Case Report

SAGE Open Medical Case Reports

Clostridium difficile colitis complicating Kawasaki disease in children: Two case reports

SAGE Open Medical Case Reports
Volume 6: 1–4

DOI: 10.1177/2050313X18781742
journals.sagepub.com/home/sco
SAGE

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Abstract

Clostridium difficile infection is increasingly diagnosed in children with a wide clinical spectrum ranging from asymptomatic carriage to fulminant colitis. Symptomatic patients typically present with diarrhea, with or without blood, fever, and abdominal pain. Kawasaki disease, a vasculitis of unknown etiology, occurs primarily in young children. Establishing the diagnosis of Kawasaki disease can be challenging given the lack of a confirmatory diagnostic test or pathognomonic features as well as the appearance of symptoms over time rather than simultaneously. In addition, commonly occurring nonspecific associated symptoms, such as diarrhea and abdominal pain, may confound the clinical presentation. We present two cases of children with Kawasaki disease presenting with fever and *Clostridium difficile* colitis to illustrate the importance of keeping a high index of suspicion for Kawasaki disease.

Keywords

Clostridium difficile infection, Kawasaki disease, children

Date received: 28 December 2017; accepted: 16 May 2018

Introduction

Clostridium difficile is an anaerobic, gram-positive bacillus that produces toxin A and toxin B. In the past two decades, the incidence of *Clostridium difficile* infection (CDI) in children has increased. In a population-based study, a 12.5-fold increase was seen from 1991 to 2009, whereas among hospitalized children, there was a 53% increase noted from 2001 to 2006.[1,2] The majority of affected children are <5 years of age and present with diarrhea with or without blood, fever, and abdominal pain. The spectrum of illness associated with CDI ranges from asymptomatic to fulminant colitis. Asymptomatic infection is common in infancy and treatment is not necessary; however, those with malignancies, inflammatory bowel disease, or immunosuppression tend to have a severe and complicated course necessitating therapy. Furthermore, extraintestinal manifestations of CDI, albeit unusual, include reactive arthritis, cellulitis, bacteremia, visceral abscesses, osteomyelitis, and prosthetic device infection.[3]

Kawasaki disease (KD) is an acute vasculitis predominantly affecting children <5 years of age. Although the etiology is unknown, an infectious etiology is suspected based on its seasonality, age distribution, and similarity to toxic shock syndrome and viral infections. Globally, the incidence is increasing, with projected incidences for KD of 1:700 and 1:1600 in Taiwan and the United States, respectively, by 2030.[4] Up to 25% of untreated patients develop coronary aneurysms. The diagnosis is based on the presence of elevated inflammatory markers with ⩾5 days of fever and at least four of the following clinical criteria: bilateral nonpurulent conjunctivitis, oral mucosal changes, cervical lymphadenopathy,

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Table 1. Patient characteristics, laboratory values, and treatment.

Features on admission	Patient 1	Patient 2
Age	5 months	4 years
Sex	Female	Male
Antibiotics prior to diagnosis with CDI	No	Yes (Penicillin)
Duration of fever when KD was diagnosed and IVIG given (days)	10	10
Gastrointestinal symptom	Watery diarrhea, abdominal distension	Non-bilious, non-bloody vomiting and abdominal distension
Gastrointestinal pathogens ruled out	*Salmonella*, *Shigella*, *E. coli* O157:H7, *Vibrio*, *Yersinia, Campylobacter*	*Salmonella*, *Shigella*, *E. coli* O157:H7, *Vibrio*, *Yersinia, Campylobacter*
Hemoglobin (g/dL)	9.5	9.2
Hematocrit (%)	28.4	27.7
WBC ($\times 10^3$ cells/μL)	9.5	9.2
Platelet ($\times 10^3$ cells/μL)	199	453
Erythrocyte sedimentation rate (mm/h)	64	110
C-reactive protein (mg/dL)	18	17.6
Serum albumin (g/dL)	2.3	2.9
Aspartate aminotransferase (IU/L)	22	13
Alanine transaminase (IU/L)	59	8
Sterile pyuria	Yes	No
Amylase (U/L)	NA	63
Lipase (U/L)	NA	267
Number of IVIG dose(s)	1	3
Duration of metronidazole treatment (days)	10	10

