Case Report

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Typhoid fever complicated by sepsis and disseminated intravascular coagulation in a 7-year-old boy

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A 7-year-old boy presented with typhoid fever complicated by sepsis and disseminated intravascular coagulation. The patient's international travel history and the presence of relative bradycardia provided important diagnostic clues. Early administration of antimicrobial therapy and general care resulted in rapid improvement in his general condition. In Japan, typhoid fever is a relatively rare infection originating overseas, but its incidence has increased in recent years. Typhoid fever should be considered if a patient exhibits fever and digestive symptoms.

Key words: Typhoid fever, sepsis, disseminated intravascular coagulation, international travel history, relative bradycardia

Abbreviations: DIC, disseminated intravascular coagulation; DS, standard deviation; CSF, cerebrospinal fluid; CT, computed tomography; CTX, cefotaxime; CTRX, ceftriaxone; NFX, norfloxacin

Introduction

Typhoid fever is an infection caused by the bacterium *Salmonella typhi*. It is mainly transmitted via the oral route through food or water contaminated by the feces or urine of an asymptomatic carrier, or a person infected with typhoid fever. A total of 40,000 people per year were diagnosed with typhoid fever in Japan from the early Shōwa era until a few years after World War II. However, this number dramatically decreased with improvements in hygienic conditions (fewer than 100 cases per year),[1,2] and most cases of typhoid/paratyphoid fever nowadays are of overseas origin.[2]

Common symptoms are fever and digestive symptoms, such as abdominal pain, diarrhea, and bloody stools. In severe cases, typhoid fever may be accompanied by intestinal perforation.[3] A roseola-like rash may be seen in some patients, but this rash does not always appear. For these reasons, obtaining information concerning a patient's international travel history is vitally important when taking the medical history. Typhoid vaccines have not been approved in Japan. They are recommended for people traveling to high-risk areas, but the inoculation rate is not high.[2] Here, we report our experience involving a case of typhoid fever in a boy who developed sepsis and disseminated intravascular coagulation (DIC) after returning to Japan from India, with a review of some relevant literature.

Case report

A 7-year-old boy presented with fever, diarrhea, vomiting, and excessive drowsiness. The patient did not have a history of any underlying disease, and his birth was a full-term, normal delivery. His father was of Indian ethnicity, his mother was Japanese, and he had no siblings. Neither parent exhibited fever or digestive symptoms.

Medical history

Two weeks following the family's return from India, the patient experienced a fever of 40℃, diarrhea, and vomiting, and was taken to an emergency medical care center. He was prescribed oral medications, including antimicrobial agents, but was unable to take them due to severe nausea. One week later, the patient was seen by his previous doctor and was hospitalized on the same

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day due to poor oral intake. The day following his hospital admission, the patient exhibited excessive drowsiness, and his blood test results revealed decreased platelet count and abnormalities of the congealing fibrinogenolysis system. Therefore, the patient was transferred to our hospital the next day.

Medical condition on admission

His body weight was 28.0 kg (+0.4 standard deviation [SD]) and his height was 128.0 cm (+0.6 SD). He did not show retractive breathing, and his breath sounds were clear; however, his breathing rate was 40 breaths per minute, indicating tachypnea. His heart rate was 102 beats per minute, and systolic blood pressure was 98 mmHg. The heart sounds were normal without extra sounds or murmurs. The capillary refill time was less than 2 seconds, and no peripheral circulatory insufficiency was noted. His level of consciousness was assessed using the Glasgow Coma Scale and the total score was 12 (Eye opening = 3, Verbal response = 4, and Motor response = 5). He had a body temperature of 40.8℃, and his facial expression was apathetic. No bulbar conjunctiva hyperemia, eye discharge, cervical lymph node swelling, or pharyngeal erythema was noted. Palpation of the abdomen revealed board-like rigidity and muscle guarding, along with extensive tenderness and rebound tenderness over the abdomen. Increased bowel sounds were also noted. The liver was palpated 4 cm below the right hypochondrium, indicating hepatomegaly. Bilateral inguinal lymphadenopathy was also identified.

