

Tuberculosis in an infant with Hirschsprung-associated enterocolitis: a case report

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Abstract

Hirschsprung-associated enterocolitis (HAEC) is a serious and life-threatening condition, and atypical tuberculosis (TB) associated with HAEC is even more serious. A male newborn aged 4 days was diagnosed with Hirschsprung disease and transanal Soave pull-through was performed at 4 months old. Six months later, he suffered from enterocolitis. Although he was treated with multiple broad-spectrum antibiotics for 2 weeks, he developed a fever without any other symptoms for TB infection. We found numerous, bilateral, uniformly distributed, small pulmonary nodules in the lower lobes in an abdominal radiograph by chance. He was then discharged with complete resolution of all symptoms after anti-TB therapy. Early diagnosis and treatment of TB can effectively improve the prognosis of children with HAEC.

Keywords

Hirschsprung-associated enterocolitis, acute miliary tuberculosis, fever, pulmonary nodule, antibiotic, infant

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Introduction

Hirschsprung disease (HD) is an infrequent disease characterized by the congenital absence of parasympathetic ganglia in the rectum and sigmoid colon, or in the entire colon.¹ HD can even extend to part of the small intestine. Hirschsprung-associated enterocolitis (HAEC) is a serious and life-threatening condition that can occur in up

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to 60% of patients with HD.² Infection is a large problem in these patients.

Approximately 10 million people suffered from TB and 1.4 million of them died in 2019, and 12% were children (aged <15 years).³ When the diagnosis and treatment of TB are delayed, the mortality rate can reach 50%.⁴ A delayed diagnosis of TB in children with HAEC is always concerning because of the limited recognition and experience of pediatricians. We present a case of atypical TB that occurred in an infant with HAEC. We also discuss the use of broad-spectrum antibiotics for this condition. We hope that our report will assist pediatricians in improving the recognition of atypical TB in children with HAEC.

Case presentation

The reporting of this study conforms to the CARE guidelines.⁵ A male neonate aged 4 days was admitted to our hospital for marked abdominal distension. He did not pass meconium within 24 hours of birth in the postnatal ward. Two days later, a radiological evaluation and histological diagnosis for HD were carried out. HD was diagnosed and transanal Soave pull-through was performed at 4 months old.

At the age of 10 months, he presented with a fever, diarrhea, and vomiting. The highest temperature reached up to 39.4°C. The diarrhea was watery mucus without blood, and it occurred 10 to 15 times/day. He had no history of cough, seizures, or food allergy. The patient had not been injected with Bacillus Calmette–Guerin vaccine and there was no family history of TB. On admission, a physical examination showed the following: temperature, 37.8°C; respiration, 35 breaths/minute; heart rate, 128 beats/minute; and blood pressure, 84/45 mmHg. The anterior fontanel was slightly sunken. Slight abdominal distension was observed without muscular tension or rebound tenderness, and the bowel sounds

were five to six times/minute. No positive signs in other systems were observed. Auxiliary examinations showed leukocytosis ($12.0 \times 10^9/L$), anemia (Hb 96 g/L), a normal serum procalcitonin concentration (0.2 ng/mL), and a high C-reactive protein concentration (60 mg/L) and erythrocyte sedimentation rate (73 mm/hour). No abnormalities were observed in blood cultures, urinalysis, stool, renal/liver function, the percentage of serum CD4 and CD8 lymphocytes, serum immunoglobulin (Ig) G, IgM, or IgA concentrations, or electrolytes. A computed tomography scan of the abdomen showed a small air–fluid level in the upper left abdomen. HAEC was considered, and therefore, the patient was temporarily fasted. We initiated empirical treatment with intravenous cefoperazone-sulbactam.

On the ninth day of admission, we intended to discharge the child with complete resolution of all symptoms. However, he presented with fever again and began to decrease milk intake. The highest temperature was 40.5°C. A physical examination was unremarkable. To further investigate the nature of the child's fever, lumbar puncture and a chest X-ray were conducted. Cerebrospinal findings showed that the monocyte count was $80 \times 10^6/L$, protein concentration was 305.7 mg/L, glucose concentration was 2.75 mmol/L, and chloride concentration was 124 mmol/L. Acid-fast staining was negative in a cerebrospinal smear. A chest X-ray showed a few scattered patch-shadows in both lung fields with pneumonia-like changes. The antibiotic was switched to meropenem for presumed atypical bacterial meningitis, which was finally proven to be tuberculous meningitis.

Unfortunately, the effects of the antibiotics were discouraging. Stool screening showed a high white blood cell count (3–5/high power). Because of severe infections in children with HAEC, we decided to treat our patient with vancomycin, meropenem, and metronidazole. To distinguish necrotizing

enterocolitis, we performed an erect abdominal radiograph, which showed numerous, bilateral, uniformly distributed, small pulmonary nodules in the lower lobes by chance (Figure 1a). A chest X-ray also demonstrated acute miliary pulmonary tuberculosis (Figure 1b). A further purified protein derivative test, T-spot assay, and a stool GeneXpert[®] MTB/RIF assay were positive for TB. The results of *Chlamydia*/*Mycoplasma* antibody, serum glucan/galactomannan tests, and blood culture were negative. Therefore, the diagnosis of TB associated with HAEC was confirmed.