CDI: *Clostridium difficile* infection; KD: Kawasaki disease; WBC: white blood cell; IVIG: intravenous immunoglobulin; NA: not applicable.

rash, and extremity changes.[5] Symptoms manifest over time; hence, watchful waiting is necessary in establishing the diagnosis. In a review of associated symptoms 10 days prior to the diagnosis of KD, gastrointestinal symptoms (diarrhea, vomiting, and abdominal pain) were common, occurring in 60% of patients.[6]

When overlapping symptoms of fever, abdominal pain, vomiting, or diarrhea occur, the diagnosis of CDI may delay establishing the diagnosis of KD. We describe two children with KD presenting with fever and CDI to illustrate the need to keep a high index of suspicion for KD.

Case presentations

Case 1

A 5-month-old previously healthy African-American female was admitted with 3 days of diarrhea and fever. She had a temperature of 103°F and a pulse of 185 beats per minute. She appeared acutely ill; however, skin rash, oral lesions, conjunctival injection, and cervical lymphadenopathy were absent. Her abdomen was soft and non-distended with increased bowel sounds. Inflammatory markers were high (Table 1). Urinalysis was positive for leukocytes and nitrites, but culture was negative. Extreme irritability led to lumbar puncture that yielded normal results. Toxigenic *C. difficile* was detected in the stool by polymerase chain reaction (PCR) for which oral metronidazole was prescribed. Despite therapy, she continued to have fever (100°F–104°F) and developed dryness and reddening of the lips and buccal mucosa, as well as edema of her face, hands, and feet. A diffuse erythematous maculopapular eruption in her groin area and conjunctival injections also appeared. Progressive abdominal distension was noted, and abdominal ultrasound showed nonspecific ascites. Echocardiogram showed a 2–3 mm pericardial fluid collection without evidence of coronary aneurysms. The diagnosis of KD was made on hospital day (HD) 7, and high-dose intravenous immunoglobulin (IVIG; 2 g/kg) was given along with high-dose aspirin. She dramatically improved with resolution of fever and diarrhea. She was sent home on low-dose aspirin 2 days later.

Case 2

A 4-year-old previously healthy White male presented with a 4-day history of fever (103°F) and non-bilious, non-bloody vomiting. Prior to admission, he received intramuscular penicillin for a positive rapid *Streptococcus pyogenes* antigen test, but he continued to have poor oral intake, increased irritability, and fever. During hospitalization, his abdomen became distended. Abdominal computed tomography showed small bowel distension without obstruction and wall thickening with mucosal enhancement of the rectosigmoid colon. His stool tested positive via PCR for toxigenic

C. difficile and he was treated with oral metronidazole. During the hospitalization, he then developed bilateral non-purulent conjunctivitis, an erythematous rash on his upper extremities, and swelling of toes and fingers. Elevated inflammatory markers and low albumin were noted (Table 1). Echocardiogram showed a small pericardial effusion with normal coronary arteries. He was diagnosed with KD and given high-dose IVIG and aspirin on HD 6. He was discharged home after 2 days with resolution of symptoms and decreased C-reactive protein (CRP) at 7.8 mg/dL. Three days after discharge, irritability and fever (101.9°F) recurred. CRP was 5.3 mg/dL, hemoglobin 7.8 g/dL, and platelets 569,000 cells/μL. Repeat echocardiogram demonstrated the left main coronary artery to be 3 mm (upper limit of normal) with continued effusion. He received a second dose of IVIG. Two weeks later, repeat echocardiogram showed the left main coronary to be dilated at 3.5–3.8 mm (Z score 3.84) with CRP even higher at 8.3 mg/dL. A third dose of IVIG was given. Echocardiogram 3 months later revealed normal coronary arteries and no pericardial effusion.

Discussion

We report an infant and a child with KD presenting initially with fever and gastrointestinal symptoms. Evaluation for gastrointestinal causes revealed the presence of *C. difficile* in the stool.