Examination findings on admission

A decreased platelet count, liver dysfunction, and a high level of ferritin were found, suggesting a strong

Table 1. Laboratory data on admission

Blood cell counts			Biochemical examination			Arterial blood gas analysis		
White blood cells	7,800	/μl	Total protein	6.0	g/dl	pH	7.507	
Neutrophils	6,107	/μl	Albumin	2.9	g/dl	$PaCO_2$	35	Torr
Monocytes	265	/μl	Total bilirubin	0.5	mg/dl	PaO_2	223	Torr
Lymphocites	1,404	/μl	Blood urea nitrogen (BUN)	7.1	mg/dl	HCO^{3-}	27.1	mmol/l
Hemoglobin	11.7	g/dl	Creatinine	0.6	mg/dl	Bass exess	4	mmol/l
Hematocrit	34.6	%	Asparate aminotransferase			Glucose	112	mg/dl
Platelets	10.4	10^4/μl	(AST)	273	IU/l	Lactate	11.2	mg/dl
Prothronbin time	12.6	sec	Alanine transaminase (ALP)	159	IU/l			
Activated partial thromboplastin time	38.8	sec	γ-glutamyl transpeptidase (γ-GTP)	308	IU/l			
Fibrinogen	192	mg/dl	Lactate dehyprogenese (LDH)	1,079	IU/l			
Fibrin degeneration product (FDP)	73.4	μg/ml	Creatininekinese (CPK)	90	IU/l			
D-dimmer	30.64	μg/ml	Natrium	132	mEq/l			
Antithronbin-III	90	%	Kalium	3.1	mEq/l			
			Chlorine	96	mEq/l			
			C-reacting protein (CRP)	2.45	mg/ml			
			Ferritin	3,188	ng/ml			
			Procarcitonin	1.74	ng/ml			

Table 2. Data for cerebrospinal fluid, viral antigen, and bacterial culture

Cerebrospinal fluid examination			Antigen tests		Bacterial culture inspection	
Property	Clear		Pheryngeal hemolytic streptococcus	Negative	Pharynx	Streptococcus pneumoniae: 10*4
Protein	24	mg/dl	Pharyngeal influenza virus	Negative	Flight	Negative
Glucose	61	mg/dl	Fecal rotavirus	Negative	Urine	Negative
Cells	3	/μl	Fecal adenovirus	Negative	Cerebrospinal fluid	Negative
			Fecal norovirus	Negative		

inflammatory response (Table 1). The levels of fibrinogen/fibrin degradation products and D-dimer were also high, and the acute DIC score was 4, leading to a diagnosis of DIC. Urinalysis revealed no significant abnormalities, the fecal occult blood test result was negative, and cerebrospinal fluid (CSF) analysis showed no abnormalities (Table 2). Results of rapid antigen tests using pharyngeal and stool specimens were negative. Plain radiography of the abdomen did not detect free air but revealed gas accumulation in the small and large intestines (Figure 1). Contrast-enhanced computed tomography (CT) of the abdomen showed intestinal wall edema, multiple enlarged mesenteric lymph nodes, and splenomegaly (Figure 2).

Based on these findings, the patient was diagnosed with bacterial enteritis, as well as DIC and sepsis as suspected complications of the bacterial enteritis, and treatment with cefotaxime (CTX) was initiated.

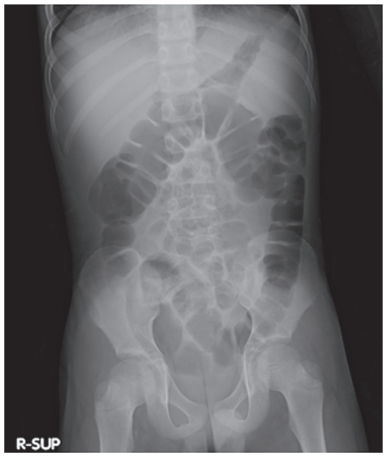

Figure 1. Plain radiography of the abdomen showing gas accumulation in the small and large intestines

