〈Case Report〉

A case of pediatric patient with acute enteritis due to CTX-M-15 extended-spectrum *β*-lactamase-producing *Salmonella* Blockley

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This clinical case report concerns a pediatric patient with acute enteritis caused by multi-drug resistant *Salmonella enterica* serovar Blockley (*Salmonella* Blockley). A 3-year-old boy presented to our emergency room with a 5-day history of fever, abdominal pain, and bloody diarrhea. Stool culture tested positive for a *Salmonella* species, while the blood culture was negative. The patient was successfully treated with an oral antibiotic regimen of fosfomycin. The stool isolate was found to be resistant to multiple drugs, including cefpodoxime, cefotaxime, ceftazidime, and aztreonam, and was confirmed to be a CTX-M-15 extended-spectrum *β*-lactamase (ESBL)-producing strain of *Salmonella* Blockley. This is the first report of a pediatric patient in Japan with acute enteritis caused by a CTX-M-15 ESBL-producing strain of *Salmonella* Blockley.

Introduction

Salmonella enterica serovar Blockley (*Salmonella* Blockley) is a strain of non-typhoidal *Salmonella* (NTS) that is isolated occasionally in infectious enteritis in Japan[1)]. Compared to other Enterobacteriaceae including *Escherichia coli* and *Klebsiella pneumoniae*, extended-spectrum *β*-lactamase (ESBL) production was previously rare in *Salmonella enterica* strains. However, the recent reports suggested that these strains show an increasing trend in the world[2)]. But, the case of human infection due to ESBL-producing NTS is rare in Japan. We report here the first pediatric case with enteritis due to CTX-M-15 ESBL-producing *Salmonella* Blockley in Japan.

Case presentation

In August 2015, a 3-year-old boy presented to the emergency room at Kyorin University Hospital (Tokyo, Japan) with a 5-day history of fever, abdominal pain, and bloody diarrhea. His medical history was unremarkable, with no recent history of any prolonged illness, hospitalization, previous antibiotics use, or similar illness in the family or preschool. His life history was unremarkable, with no history of eating eggs or raw foods or traveling abroad, but he did have a dog. His parents also had never been abroad ever. Initial vital signs showed a temperature of 38℃, while other vital signs were normal. Physical examination revealed abdominal pain around the umbilicus. Other systemic examinations were normal. Laboratory data showed a white blood cell count of 7,700/mm^3 (neutrophils: 51.5%), platelet count of 233,000/mm^3, hemoglobin 11.3 g/dl, and C-reactive protein 1.86 mg/dl. Liver and renal function tests showed no abnormalities. Infectious enteritis was suspected, and stool and blood cultures were performed. The stool culture tested positive for a *Salmonella* species, but the blood culture was negative. The stool isolate was resistant to ampicillin, cefazolin, cefpodoxime, cefotaxime, ceftazidime, cefepime, and aztreonam, but susceptible to meropenem, ampicillin-sulbactam, piperacillin-tazobactam, trimethoprim-sulfamethoxazole, ciprofloxacin, levofloxacin, minocycline, and fosfomycin. Given its resistance to third generation cephalosporins and monobactams, we suspected an ESBL-producing *Salmonella* species. It was serotyped as *Salmonella* Blockley using anti-O, -H sera, and the presence of a $bla_{\text{CTX-M}}$ β-lactamase gene was confirmed through polymerase chain reaction (PCR) with CTX-M universal primers F(5′-TTTGCGATGTGCAGTACCAGTAA-3′) and R(5′-CGATATCGTTGGTGGTGCCATA-3′), as described previously Edelstein *et al.*[3]; the isolate tested positive for $bla_{\text{CTX-M}}$. Next, we confirmed the presence of a $bla_{\text{CTX-M-15}}$ β-lactamase gene using PCR, with primers F(5′-ATGGTTAAAAAATCACTGCG-3′) and R(5′-GGTGACGATTTTAGCCGCCGA-3′) (NG 048935; 101-120, 664-644), the amplified PCR product was sequenced to find that it completely matched with corresponding part of the known $bla_{\text{CTX-M-15}}$ sequence. Three different PCR assays run at the National Institute of Infectious Diseases to test for bla_{TEM}, bla_{CMY}, and $bla_{\text{CTX-M-15}}$, detected only $bla_{\text{CTX-M-15}}$. The patient was treated immediately with an oral antibiotics regimen of fosfomycin (90 mg/kg/day) for 5 days, after which his condition improved. A follow-up stool culture was negative for *Salmonella* Blockley. Source of infection could not be identified.

