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Website: www.jlponline.org
DOI: 10.4103/JLP.JLP_165_18

# *Salmonella* osteomyelitis: A rare extraintestinal manifestation of an endemic pathogen

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## Abstract:

*Salmonella enterica* serovar Typhi and Paratyphi usually cause enteric fever in humans characterized by fever and gastrointestinal symptoms such as diarrhea. Bacteremia is a constant feature of enteric fever, and occasionally, dissemination of bacilli throughout the body results in the establishment of one or more localized foci of persisting infection. This happens especially in patients with preexisting conditions such as hemoglobinopathies, previous joint trauma, surgery, connective tissue diseases, lymphoma, diabetes, alcoholism, immunosuppressive state, and extremes of ages. Rarely, these extraintestinal *Salmonella* infection cases have also been reported in immunocompetent individuals without any obvious predisposing factors. *Salmonella* osteomyelitis, a rare sequelae of typhoid, may occur as a result of hematogenous seeding of the bone or joints due to a bacteremic episode. It may also spread from nearby areas of infection or penetrating trauma. Timely diagnosis and treatment of this condition are necessary because if left untreated, it can lead to permanent functional deficits later on. We hereby present a case series with brief review of literature on *Salmonella* osteomyelitis in immunocompetent patients without any known predisposing conditions over a period of 1 year (2017–2018) from a Tertiary Care Teaching Hospital in Uttarakhand, India.

## Key words:

Enteric fever, immunocompetent, *Salmonella* osteomyelitis

## Introduction

The genus *Salmonella* consists of enteropathogenic Gram-negative bacilli comprising of two species namely *Salmonella enterica* and *Salmonella bongori*.<sup>[1]</sup> An estimated 11–20 million people get sick from typhoid and between 1, 28,000 and 1, 61,000 people die from it every year.<sup>[2,3]</sup>

It is an important public health problem in developing countries like India. Morbidity and mortality owing to these infections are increasing with the emergence of multidrug resistance. In addition, strains cause infections at aberrant sites, i.e., extraintestinal infections which cause increased morbidity.

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*S. enterica* serovar Typhi and Paratyphi usually cause enteric fever in humans characterized by fever and gastrointestinal symptoms such as diarrhea. Bacteremia is a constant feature of enteric fever, and occasionally, dissemination of bacilli throughout the body results in establishment of one or more localized foci of persisting infection. This happens especially in patients with preexisting conditions such as hemoglobinopathies, previous joint trauma, surgery, connective tissue diseases, lymphoma, diabetes, alcoholism, immunosuppressive state, and extremes of ages.<sup>[4]</sup>

Rarely, these extraintestinal *Salmonella* infection cases have also been reported in immunocompetent individuals without any obvious predisposing factors.<sup>[5]</sup> *Salmonella*

**How to cite this article:** Rohilla R, Bhatia M, Gupta P, Singh A, Shankar R, Omar BJ. *Salmonella* osteomyelitis: A rare extraintestinal manifestation of an endemic pathogen. J Lab Physicians 2019;11:164-70.

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Submission: 08-12-2018

Accepted: 13-02-2019

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osteomyelitis, a rare sequelae of typhoid, may occur as a result of hematogenous seeding of the bone or joints due to a bacteremic episode. It may also spread from nearby areas of infection or penetrating trauma. Symptoms may include pain in a specific bone with overlying redness, fever, and weakness. Diagnosing and treating on time is necessary because if left untreated, it can lead to permanent functional deficits later on.

We hereby present a case series on *Salmonella* osteomyelitis with brief review of literature in immunocompetent patients without any known predisposing conditions over a period of 1 year (2017–2018) from a tertiary care teaching hospital in Uttarakhand, India.

## Case Reports

### Case 1

An 80-year-old male patient came to the orthopedics outpatient department with chief complaints of acute pain and restriction of movements in the right knee for 5 days. The patient did not give any history of fever over the preceding months. There was no history of trauma, prior surgery, abdominal discomfort, or any illness suggestive of enteric fever. Local examination of the right knee showed red, swollen joint with severe tenderness and the movements were painfully restricted. The laboratory findings were hemoglobin 12.8 g/dl and white blood cell count 12,180 cells/cu. mm with neutrophilic leukocytosis. Erythrocyte sedimentation rate (ESR) was 32 mm/h. X-ray right knee showed age-related early osteoarthritic changes as depicted in Figure 1. Pus was aspirated from the knee joint and was inoculated in brain heart infusion broth, nutrient agar, 5% sheep blood agar, and MacConkey agar and incubated overnight aerobically. Gram-stained smear of pus showed plenty of pus cells and Gram-negative



**Figure 1:** Anteroposterior and lateral views of X-ray right knee showing age-related early osteoarthritic changes

bacilli. Aerobic culture yielded *S. enterica* subspecies *enterica* serovar Typhi using conventional methods and serotyping (Difco, Becton and Dickinson, New Jersey, USA).<sup>[6]</sup> Nonlactose-fermenting colonies obtained on MacConkey agar have been shown in Figure 2.

The isolate was found to be susceptible to ampicillin, chloramphenicol, ciprofloxacin, cefotaxime, ceftriaxone, cefepime, piperacillin-tazobactam, and amoxicillin-clavulanic acid by Kirby–Bauer disk diffusion method.

Blood culture, Widal test, and stool culture were simultaneously performed to search for foci of infection. Blood sample of this patient was subjected to aerobic culture by BACTEC 450 automated blood culture system (Difco, Becton and Dickinson, New Jersey, USA) and was found sterile. Both Widal test and stool culture were nonsignificant.