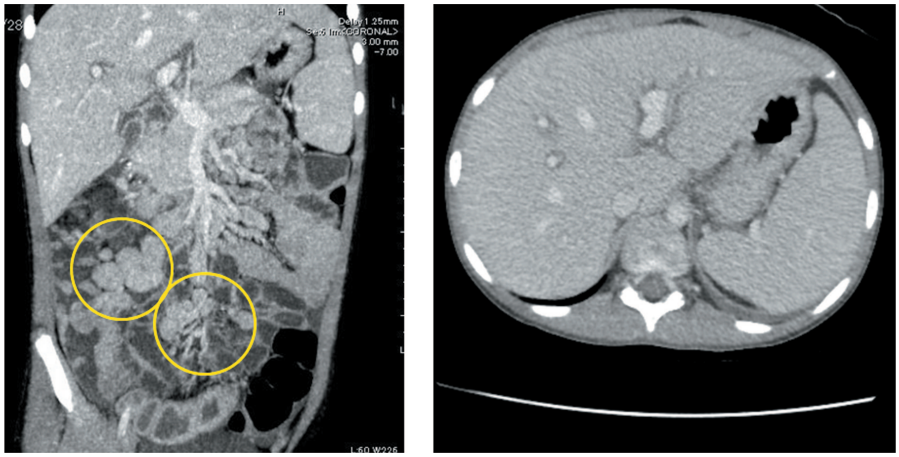

Figure 2. Contrast-enhanced computed tomography of the abdomen showing intestinal wall edema, multiple enlarged mesenteric lymph nodes, and splenomegaly

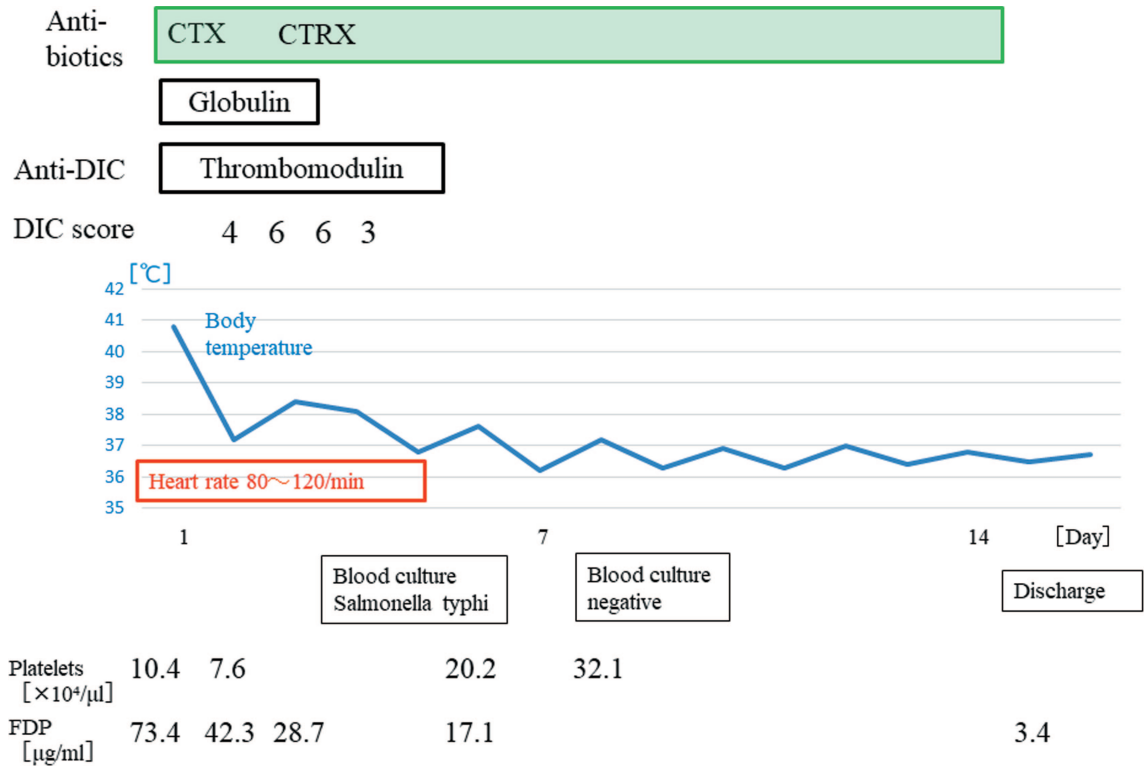

Figure 3. Clinical course during hospitalization

Clinical course during hospitalization

Figure 3 shows the clinical course during hospitalization. Despite the high fever and tachypnea, the heart rate remained between 80 and 120 beats per minute. The patient was admitted to our pediatric intensive care unit where a rectal tube was inserted to decompress the intestinal tract. Antimicrobial therapy with CTX was administered initially, but the results of a blood culture was suggestive of *Salmonella* infection. Based on the patient's international travel history, the possibility of *Salmonella typhi* infection was considered, and CTX was switched to ceftriaxone (CTRX), recommended for patients infected with this bacterium. A subsequent blood culture confirmed the presence of *Salmonella typhi*, and a diagnosis of typhoid fever was confirmed. Bacterial cultures from pharyngeal, stool, urine, and CSF samples were negative. Treatment with the antimicrobial agent, anti-DIC therapy, and general care rapidly improved the patient's consciousness, platelet count, DIC score, and liver dysfunction, and he was transferred to the general ward on day 3 of hospitalization. From day 4, oral intake was started and antimicrobial therapy was continued for 14 days before being discharged from hospital.

