Indolent Non-Typhoidal *Salmonella* Vertebral Osteomyelitis in a Diabetic Patient

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**Abstract**

We herein describe the case of a 59-year-old Japanese man with diabetes mellitus who presented with vertebral osteomyelitis caused by *Salmonella enterica* subspecies *enterica* serovar Enteritidis. The patient presented with a persistent fever without back pain. Extraintestinal infections of *Salmonella* species are well known and are often reported in immunocompromised patients; however, they are rare in non-immunosuppressed patients. The protracted course and atypical presentation of osteomyelitis in diabetic adults can lead to major diagnostic delays. Moreover, in recent years, decreased fluoroquinolone susceptibility against salmonellosis has become a problem worldwide, a problem that needs to be urgently addressed.

**Key words:** non-typhoidal *Salmonella*, *Salmonella* Enteritidis, vertebral osteomyelitis, indolence

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**Introduction**

Non-typhoidal *Salmonella* are important food-borne pathogens that generally cause gastroenteritis and are most commonly transmitted by beef, poultry, or eggs (1, 2). Fewer than 5% of individuals with documented *Salmonella* gastroenteritis develop bacteremia (3, 4); however, if bacteremia does occur, the infection can be severe. Extraintestinal focal infections (EFIs), the most common of which include mycotic aneurysm, septic arthritis, osteomyelitis, pneumonia, or meningitis, are identified in 15.7-39.5% of non-typhoidal *Salmonella* bacteremia cases (5, 6). *Salmonella* vertebral osteomyelitis is typically seen among patients with sickle cell disease (7) and in immunocompromised hosts, such as patients with human immunodeficiency virus (HIV) infection (4). However, the incidence of *Salmonella* osteomyelitis is low and has been reported in only 0.75% (59 of 7,779 cases) of patients with salmonellosis (3).

We herein report a rare case of vertebral osteomyelitis caused by *Salmonella enterica* subspecies *enterica* serovar Enteritidis (*Salmonella* Enteritidis) in a diabetic patient.

**Case Report**

A 59-year-old Japanese man with diabetes mellitus presented with an 11-day history of fever. Under treatment with sitagliptin 50 mg and metformin 750 mg per day, without insulin, his hemoglobin A1c had gradually deteriorated from <7.0% one year previously to 8.0% one month previously. He had traveled to Singapore for 4 nights and Malaysia for 1 night on a business trip on pre-admission days 19 to 13. On day 14 before admission, he noticed a fever, and 7 days before admission, he was administered 500 mg azithromycin orally once daily for 3 days at a local clinic. However, his fever, without nausea, diarrhea, or rash, did not improve. He had not ingested unpasteurized dairy products, well water, ice, or raw meat/fish. He was not taking an H2-blocker or a proton pump inhibitor.

At presentation to our clinic (3 days prior to hospital admission), the physical examination showed a temperature of 39.2°C (102.6°F) and a pulse rate of 126 beats per min. There was no evidence of abdominal tenderness, vertebral tenderness, or rash. A neurological examination was unremarkable.

Initial laboratory test results showed a normal white blood...
cell count (4,570/mm³, normal range 3,500-8,500/mm³), high concentration of C-reactive protein (CRP; 113 mg/L, normal range 0-30 mg/L), high erythrocyte sedimentation rate (ESR; 69 mm/h, normal range 0-10 mm/h), high liver function tests (aspartate transaminase 71 IU/L, normal range 13-33 IU/L; alanine transaminase 92 IU/L, normal range 8-42 IU/L), and high hemoglobin A1c (8.4%). Tests for HIV antibodies were negative. The results of the dengue rapid diagnostic tests (SD Dengue Duo®, Standard Diagnostics, Gyeonggi-do, Korea) for NS1 antibody, immunoglobulin (Ig) M, and IgG were negative. The results of a malaria rapid diagnostic test (BinaxNOW® Malaria, Alere, Orlando, USA) and a blood smear for malaria were also negative.