The patient was then administered four anti-TB drugs (isoniazid 10 mg/kg/day, rifampicin 15 mg/kg/day, ethambutol 20 mg/kg/day, and pyrazinamide 35 mg/kg/day). After 3 days of treatment, he symptomatically improved. The child was then discharged and prescribed anti-TB drugs as an outpatient without sequelae.

Discussion

HD is a congenital abnormality that can be surgically corrected. However, HAEC

remains a significant cause of morbidity and mortality in infants with HD, and more than half of HAEC episodes occur within the first year of an operation.⁶ Therefore, we initiated empirical treatment of antibiotics early in our patient.

Our patient was in good health after the operation, but TB spread within 5 days. Other causes of TB infection were ruled out and we attempted to explain the reason for TB from the perspective of intestinal microbes. We constantly adjusted antibiotics, but ignored the frustrating effects of these antibiotics. An infant's immune system is not fully functional, and the intestinal microbiota is immature until 2 to 3 years old⁷. In children with HAEC, intestinal dysbiosis and impaired intestinal renewal are easily caused by an operation.^{8,9} Furthermore, recurrent antibiotic administration can destroy the normal commensal intestinal bacteria. Commensal intestinal bacteria regulate adaptive and innate immunity by producing metabolites.¹⁰ Recent research has indicated that intestinal dysbiosis compromises alveolar macrophage immunity, leading to an increased

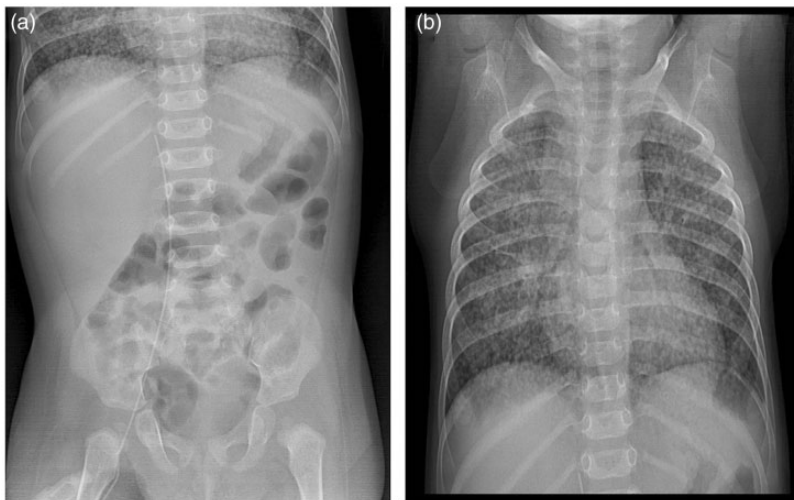


Figure 1. Erect abdominal radiograph (a) and chest X-ray (b) show that the lower lobes contain numerous, bilateral, uniformly distributed, small pulmonary nodules.

susceptibility or recurrence of TB.^{11,12} Therefore, in our patient, we speculated that antibiotic-driven dysbiosis may have played an important role in TB infection and spread on the basis of HAEC. Notably, the consequences due to broad-spectrum antibiotic treatment are more severe and long-lasting in infants compared with adults.¹³ Therefore, when there is no etiological evidence, broad-spectrum antibiotics should be used with caution in these patients. Additionally, when broad-spectrum antibiotics need to be used, TB infections should be screened as early as possible, even if there are no related symptoms.

We are unsure where the primary focus of TB was in our patient. His first chest X-ray did not show pulmonary TB, but acute miliary tuberculosis of the lungs rapidly progressed within 5 days without any respiratory symptoms. Additionally, there was no family history of TB or chronic cough. We assumed that the lungs were not the primary focus of TB. The patient suffered an unexplained intestinal obstruction and the stool GeneXpert[®] MTB/RIF assay was positive. Cases of intestinal TB in infants have been reported.¹⁴ Therefore, we believe that children may suffer from intestinal TB, which spreads to the lungs and brain by the bloodstream. Unfortunately, the guardians of our patient refused to allow endoscopy to be performed. Therefore, we were unable to determine if there was intestinal obstruction.

A variety of factors diverted our patient's diagnosis to the possibility of other diseases, which led to a delay in the diagnosis and differential diagnosis. Early diagnosis and treatment of TB can effectively improve the prognosis of children with HAEC. The findings in our case should promote awareness of this condition in pediatricians. Our findings suggest the following. First, manifestations and cerebrospinal fluid analysis of TB can be

non-specific, even without any TB symptoms, except for a fever. Second, TB should always be considered in the differential diagnosis in children with a history of abdominal surgery and persistent fever, especially in developing countries. Finally, broad-spectrum antibiotics should be adjusted cautiously in patients with HAEC when there is no clear etiological evidence because antibiotics may cause complications.

Conclusion

TB associated with HAEC in young patients represents a diagnostic challenge for pediatricians. TB should be considered in children with abdominal surgery and persistent fever, even if there are no other symptoms of TB infection, especially in developing countries. When there is no evidence of bacterial infection, broad-spectrum antibiotics should be cautiously used. Early diagnosis and treatment of TB can effectively improve the prognosis of children with HAEC.

Ethics statement

This research was approved by the Ethics Committee of West China Second University Hospital, Sichuan University (Medical Research No. 2020(004)). Written informed consent was obtained from the patient's parents for the publication of this case report and the accompanying images.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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