Discussion

The incubation period of *Salmonella typhi* in typhoid fever is 1 to 2 weeks. It manifests as a fever complicated by digestive symptoms. In a typical case, a gradual increase in body temperature, relative bradycardia, roseola-like rash, and hepatosplenomegaly are observed in the first week after onset. In the second week, the patient presents with a sustained fever and may exhibit apathetic facial expression (typhoid face) and consciousness disorder. In the third week, the patient may experience gastrointestinal bleeding and/or intestinal perforation, reported as being due to impairment of Peyer's patches in the small intestine.[4] The fourth week normally marks the recovery phase. For a diagnosis of typhoid fever, detection of *Salmonella typhi* via a blood or stool bacterial culture is necessary. In Japan, 70% to 80% of patients with typhoid fever have a history of traveling to the Indian subcontinent or Southeast Asia.[2] Therefore, medical history taking that includes information on a patient's international travel history is essential. According to the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases, typhoid fever is categorized as a Category III Infectious Disease. Once a diagnosis of typhoid fever is made; the nearest public health center should be notified immediately. Typhoid fever is also classified as a Type III Infectious Disease in the School Health and Safety Act, and students infected with the disease are advised not to attend school until completely free of the disease.[2]

This 7-year-old boy had recently travelled to India; therefore, we considered typhoid fever, paratyphoid fever, and other infectious diseases of overseas origin as candidate conditions for the differential diagnosis. The patient's vital signs revealed a heart rate inconsistent with his high body temperature and tachypnea (relative bradycardia). Relative bradycardia is also seen in patients with paratyphoid fever, chlamydia pneumoniae, psittacosis, Legionella, brucellosis, malaria, drug-induced fever, meningitis, diseases of the central nervous system, and malignant lymphoma. According to Cunha, the average heart rate of patients aged 13 years or older with no arrhythmia, beta-blocker medication, or thyroid dysfunction is 140 beats per minute at a body temperature of approximately 40.7℃.[5] In the present case, the patient's heart rate was 100 beats per minute at a body temperature as high as 40.8℃, which was relatively low considering that the patient was 7 years old. Additionally, he presented with hepatosplenomegaly and a typhoid face appearance, along with other physical features of typhoid fever, but the roseola-like rash was absent.

First-line treatment for typhoid fever involves new quinolone antimicrobial agents such as norfloxacin (NFX). However, resistance to new quinolones has been noted in an increasing number of patients with typhoid fever, mainly those with a history of traveling to India. Therefore, in cases where a bacterial culture shows resistance to nalidixic acid (the first-generation quinolones), CTRX or CTX is also administered in combination with NFX.[2] With either agent, it is recommended that antimicrobial therapy be administered for two weeks.[2] In the present case, CTX was initially used based on a suspected infection of the gastrointestinal tract of unknown origin and sepsis. However, once the blood culture test identified the genus *Salmonella*, CTX was switched to CTRX, as it is recommended more for patients infected with *Salmonella*. *Salmonella typhi* was identified, but NFX was not used due to nalidixic acid resistance revealed using a drug sensitivity test. A blood bacterial culture performed after the treatment confirmed a negative result.

Reported complications of typhoid fever involve gastrointestinal bleeding and intestinal perforation. Here, multiple fecal occult blood tests were performed, but no gastrointestinal bleeding was observed throughout the course. The incidence of DIC secondary to typhoid fever is reported to be high.[6] The fundamentals of treatment and management are to treat the primary disease or the

infection, but we also selected thrombomodulin as supportive therapy. The decreased platelet count and blood coagulation disorder gradually improved over time, most likely as a result of the primary treatment involving early administration of antimicrobial therapy.

Relevant information concerning rare diseases is extremely important for accurate diagnosis, adequate treatment, and prevention of infection transmission. We encountered a pediatric case of typhoid fever, which is extremely rare in Japan. The patient's international travel history, obtained by taking a thorough medical history, and the presence of relative bradycardia among other physical findings, provided vital information for treatment and diagnosis. These findings may be useful in the differentiation of gastrointestinal symptoms.

Conflicts of interest

None

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