The significance of the detection of *C. difficile* in the stool among infants remains controversial, and a positive result necessitates careful interpretation. Asymptomatic colonization is seen in 37%, 30%, and 14% of infants <1 month, between 1 and 6 months, and 6–12 months of age, respectively.[7] While not completely understood, asymptomatic infection in infants occurs because of immature intestinal microbiota, colonization by less pathogenic *C. difficile* strains, and decreased toxin receptors in the intestinal epithelium.[7] The diagnosis of *C. difficile*-associated diarrhea (CDAD) for the first patient was based on the case definition used in the study by Khanna et al.[1] that included the presence of diarrhea, the detection of *C. difficile* toxin, and the absence of other causes of diarrhea.

Our second patient presented with vomiting but without diarrhea. Paralytic ileus with minimal or no diarrhea may be seen in patients with severe CDI. Although *Streptococcus pyogenes* was detected by rapid antigen test and the patient received penicillin, this was a red herring, as the child never complained of sore throat and did not have signs of pharyngitis on physical examination. In both our cases, *C. difficile* was the only pathogen identified in our evaluation for causes of diarrhea (Table 1). Possible interpretations of these clinical and laboratory findings include the following: (1) asymptomatic CDI, rather than CDAD, and that the diarrhea was part of the symptomatology of KD; (2) diarrhea is related to both CDAD and KD; (3) diarrhea is due to another unidentified cause. Given the severity of symptoms at the time of presentation, the clinical findings indicated CDAD for which treatment was warranted.

Gastrointestinal symptoms in association with KD are common.[5,6] However, the acuity of onset and predominance of gastrointestinal symptoms relative to principal symptoms of KD may make establishing the diagnosis difficult.[8,9] In a cohort of 219 patients with KD, 10 (4.6%) patients had acute surgical abdomen as the presenting manifestation.[8] Of the 10, 9 had incomplete diagnostic criteria for KD at the time of presentation. Postoperative findings included gallbladder hydrops, paralytic ileus, appendicitis, and duodenitis. Acute febrile cholestatic jaundice is a known presentation of KD but may potentially confound the clinician.[9]

There is increasing recognition that patients with KD may have concurrent infections with bacteria and viruses. The detection of organisms does not exclude the diagnosis of KD.[10] The role of infections in the pathogenesis of KD has been studied extensively without clear evidence of a single causative pathogen.

It has been suggested that the respiratory tract may serve as an entry point for etiologic agents in patients with KD. Examination of the trachea of patients who died of KD showed infiltration of IgA plasma cells comparable to what is seen in fatal viral respiratory infections.[11] Similarly, the gastrointestinal tract, with its vast surface area, exposure to considerable foreign antigens, and abundant presence of major histocompatibility complex (MHC) Class II molecules needed for T cell activation in KD, has been postulated as an entry point for etiologic agents in patients with KD.[12,13] Investigators have speculated on the association of KD with *Yersinia pseudotuberculosis*, an enteric pathogen capable of producing superantigens able to activate T cells.[14]

Both *Y. pseudotuberculosis* and *C. difficile* are enteropathogens capable of disrupting intestinal barriers.[15] It is suggested that increased permeability of the intestinal tract facilitates entry of bacterial antigens with subsequent development of an inflammatory response, as seen in reactive arthritis associated with these infections.[3,13,15–17]

We hypothesize that CDI resulted in disruption of intestinal barrier, thereby allowing entry of *C. difficile* toxins, or quite possibly other unidentified agents that triggered a systemic immune response seen in KD.

Conclusion

This is the first report demonstrating KD and CDI in children. CDI and KD may occur concomitantly in children, making the diagnosis and management of both more challenging. We speculate that a permeable gastrointestinal tract, as in the case of CDI, may serve as portal of entry for *C. difficile* toxins or other unidentified agents capable of eliciting systemic inflammation leading to KD. An alternative hypothesis is that KD may be triggered by clostridial infection. Given both CDI and KD have increasing incidences, predominantly occurring in young children and with overlapping symptoms of diarrhea,

vomiting, abdominal pain, and fever, prospective research to investigate the potential association of CDI and KD will be valuable in our understanding of these diseases.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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