On admission, a blood culture obtained at the initial clinic visit was positive for Gram-negative bacteria, as determined using BACTEC (Becton Dickinson, Sparks, USA), an automated blood culture system. Intravenous ceftriaxone (2 g) once daily was therefore initiated, due to the possibility of Salmonella Typhi and Salmonella Paratyphi infection. Salmonella Enteritidis was identified from the blood specimen cultures using MicroScan WalkAway 96SI (Siemens, Munich, Germany), and O antigen and H antigen tests revealed O9 and H-G antigen expression, respectively.

Because the Salmonella strain showed intermediate susceptibility to ciprofloxacin (minimal inhibitory concentration = 0.19) based on antibiotic susceptibility testing, in accordance with breakpoints for extraintestinal Salmonella from the 2013 Clinical Laboratory Standard Institute (CLSI) M100-S23, ceftriaxone treatment was continued.

Although repeat blood cultures were negative for bacteria, his temperature did not return to normal. Hence, azithromycin (500 mg) orally once daily for 1 week was administered on day 10 after admission. Defervescence occurred once for 3 days; however, his temperature returned to 39°C upon the discontinuation of azithromycin. We attempted to identify the focus of the infection, including an abscess, infected aneurysm, or osteomyelitis. Enhanced computed tomography of the whole body showed unremarkable findings. Positron emission computed tomography showed enhanced 2-F-18-fluoro-2-deoxy-d-glucose uptake in the 8-9th thoracic spine (Fig. 1). Magnetic resonance imaging (MRI) showed vertebral osteomyelitis and discitis of the 8-9th thoracic spine without destruction, compression, or epidural abscess (Fig. 2).

After 24 days of ceftriaxone administration, the medication was changed to 6 tablets of trimethoprim-sulfamethoxazole orally daily (trimethoprim 7.4 mg/kg/day) as the patient was believed to have developed a ceftriaxone-related drug fever. Two days after ceftriaxone cessation, he was completely antipyretic. We carefully observed the changes in his fever during, and for a few days after, ceftriaxone administration again to confirm the diagnosis of having a drug fever. The patient was discharged 9 weeks after admission. Antibiotics were continued for a total of 4 months until the CRP level and ESR were within the normal ranges. At the 2-month follow-up, there were no signs of recurrence such as a fever, changes in the CRP or ESR values,
or evidence of a relapse upon MRI.

Discussion

We herein described a rare case of Salmonella Enteritidis vertebral osteomyelitis in a diabetic patient. In Japan, the frequency of salmonellosis has been decreasing. Similarly, according to the statistics of the Ministry of Health, Labour and Welfare in Japan, food poisoning caused by Salmonella has also been decreasing annually, from 7,000 cases in 2000, to 2,500 cases in 2010, to 860 cases in 2013 (8). Furthermore, invasive non-typhoidal Salmonella disease is rare in non-immunosuppressed adults. The frequency of vertebral osteomyelitis with EFIs is also low. Previous reports are confined to patients with immunosuppressive conditions such as HIV infection and malignant diseases; however, the frequency of vertebral osteomyelitis in terms of EFIs caused by non-typhoidal Salmonella species is estimated to be approximately 5% (5). Moreover, patients with Salmonella vertebral osteomyelitis generally have symptoms of back pain (92-100%) and a fever (75-87%) (9, 10), yet our patient did not experience back pain. The absence of an underlying severe immunosuppressive disease and physical signs such as back pain led to a delay in his diagnosis.

In addition, the severity of non-typhoidal Salmonella infection is proposed to be serotype-dependent. Generally, Salmonella Enteritidis does not cause severe infections. The frequency of invasive diseases caused by Salmonella Enteritidis accounts for 6.7% of Salmonella Enteritidis infections (11). In comparison, some rare or host adapted serotypes, such as Salmonella Dublin in cattle and Salmonella Choleraesuis in swine, are more likely to cause invasive disease in humans (11, 12).

