline. Subsequent clinical course was smooth with full enteral feedings achieved and tolerated well.

2. Discussion

CMV enterocolitis is rare in newborns according to literatures and is frequently overlooked. Gastrointestinal manifestations of CMV infection can vary from mild diarrhea to clinical picture similar

to fulminate necrotizing enterocolitis. CMV enterocolitis differs from NEC in that it presents with ulceration progressing to stricture, rather than gangrene and perforation [9,10]. The suspicion of CMV-related gastrointestinal disease is often overlooked until a more severe complication such as strictures present requiring surgical intervention [11,12].

Our case presented initially with clinical picture mimicking recurrent necrotizing enterocolitis and intestinal obstruction. Medical treatment failed and our patient subsequently required surgical intervention. The diagnosis of CMV enterocolitis and colonic stricture was not made until the specimen was examined histologically. Clinicians are advised to be more aware of this unusual clinical manifestation. The true incidence of CMV enterocolitis might be higher than previously thought because screening of CMV is not routinely performed for neonates with refractory necrotizing enterocolitis and the diagnosis is often overlooked by clinicians. We suggest non-invasive screening such as stool and urine PCR examination for CMV, and blood for CMV antigen be considered early in all refractory enterocolitis in the neonatal population in order to establish an earlier diagnosis of CMV enterocolitis and be able to initiate earlier antiviral treatment to minimize devastating complications and long-term sequelae of bowel stricture.

Another learning point from our case is the efficacy of daily distal loop saline instillation to minimize size discrepancy between proximal and distal bowel ends. The size of bowel distal to the stricture may be significantly smaller than the proximal part due to chronic disuse. The greater the discrepancy, the more technically demanding while closing the colostomy. Some centers suggested performing an end-to-side anastomosis when the discrepancy between two ends was greater than 4:1 [13,14]. In our case, to prepare for closure of colostomy in view of 10:1 discrepancy between proximal and distal bowel ends, daily normal saline instillation to distal loop was performed. At the time of closure of colostomy, only mild discrepancy between proximal and distal bowel limbs was noted. In our center, distal mucous fistula refeeding with proximal bowel contents in premature neonates with short bowel syndrome and enterostomies has been our preferred method before stomal closure [15]. The aims of both refeeding with proximal bowel contents or the above-mentioned normal saline instillation were to prevent disuse atrophy in the distal loop and facilitate subsequent reanastomosis.

In summary, we would like to reinforce the importance of considering CMV infection in the differential diagnosis of unusual gastrointestinal manifestations in neonates.

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