

Case Report

Salmonella osteomyelitis in a patient with adult-onset still's disease: case report and review of the literature

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Abstract: *Salmonella* septic arthritis and osteomyelitis combined with connective tissue disease (CTD) is very rare and can be easily misdiagnosed since the symptoms are not specific. Though the incidence is low, the severe effects of the disease on bone and joint function warrant attention. However, *Salmonella* septic arthritis and osteomyelitis has only been reported in few cases associated with SLE and RA-no cases in AOSD patients have been described. We report here a rare case of AOSD involving *Salmonella* osteomyelitis and reviewed the clinical features suggested in the related literature. If CTD patients have bone pain with persistently elevated CRP levels, it may be appropriate to draw the blood cultures and bone marrow samples, and begin treatment for osteomyelitis to maximize the patient's joint function.

Keywords: Connective tissue disease (CTD), *salmonella*, osteomyelitis, septic arthritis

Introduction

Adult-onset still's disease (AOSD) is a connective tissue disease (CTD) typically presenting with high fever, a transient rash, joint pain, hepatosplenomegaly, lymphadenopathy, and leukocytosis. Arthralgias and arthritis have been found to be the main symptom with an incidence ranging from 64 to 100% with a predominance of wrist, knee, and ankle involvement [1]. Symptoms of AOSD are similar to bacterial infection, making it difficult to differentiate these conditions.

Salmonella is a zoonotic Gram-negative (G-) bacteria, usually causing infection in the gastrointestinal tract. *Salmonella* septic arthritis and osteomyelitis is very uncommon, most commonly found in adults with sickle cell, immunosuppression, or other underlying diseases, and healthy children. However, it is very rarely seen in healthy adults [2]. The disease is often refractory and tends to be relapsing, chronic, and difficult to eradicate. Multiple surgical debridements may be needed [2].

Salmonella septic arthritis and osteomyelitis in a patient with CTD can lead to severe joint dis-

ability without effective treatment. To analyze the clinical features of the disease, we report here a rare case of *Salmonella* osteomyelitis in ASOD patients.

Case report

A 44-year-old female was admitted to the First Hospital of Ningbo with fever and knee pain for 3 days. The patient's maximum temperature was 40°C (104°F). She was diagnosed with AOSD 9 years ago and was maintained on prednisone 10 mg TID and tripterygium glycosides 10 mg TID. Her admission temperature was 38.7°C (101.7°F), and physical examination revealed swelling and slight tenderness on bilateral knees. Muscle strength in both left and right lower limbs was 4/5. Laboratory tests demonstrated raised white blood cell (WBC) count ($17.5 \times 10^9/L$) and elevated C-reactive protein (CRP) level (133.45 mg/L). Erythrocyte sedimentation rate (ESR) was 40 mm/h, showing a moderate elevation. Ferritin testing was 842.5 g/L. The other laboratory tests including tumor markers, biochemical, coagulation studies, thyroid function, tuberculosis antibody and HIV antibody were normal. Blood cultures confirmed *Salmonella* infection. The patient was