Suggested host risk factors for non-typhoidal Salmonella bacteremia are old age (>50 years of age) and immunosuppressive conditions, including malignancy, systemic lupus erythematosus, tumor necrosis factor (TNF) blocker use, transplantation, or HIV infection (6, 13-16). The case in the present report was >50 years of age, which is one of the proposed risk factors. However, these results are in line with previous studies that were performed in China and Israel (17, 18), and the average life expectancies in these areas differ from that of Japan. Thus, it is unclear whether this finding also applies to our patient. Furthermore, the present case had diabetes mellitus as an underlying disease. While diabetes mellitus can be a risk factor for Salmonella infection (19, 20), there are no statistically significant data showing that diabetes mellitus is also a risk factor for Salmonella bacteremia or EFIs (6, 13, 21). However, we speculate that diabetes mellitus, which can cause partial immune dysfunction, may facilitate the development of severe salmonellosis such as bacteremia and EFIs. In a previous report of 46 cases of Salmonella vertebral osteomyelitis without HIV infection and malignant diseases, while the most common underlying diseases were atherosclerosis (28%) and sickle cell disease (13%), diabetes mellitus was also detected in 11% of the patients (9), and the median duration from the symptom onset to diagnosis was reported to be 8 weeks. The diagnosis in the present report was confirmed at 32 days from the onset of a fever (on admission day 18), which is earlier than that described in previous reports.

Referring to the previous studies on this topic, a chronic disease course, advanced age, HIV infection, and acid-fast bacilli (such as Mycobacterium tuberculosis) or organisms of low virulence (such as coagulase-negative staphylococci, viridans streptococci, or Propionibacterium acnes) have been reported to be related to “indolent” vertebral osteomyelitis (22-25). However, the patient in this report did not have any of these features, and thus, it remains unclear why our patient experienced such an unusual presentation of painless vertebral osteomyelitis.

Fluoroquinolones are one of the most important treatment alternatives for invasive, systemic, and extraintestinal focal non-typhoidal Salmonella infection (26), as they have excellent intracellular penetration. It has been reported that ceftriaxone therapy is associated with a higher rate of treatment failure and relapse than fluoroquinolone therapy, especially in enteric fever (27-30). However, it has been well established that bacterial isolations susceptible for ciprofloxacin, but showing resistance to nalidixic acid, can lead to poor clinical outcomes and treatment failure (31, 32). According to the increasing number of isolated strains of Salmonella with decreased fluoroquinolone-susceptibility, the breakpoints for extraintestinal Salmonella were revised in the CLSI guidelines in 2012 and 2013 (33). Furthermore, bacteria producing extended-spectrum beta-lactamase genes are emerging and are now becoming increasingly widespread, a problem that needs to be urgently addressed (34, 35).

According to the treatment protocol in our hospital for enteric fever, we temporarily initiated azithromycin for 1 week, because the patient’s fever had lasted for over 7 days under ceftriaxone treatment, which was regarded to indicate clinical treatment failure. In previous reports of enteric fever, it has been reported that ceftriaxone and azithromycin combination therapy is superior to ceftriaxone monotherapy in terms of the fever clearance time (36). We speculate that the transient defervescence observed during the combination therapy of ceftriaxone and azithromycin may have occurred as a result of the bacterial amount of vertebral osteomyelitis having temporarily decreased due to the administration of azithromycin.

There are some limitations associated with the present report. First, we did not perform a computed tomography-guided or open surgical biopsy of the spine. However, the diagnosis of vertebral osteomyelitis caused by Salmonella Enteritidis in this report was considered reasonable according to the other findings. Second, because a stool culture was not performed in this case, we could not determine whether the patient was a convalescent or chronic carrier. In the future, performing stool cultures after treatment in extraintestinal Salmonella infections should be considered in similar cases, according to the presence of enteric fever.
It should be noted that *Salmonella* vertebral osteomyelitis can occur even in diabetic adults. The protracted course and atypical presentation of osteomyelitis in diabetic adults may lead to major diagnostic delays. It is important to consider invasive diseases in patients with a persistent fever, even in patients without HIV infection or malignancy.

The authors state that they have no Conflict of Interest (COI).

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