Discussion

NTS represents one of the principal pathogens implicated in food-borne enteritis worldwide. All cases of *Salmonella* food poisoning of outbreak in Japan are required to be reported to the Ministry of Health, Labour and Welfare. Incidences of *Salmonella* food poisoning has shown a

clear reduction since 2000 in Japan, such that the yearly incidence has remained under 50 for the past few years. On the other hand, incidences of infectious enteritis by NTS with individual case are unclear. Cases for which NTS was isolated at our hospital have increased since 2007, as follows: 11 ceses in 2007–2009 (5 children, 6 adults), 18 cases in 2010–2012 (4 children, 14 adults), and 31 cases in 2013–2015 (13 children, 18 adults). We surmise that infectious enteritis by NTS without *Salmonella* food poisoning may have increased due to the diversified dietary culture and increased overseas travel. ESBL-producing NTS has not been isolated in our hospital. Although the case of human infection due to ESBL-producing NTS is rare in Japan, the three cases were reported. CTX-M-14 ESBL-producing *Salmonella* enteritidis was first isolated from a pediatric patient with enteritis in 2005, CTX-M-2 ESBL-producing *Salmonella* Heidelberg was isolated from a pediatric patient with enteritis in 2013, and CTX-M-55 ESBL-producing *Salmonella* enteritidis was isolated from an adult patient with liver abscess in 2014[4~6].

Several organisms producing clavulanic acid-inhibited Ambler class A ESBL have been reported, mostly in Enterobacteriaceae, in addition to those producing TEM- and SHV-type ESBL. Among these enzymes, the CTX-M-type β-lactamases are plasmid-mediated ESBL and confer a high level of resistance to cefotaxime, ceftriaxone, aztreonam and have only marginal effects on the minimal inhibitory concentration of ceftazidime[7]. The CTX-M-15 ESBL were identified in Enterobacteriaceae isolates in India in 2001, and demonstrated significant hydrolytic activity against ceftazidime, in contrast to the majority of CTX-M enzymes[8]. The initial reports of CTX-M-15-producing NTS came from France and Senegal in 2004[9]. Clinical isolation of CTX-M-15-producing NTS was reported at our country in 2014[10]. CTX-M-type ESBL-producing Enterobacteriaceae are important nosocomical infectious agents raising considerable concern in the public health community. While no marked increases in CTX-M ESBL-producing NTS have been reported in Japan, detection rates should be monitored closely.

The most common clinical illness caused by NTS inclucing *Salmonella* Blockley is acute enteritis. Symptoms of acute enteritis by NTS usually resolve within a week in healthy children without antibiotic therapy, and thus antibiotics are not routinely indicated[11]. However, transient bacteremia during NTS gastroenteritis is believed to occur in 1–5% of patients. In these instances, NTS can enter the bloodstream and become uniquely capable of metastasizing and causing a focal suppurative infection of almost any origin[12]. Children with bacteremia or extraintestinal focal *Salmonella* infection should receive antimicrobial therapy, for which fluoroquinolones and third generation cephalosporins would be the antibiotics of choice. In a report of fetal acute pyogenic meningitis caused by ESBL-producing *Salmonella typhimurium*, the patient was empirically started on an intravenous antibiotic regimen of cefotaxime and gentamicin, but died from acute pyogenic meningitis[13]. As fluoroquinolones are not indicated in pediatric patients, third generation cephalosporins are recommended instead. Because there is a case of enteritis due to ESBL-producing *Salmonella* species, it is necessary to pay attention to the selection of antimicro-

bial agents.

We are the first to report on the identification of a CTX-M-15 ESBL-producing *Salmonella* Blockley isolate associated with pediatric enteritis in Japan. While clear increases in ESBL-producing NTS have not been noted in Japan, close attention should be paid to the selection of antimicrobial agents for treatment, and to potential resistance against antimicrobial agents by NTS.

Conflict of interest

None.

References

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