Salmonella osteomyelitis with adult-onset still's disease

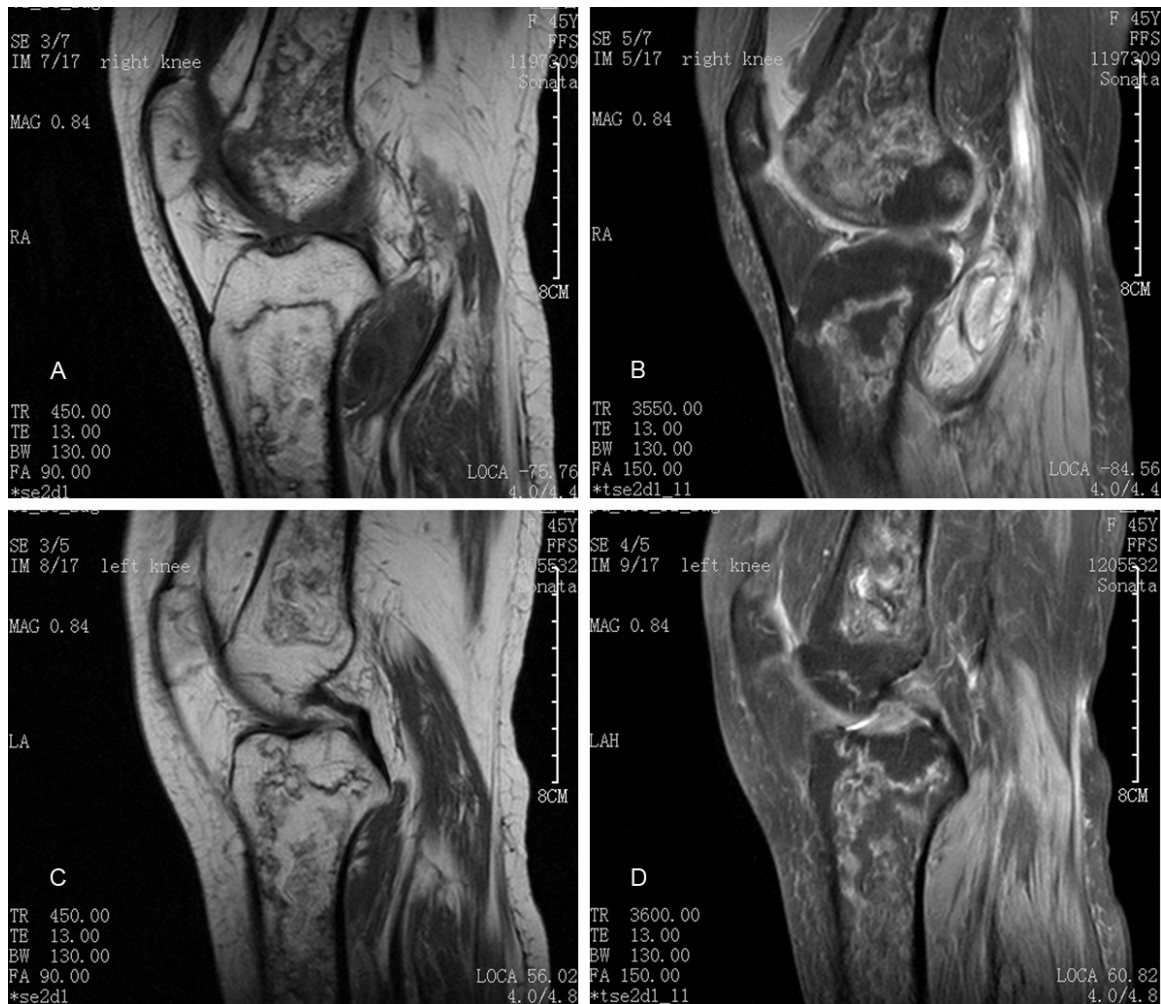


Figure 1. MRI showing multiple soft tissue abscesses formed around the knee. A. Right knee joint T1 phase; B. Right knee joint T2 phase; C. Left knee joint T1 phase; D. Left knee joint T2 phase.

treated with IV meropenem 0.5 g Q8H, and her temperature returned to normal 5 days later. However, the pain at the knee joint was unchanged. The patient then underwent magnetic resonance imaging (MRI), which showed diffuse abnormal signals from the femur, tibia and patella, bilaterally (**Figure 1**). To confirm the pathogen, bone marrow culture and biopsy were done. Bone marrow culture indicated the presence of *Salmonella typhimurium*. Histopathologic examination with H&E stain showed mild or moderate fibrosis and collagenization (**Figure 2A**) of bone marrow from the proximal tibia and moderate to severe fibrosis and sparse infiltration with lymphocytes and plasma cells of bone marrow from distal femur (**Figure 2B**).

Based on the above evidence, we made the diagnosis of *Salmonella* osteomyelitis and continued the meropenem regimen (0.5 g Q8H) for a

total of 40 days. Since the patient was afebrile, we de-escalated the antibiotics to ceftriaxone (2.0 g QD) and aztreonam (2.0 g Q8H) - this regimen was given for 14 days. Unfortunately, the patient became febrile again, and the antibiotics were changed to cefoperazone-sulbactam (3.0 g Q8H) and amikacin (0.6 g QD). This regimen was continued for 4 months. The patient's temperature gradually normalized, but she ultimately failed to get relief of her joint pain during the antibiotic therapy. She was then treated with surgical debridement and drainage, resulting in transient improvement. However, a number of bone infarctions and sinus tracts were formed at the infection site, leading to bilateral lower extremity paralysis.

Discussion

In recent years, as the life expectancy of patients with CTD grows, infection has emerged

