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C A S E R E P O R T

***Clostridium difficile* bacteremia and meningitis as a complication of prolonged cephalosporin therapy in a case of staphylococcal pyogenic arthritis**

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Abstract:

Pseudomembranous colitis is increasing in the recent years. With increasing incidence, several extra-intestinal manifestations of the organism has been unmasked which include bacteremia, brain abscess, pericarditis etc. We report a rare and interesting case of Clostridium difficile bacteremia and subsequent meningitis in a 10 year old child. The child was immune competent, which further raises the question about the virulent possibilities of the organism and its implications in the near future. The condition resulted from a prolonged treatment with I.V. cefotaxime for staphylococcal pyogenic arthritis. The child recovered from the septic arthritis but on the 7th day post-admission developed features of bacteremia. The child was later treated with I.V. metronidazole and I.V vancomycin and he was discharged on the 21st day post-admission. No recurrence of symptoms was noted.

Keywords: *Clostridium difficile*, meningitis, bacteremia

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Introduction

Clostridium difficile induced diarrhea is a common nosocomial infection and occurs due to altered bowel flora with long term use of virtually all known antibiotics particularly ampicillin, amoxicillin, clindamycin and cephalosporins.^{1,2,6} *Clostridium difficile* causes pseudomembranous colitis, the classical picture of which is diarrhea with blood and mucus, accompanied by fever, cramps, abdominal pain, nausea, and vomiting.¹ The intra-abdominal complications of *Clostridium difficile* include dehydration, renal failure, bowel perforation, toxic megacolon and even death. In our case the typical features of pseudomembranous colitis were notably absent. Important independent predictors of serious adverse events due to *Clostridium difficile* infection include severe leucocytosis and a rise in the serum creatinine level over

50% above baseline and these patients need intensive care and surgical consultations.⁵ The severity of the disease may increase in patients with cystic fibrosis, malignancy, chronic obstructive pulmonary disease, renal failure, immunosuppressive and in patients taking antiperistaltic medications.⁷ Rarely extra intestinal complications from *Clostridium difficile* infection may occur which include brain abscess, chronic osteomyelitis, lung abscess, bacteremia etc.^{1,8} However, *Clostridium difficile* bacteremia and subsequent meningitis has never been reported.

Case Report

A 10 year old boy (body weight 32 kg) was admitted in the pediatric ward with pain in the right hip for the last 3 days. The pain was sudden in onset and he had low grade fever

(100⁰-102⁰F) for the same duration. No past history of any joint disease or any similar illness was found. No other joint was involved. His immunizations were up to date.

On examination, there was redness and tenderness over the affected area, but no obvious swelling was noted. All the movements in the affected joint were restricted. Vital signs were temperature, 102⁰ F, respiratory rate 22/min and heart rate, 108/min. Routine blood examination showed: hemoglobin, 14.2 g/dl; total WBC count, 14000/ μ L with 78% neutrophil; platelet count, 260000/ μ L. A joint fluid aspiration was done which yielded a cloudy fluid and culture of the fluid was positive for *Staphylococcus aureus*, susceptible to cefotaxime.

The patient was started on intravenous (I.V.) cefotaxime (50mg/kg every 6hrs) for 7 days. I.V. fluids and oral ibuprofen (10mg/kg every 6hrs) were also given. After 5 days of treatment the patient became afebrile, the pain significantly decreased and the redness disappeared along with improvement of the range of movement of the hip joint.

On the 7th day of treatment the patient became febrile again with the temperature of 100⁰F; heart rate, 110/min; respiratory rate 22/min; blood pressure, 110/70 mm of Hg. He also complained of vague epigastric discomfort, nausea and he vomited once. The fever was continuous in nature but was not associated with chill or rigor. He had no other gastrointestinal symptoms. On examination, the child had a toxic look; mild epigastric tenderness was noted with no obvious organomegaly. There was no redness, swelling or tenderness in the previously affected joint and the range of movement was near normal. The remainder of the abdominal physical examination findings was unremarkable. Routine blood examination showed hemoglobin 14 g/dl; total WBC count 16000/ μ l with 76% neutrophil; platelet count 220000/ μ l; ESR 40mm in 1st hour; C-reactive protein 35.2 mg/L (immunoturbidimetric method, normal < 6mg/L). Serum glucose, electrolytes and liver function test were within normal limits. A routine urine examination and chest X-ray was normal. Blood and urine were sent for culture. A stool examination was not done. Cefotaxime was suspended and the patient was started on I.V. ceftriaxone (60mg/kg/day every 12hrs) along with I.V. fluids and oral paracetamol (60mg/kg/day every 6hrs). While awaiting culture results, the patient developed high fever (103⁰F), headache and photophobia on the 8th day post-admission. On examination, neck rigidity was found and both Kernig's and Brudzinski's sign were positive. Apart from this no neurological abnormalities were noted. Cardiopulmonary examination

was unremarkable and no dyspnea or cyanosis was found. Remainder of the examination findings was unremarkable. A CT scan of brain was done and was normal. The first set of urine and blood culture were negative after 48hrs. On the 9th day post-admission, a lumbar puncture was done and CSF was sent for routine examination and culture; 2 sets of new specimen of blood (blood drawn from right and left cephalic veins) were sent for both aerobic and anaerobic culture. During this time, the fever, headache, photophobia and neck stiffness persisted but the epigastric tenderness had subsided.

