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Case Report / Vaka Sunumu

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Cases of enteric fever secondary to gastrointestinal infections

Gastrointestinal enfeksiyonlara sekonder enterik ateş vakaları

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ABSTRACT

Acute gastroenteritis is one of the most prevalent infectious diseases in childhood. It constitutes one of the major causes of morbidity and mortality among children under 5 years of age. Although most cases of acute gastroenteritis in children are self-limited and treated with only supportive therapy, clinical deterioration can sometimes be observed during the clinical course. Persistence of high fever or a second peak secondary to diminished fever with no obvious source in children with gastroenteritis should raise suspicion of secondary bacteremia. In this case report we have reviewed two cases of enteric fever with acute gastroenteritis secondary to Clostridium difficile and rotavirus gastroenteritis.

Keywords: *Clostridium difficile, rotavirus, enteric fever, gastrointestinal infections*

ÖZ

Akut gastroenterit, çocukluk çağındaki en yaygın enfeksiyon hastalıklarından biridir. Beş yaş altındaki çocuklar arasında morbidite ve mortalitenin major nedenlerinden birini oluşturur. Çocuklardaki birçok akut gastroenterit vakası kendini sınırlayan ve yalnızca destek tedavisi ile tedavi edilir olsa da klinik seyir esnasında vakalarda kötüleşme gözlenebilir. Gastroenteritli çocuklarda belli hiçbir kaynak olmadan inatçı ateş ya da azalan ateşe sekonder pik, sekonder bakteriyemi şüphesini artırmalıdır. Bu vaka raporunda, Clostridium difficile ve rotavirüs gastroenteritine sekonder iki akut gastroenteritli enterik ateş vakasını gözden geçirdik.

Anahtar kelimeler: *Clostridium difficile, rotavirüs, enteric ateş, gastrointestinal enfeksiyonlar*

INTRODUCTION

Acute gastroenteritis (AGE) is described as a decline in stool density and/or increasing in the frequency of evacuations with or without vomiting, and is a common infectious disease mostly seen in childhood. It remains one of the major causes of morbidity and mortality among children under 5 years of age[1]. Although gastroenteritis limits itself and is a mild disease, it is also a frequent cause of hospitalization[2]. Viruses are leading causes of AGE, and rotavirus is the main pathogenic agent of viral gastroenteritis in infants and young children[3]. Bacterial agents such as *Clostridium difficile* may be responsible for AGE in childhood which is mostly a nosocomial pathogen, resulting in a spectrum of intestinal diseases ranging from asymptomatic carriage and mild diarrhea to potentially fatal pseudomembranous colitis. In pediatric population, epidemiological studies demonstrated a change in the epidemiologic pattern of *C. difficile* infections, showing a two-fold increase within the last 5 years, but the incidence of severe complications did not increase[2-4].

Clinical syndromes caused by Salmonella species in humans are basically grouped as enteric or typhoid fever caused by *Salmonella typhi* or *S.paratyphi*, with a spectrum of clinical syndromes including diarrheal disease caused by a large number of non-typhoid salmonellae (NTS)[5].

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Although most AGE cases in children are self-limited, and treated with only supportive therapy, clinical deterioration can sometimes be observed during the clinical course. Clinical and laboratory findings compatible with a severe bacterial infection should alert physicians about the possibility of secondary bacterial infections. We present two cases of enteric fever secondary to *C. difficile* and rotavirus gastroenteritis.

CASE REPORTS

Case 1: A 2 year-old boy was admitted to our hospital with fever, vomiting, and mucoid defecation within previous 3 days. His body temperature was 39°C, pulse rate 120/min, blood pressure 90/60 mmHg, and respiratory rate 50/min. Moderate dehydration, hepatomegaly (4 cm below the costophrenic margin) and splenomegaly (3 cm below the costophrenic margin) were observed. Laboratory examinations results were as follows: white blood cell count, $15x10^9$/L (neutrophil count $9x10^9$/L); hemoglobin, 8.8 g/dL, platelet count, $78,000x10^9$/L; C-reactive protein (CRP) 19 mg/dl (normal; <5 mg/dl), and negative direct Coomb's test. Left shift and toxic granulation were observed in peripheral blood smear.

Serum biochemistry was normal, except for albumin 2.7 g/dl, and D-dimer, 3.41 µg/ml (0-0.55) while activated partial thromboplastin time (APTT) 19.4 (21-35), prothrombin time (PT) 14.3 (10.5-14.9) and International Normalized Ratio (INR) 1.16 (0.8-1.2) were within normal limits. Stool examinations for adenovirus and rotavirus antigens were negative. Treatment was started with ceftriaxone (75 mg/kg/day) and vancomycin (45 mg/kg/day). Oral metronidazole (30 mg/kg/day) was added to treatment following positive *C. difficile* toxin A-B results and was maintained for 10 days. Intravenous immunoglobulin and erythrocyte suspension were used for resistant anemia and thrombocytopenia due to probable disseminated intravascular coagulopathy. Both blood and stool cultures yielded *S. typhi* strains which were sensitive to ceftriaxone and amikacin. Vancomycin treatment was stopped. Immunological examination, and evaluation of immunoglobulin levels, lymphocyte subgroups, and interferon-γ and IL-12-binding receptor levels revealed no immunodeficiency. On the eighth day of the treatment, clinical improvement, negative control blood culture, and normal laboratory values were observed. He was discharged on the 14^{th} day of the antibiotic therapy.