Salmonella osteomyelitis with adult-onset still's disease

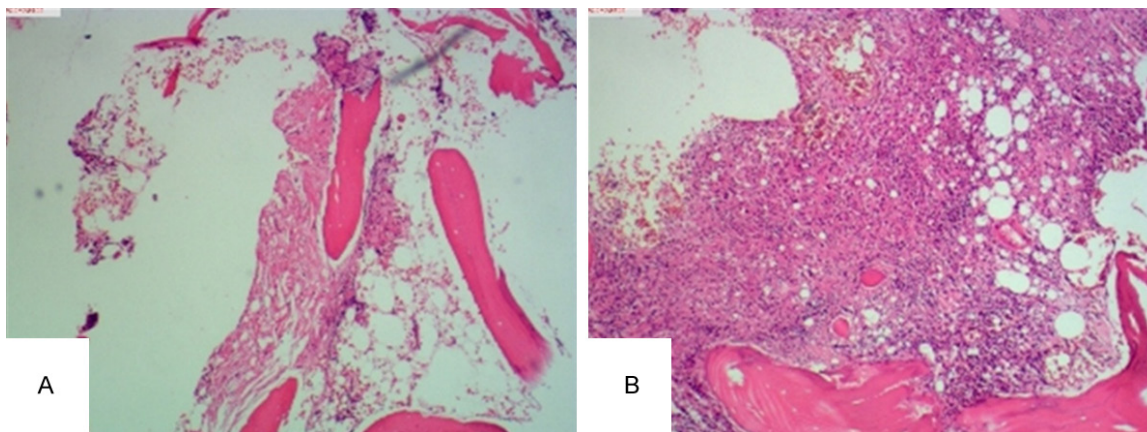


Figure 2. Histopathological specimen (H&E staining, original magnification: 10×). A. Bone marrow from proximal tibia shows fragmented tissues with extrusion deformation and mild to moderate hyperplasia and collagenization of focal fibrous tissue. B. Bone marrow from distal femur indicates moderate to severe hyperplasia of fibrous tissue and sparse infiltration with lymphocytes and plasma cells, interstitial edema and focal collagen fibers hyperplasia.

as a leading cause of death [3]. Long-term use of immunosuppressants and glucocorticoids (GC) can increase the infection risk. Up to half of all SLE patients develop major infections during the course of their disease [4]. The risks of infection in rheumatoid arthritis (RA) patients receiving systemic GC therapy are 1.67 times of that in patients without GC therapy [5]. Severe infection in CTD patients has many consequences, including worsening the primary disease or even death. Though its incidence is low, the severe effects of *Salmonella* septic arthritis and osteomyelitis on bone and joint function warrant attention.

Acute osteomyelitis, most commonly occurring in children, has a morbidity rate of about 8 per 100,000 in developed countries [6]. *Salmonella* osteomyelitis is very rare, consisting of 0.45% of all cases of osteomyelitis and 0.8% of all cases of *Salmonella* infection [2]. Nevertheless, Huang *et al* [7] reviewed 3,127 SLE patients in a 20-year retrospective study and found 29 SLE patients had septic arthritis. *Salmonella* infection accounted for 59%, which was significantly higher percentage compared to patients without CTD. The proper mechanism accounting for the increased susceptibility to *Salmonella* infection of CTD patients remains somewhat unclear yet. Many possibilities have been proposed, including a phagocytosis defect, hypocomplementemia, a cellular defect, and the use of immunosuppressant drugs [7].

In recent years, *Salmonella* septic arthritis and osteomyelitis has only been reported in cases

associated with SLE and RA—no cases in AOSD patients have been described [8-13]. The case we present here appears to be the first of this nature and provides supporting evidence that AOSD patients also have an increased susceptibility to *Salmonella* infections. Our patient had a 9-year history of GC use and immunosuppressive agents, which seemed to be a major risk factor. Lower limb long bones were mainly involved in this patient's infection, consistent with the literature [8-13]. The major clinical manifestation was bone pain, followed by fever. Since most CTD patients in the literature do not have an elevated WBC count, it was even harder to differentiate septic arthritis and osteomyelitis from their primary disease. However, all cases we reviewed had significantly increased CRP levels. Suh *et al* [14] suggested that CRP > 50 mg/L indicates the presence of infection for CTD patients. Our patient had a CRP of 133.45 mg/L, highly above this 50 mg/L threshold. Furthermore, Kim *et al* [15] showed the blood culture was positive (71% of the time) for the patients having a *Salmonella* bone infection. Given these findings, we suggested immediately drawing blood cultures, joint fluid and bone marrow samples if a patient's severe bone pain and elevated CRP level cannot be explained by CTD.

The mainstay treatment of acute septic arthritis and osteomyelitis is IV antibiotics with surgical debridement. Currently no randomized controlled trials for antibiotics selection have been performed. The optimal duration of treatment

with antibiotics for *Salmonella* septic arthritis and osteomyelitis is also unknown. This has traditionally been based on clinical signs and symptoms, as well as inflammatory markers. The literatures [8-13] describe a long-term antibiotic therapy with third generation cephalosporins or quinolones for >2 months for all patients. Despite the combination of long-term antibiotics with surgical debridement, prognosis remains poor. Few patients have complete recovery; most are left with joint dysfunction or recurrent osteomyelitis or arthritis. Our patient was given 6 months of carbapenems and third generation cephalosporins successively, per susceptibility testing, which proved to be effective in treating this *Salmonella* infection. However, these antibiotics did not treat all clinical symptoms of infection-bone pain and joint function remained present, despite resolution of her fever. Surgery was also not successful in treating her disease. This case is just one example of the difficulties in achieving a complete cure of *Salmonella* osteomyelitis in a CTD patient.

In conclusion, CTD patients are susceptible to *Salmonella* septic arthritis and osteomyelitis, and the prognosis is poor. Due to lack of specific clinical manifestations, it can be easily misdiagnosed, leading to delayed treatment and permanent disability. We presented a rare case of AOSD involving *Salmonella* osteomyelitis and reviewed the clinical features suggested in the related literature. If CTD patients have bone pain with persistently elevated CRP levels, it may be appropriate to draw the blood cultures and bone marrow samples, followed by initiating treatment for osteomyelitis. This prompt action may lead to maximized future joint function.

Disclosure of conflict of interest

None.

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