The CSF opening pressure on lying posture was 25 cm H₂O. The routine examination of CSF showed a cloudy fluid with Cell count 1200/mm³; neutrophil 88%; protein 102 mg/dL; glucose, 25mg/dL. The gram stain and PCR for TB were negative. A provisional diagnosis of bacterial meningitis was made. The patient was started on steroid (Dexamethasone .15mg/kg every 6hrs). All the other drug treatments were continued.

On the 11th hospital day the anaerobic culture for blood (BacT/Alert FN culture media; Biomerieux, Kolkata, India) came positive (in both sets of blood specimen) for an anaerobic gram positive rod. The colonies were brownish in color and had characteristic horse-manure like odor. The diagnosis of *Clostridium difficile* bacteremia was confirmed by detection of the organism by the VITEK ANI card (Biomerieux, Kolkata, India). Detection of Toxin A from the colonies was done by a commercial ELISA method. Sensitivity to antibiotics revealed susceptibility to metronidazole and vancomycin and resistance to ceftriaxone. The CSF culture was found to be negative for any bacterial growth. A repeat L.P. was done and a new CSF specimen was sent for both aerobic and anaerobic culture.

Consequently, I.V. ceftriaxone was suspended and the patient was started on I.V. vancomycin (60mg/kg/day every 6hrs) and I.V. metronidazole (20mg/kg/day every 6hrs). The condition of the child markedly improved from 2nd day onwards of starting definitive treatment. The headache, neck stiffness disappeared by the 2nd day and he became afebrile by the 3rd day of starting I.V. vancomycin and metronidazole.

Discussion

The diagnosis of *Clostridium difficile* meningitis was made on the 13th day post-admission when the CSF anaerobic culture (BacT/Alert FN culture media; Biomerieux, Kolkata, India) was found to be positive for a gram positive rod. The colonies had a similar characteristic to

the ones found on blood culture and presence of *C. difficile* was confirmed by the VITEK ANI card (Biomérieux, Kolkata, India). Toxin A was detected from the strain by the ELISA method.

Clostridium difficile induced diarrhea is a common nosocomial infection and occurs due to altered bowel flora with long term use of virtually all known antibiotics particularly ampicillin, amoxicillin, clindamycin and cephalosporins.^{1,2} *Clostridium difficile* causes pseudomembranous colitis, the classical picture of which is diarrhea with blood and mucus, accompanied by fever, cramps, abdominal pain, nausea, and vomiting.¹ However, in our case these typical symptoms were notably absent.

Rarely,³ extra intestinal complications from *Clostridium difficile* infection may occur, which include brain abscess, chronic osteomyelitis, lung abscess, bacteremia, pericarditis etc.^{1,4} and the extra intestinal manifestations are usually preceded by disturbance in gut micro-flora.³ This patient was not under any concomitant medications (other than cephalosporins), not immunocompromised and had no known risk factors that might result in severe complications from *Clostridium difficile* infection.⁵

In our case the probable mechanism of this meningitis is as follows: Prolonged antibiotic therapy (using cephalosporins) → Disturbance in gut micro-flora → *Clostridium difficile* colonization → Bacteremia → Hematogenous spread → Meningitis.

Though the first blood culture (9th day post-admission) was negative, the suspicion of a bacteremia could not be excluded because of the typical presentation of the patient. Furthermore, even though the stereotypical presentation of a *Clostridium difficile* associated diarrhea was not found, it was still considered as the differential diagnosis due to the fact that this child had a history of prolonged antibiotic usage; sudden onset of fever and epigastric pain on the 7th hospital day after the initial symptoms due to septic arthritis subsided. From the routine examination of CSF the chance of viral or tubercular meningitis was excluded. A stool examination and culture was not done as the bowel movements were normal.

A chance of contamination of the blood samples sent for culture cannot be disregarded but it is unlikely as 2 sets of sample were sent and each were drawn from different sites and at different point of time. The result of the CSF culture matches the finding from the blood but, as a repeat LP & CSF culture was not done the chance of contamination still remains. But, it is still unlikely as the features of both meningitis and bacteremia improved rapidly upon

treatment with I.V. vancomycin. The treatment with vancomycin and metronidazole was continued for 10 days and the child was discharged on the 21st day post-admission. Routine follow up was done and no recurrence of symptoms was noted.

Though a few cases of bacteremia have been reported⁴, *Clostridium difficile* has never been reported as a causative agent for meningitis in children. *Clostridium difficile* induced bacteremia and anaerobic meningitis is undoubtedly a very rare extra-intestinal manifestation of the organism.

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