Case 2: An 8 month-old boy presented with a 10-day history of fever and watery diarrhea. His vital signs and physical examination findings were unremarkable. White blood cell count was $10.3x10^9$/L, hemoglobin level 11.8 g/dl, platelet count $392,000x10^9$/L, and CRP 2.7 g/dl. Serum biochemistry was normal. Rotavirus antigen was detected at stool examination. Intravenous fluid replacement was started while monitoring oral intake. Two days later, fever increased to 39.5°C. Blood and stool culture were taken, and ceftriaxone therapy (75 mg/kg/day) was started in case of secondary bacteremia. On the second day of the antibiotic treatment, his fever diminished and diarrhea regressed. No growth was observed in stool culture, while his blood culture yielded *S. typhi*, which was sensitive to ceftriaxone. Immunological investigation (immunoglobulin levels, lymphocyte subgroups, and interferon-γ and IL-12-binding receptor levels) was normal. Antibiotic treatment was given for 14 days and he was discharged with negative blood cultures and without symptoms.

DISCUSSION

We have described two cases of gastroenteritis complicated with secondary Salmonella bacteremia. The hallmark of these secondary bacteremia cases was increased body temperature with no apparent source. Bacteremia following AGE is well-documented. Systemic manifestations (bacteremia, sepsis, and involvement of other organs like meninges, bones and lungs,) can complicate gastrointestinal infections caused by *Yersinia, Shigella, Salmonella,* and *Campylobacter spp.*[2]. In previous studies the prevalence rates of bacteremia secondary to gastroenteritis have been reported to range between 0.32, and 1.3% 6,7. Typhoid (enteric) fever is an acute and

often life-threatening febrile disease caused by *Salmonella enterica serotype typhi*, and it is a significant public health concern especially in low and middle-income countries[5]. Typhoid fever affects nearly 21 million people each year, resulting in 200,000 to 600,000 deaths annually[8]. The case-fatality rate in inappropriate antibiotic using patients is 10-30%[9]. Consumption of food or drink contaminated with feces is generally responsible for the transmission of *S. typhi* and, *S. paratyphi A*. and *Salmonella spp.*, which cause several clinical manifestations, ranging from AGE to typhoid fever and bacteremia[10]. Data regarding the prevalence of secondary enteric fever are limited in number . Torrey et al. [11] reported a prevalence of non-typhoidal Salmonella bacteremia of 6.5% in children with AGE due to Salmonella spp. Similarly, our first patient experienced salmonella gastroenteritis secondary to enteric fever.

In our first case, *C. difficile toxin A-B* was detected, and the patient was treated accordingly. Although *C. difficile* infection (CDI) is an etiological agent of hospital-associated gastrointestinal illness with substantial morbidity and mortality, community-acquired, and nosocomial infection rates are increasing among children[12]. Symptoms of CDI are very diverse and range from an asymptomatic carrier stage to life-threatening events, such as toxic megacolon. While it generally presents with mild to moderate, non-bloody diarrhea, and lower abdominal cramping, severe CDI causes systemic symptoms, like abdominal pain and distention, watery diarrhea and fever[13]. CDI results from normal colonic flora alteration then colonization and subsequent proliferation of the organism and expression of its toxin due to inappropriate antibiotic use[12-14]. Other risk factors for CDI are exposure to *C. difficile*, exposure to gastric acid suppressing agents, underlying illnesses such as inflammatory bowel diseases, malignancies, immunodeficiencies, hematopoietic stem cell transplants and solid organ transplants[12]. *C. difficile* or its toxin in stool can represent colonization, particularly in infants and younger children, and positive results should therefore be evaluated with caution[15]. Our patient had no history of antibiotic exposure and no other risk factors. Despite the possibility of colonization and antibiotic treatment not being completely appropriate, he was given oral metronidazole due to a deteriorating clinical picture. Diagnosis of CDI typically relies on a high index of clinical suspicion and laboratory confirmation in stool. CDI can be confirmed by the presence of toxins A and B in the stool sample, anaerobic stool culture, and polymerase chain reaction. Toxin detection in the stool has a sensitivity of 70-80% due to the large number of false negatives[13]. We diagnosed CID in our patient based on a positive stool test for *C. difficile* toxin. Patients with non-severe CDI can be treated with oral metronidazole for 10 days and severe cases should receive oral vancomycin or oral fidaxomicin[16].

Rotavirus gastroenteritis generally limits itself in otherwise healthy children. Despite the high frequency of rotavirus gastroenteritis, secondary bacteremia in the course of the illness has rarely been reported[6]. Although its exact mechanism is not known, it is thought that infected enterocytes become more unprotected to bacterial invasion as a consequence of intestinal epithelium dysfunction caused by rotavirus[17]. Bacterial translocation induced by the damage to the intestinal mucosa occurs later in the course of the disease. In the second patient, rotavirus gastroenteritis with Salmonella bacteremia was diagnosed and treated successfully.

The first line treatment options in typhoid fever is chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole. However, newer quinolones and third generation cephalosporins are associated with higher cure rates[18]. Despite appropriate treatment, 2-4% of the infected children may relapse after initial clinical response[18]. In both of our cases, the bacteria were sensitive to empirically started ceftriaxone, and neither patient developed relapse or complication. Disseminated infections such as bacteremia due to *S. typhi* after AGE are not a frequent condition in immunocompetent patients[19]. Nevertheless, immunological investigations of both patients were normal.

CONCLUSION

Enteric fever is a serious clinical condition that pediatricians may well encounter. Salmonella typhi bacteremia secondary to AGE is probably possible although it is rarer than other bacteria, management of these cases is similar. Persistence of high fever or a second peak during diminished fever with no obvious source in children with gastroenteritis should raise suspicion of secondary bacteremia. The first step is consideration of prompt and rapid start of antibiotic treatment after blood cultures are taken.

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