Treatment with ciprofloxacin 500 mg twice daily was instituted for 3 weeks along with repeated aspirations. On follow-up, the patient was relatively asymptomatic.<sup>[7]</sup>

### Case 2

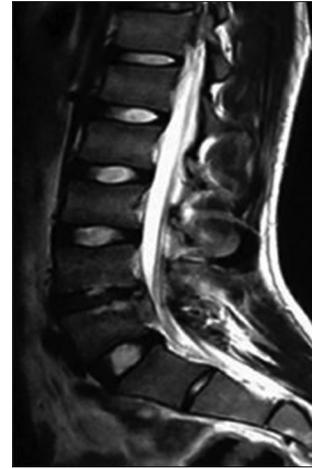
A 17-year-old male patient presented with complaints of backache in the lumbar region for 1 month and reduced sensation in both lower limbs. On physical examination, the patient was afebrile with excessive paraspinal muscle spasm and lumbar lordosis. There was severe tenderness over L2–L5 region with restriction of movements. Neurological examination revealed sensory deficit below L4 level bilaterally, but there was neither bowel/bladder involvement nor saddle anesthesia. The total leucocyte count, ESR, and C-reactive protein were found to be 12,540 cells/cu. mm, 92.5 mm/h, and 14 mg/L, respectively. Figure 3 shows X-ray spine which revealed paradiscal erosions at the level of L3–L4 with the reduction of disc spaces. Magnetic



**Figure 2:** Nonlactose-fermenting colonies obtained on MacConkey agar



**Figure 3:** Preoperative X-ray lateral view showing reduction of disc spaces between L4 and L5 with irregularity of end plates



**Figure 4:** Preoperative T2-weighted magnetic resonance imaging of the patient showing spondylodiscitis at L4–L5 level with destruction of intervertebral disc, epidural collection, cord compression, and edema

resonance imaging (MRI) of dorsolumbar spine showed spondylodiscitis at L2–L5 and epidural collection at L4–L5 level as depicted in Figure 4.

Correlating patient's history and radiological findings, a provisional diagnosis of Pott's spine was made, and antitubercular therapy (ATT) was started. On the 5<sup>th</sup> day of admission, the patient gave a history of 2–3 episodes of passing loose stools with blood which subsided on its own. Keeping in mind the possibility of any pathology of gastrointestinal tract coexisting with the spinal condition, a detailed history was taken. On repeated history taking, it was revealed that the patient had fever and abdominal pain 3 months before developing back pain. He was prescribed antipyretics and analgesics which provided partial relief, but subsequently, he had loss of appetite and weight. Microscopic examination of stool sample did not reveal the presence of ova or cysts. Blood samples were collected from three different sites and subjected to aerobic culture using BACTEC-450-automated blood culture system (Becton and Dickinson, New Jersey, United States). *S. enterica* subspecies *enterica* serovar Typhi was isolated from all three samples. Identification was confirmed using conventional methods and serotyping using antisera (Difco, Becton and Dickinson, New Jersey, USA). Moreover, immunoglobulin M (IgM) immunochromatographic card test (Typhidot IgM, Enteroscreen – WB, Zephyr Biomedicals, Tulip Diagnostics Pvt. Ltd., Goa, India) was also positive.

The patient underwent open disc biopsy and decompressive laminotomy at L4–L5 region. Intraoperatively, aspirated pus was negative for acid-fast bacilli, but on aerobic culture, *S. Typhi* was isolated which was sensitive to aminoglycosides, cephalosporins (including ceftriaxone and cefuroxime), and  $\beta$ -lactam drugs by Kirby–Bauer disk diffusion method. Mycobacterial culture and Gene X-pert found no

evidence of tuberculosis. ATT was stopped immediately, and the patient was started on injection cefuroxime for 3 weeks on inpatient basis which was continued orally for a total of 6 weeks. The patient responded well to treatment and showed rapid symptomatic and neurological improvement. Follow-up after 6 months showed that the patient was asymptomatic with no neurological deficit.<sup>[8]</sup>

### Case 3

A 24-year-old male was admitted with complaints of significant pain and swelling in the right thigh extending up to the knee for 3 months. He also had low-grade fever of 2 months' duration. His symptoms had worsened over the last 1 month as a result of which he found it exceedingly difficult to maintain an upright posture and walk. He also gave a history of diarrheal illness 3 months back, with complete recovery within 6–7 days without any medication. There was no history suggestive of hemoglobinopathy or any other underlying comorbidity. Conservative management by local health care practitioners using analgesics and physiotherapeutic measures over several weeks brought no relief to his current ailment.

At the time of presentation, the patient was conscious, oriented, and afebrile. Physical examination revealed tenderness and swelling over distal two-third of the right thigh over anterior aspect extending up to the knee joint. No scar, sinus, ulcer, or discharge was visible. On palpation, temperature was raised over the swelling, and distal pulses were palpable.

Complete haemogram revealed hemoglobin 11.3 g/dl, total leucocyte count of 21,720/cu. mm (neutrophils – 89.8%), platelet count 2.92 lakhs/cu. mm, and ESR 65 mm/h. Liver and kidney function tests were within normal

limits. X-ray showed ill-defined irregular intramedullary radiolucency over distal two-third of femur suggestive of osteolytic lesions with gross periosteal reaction and internal sclerotic bone fragments likely to be a sequestrum as depicted in Figure 5. Figure 6 shows MRI findings which revealed the presence of large intramedullary collection with sclerotic bone fragments at distal end of femur with marked synovial effusion and periarticular soft tissue edema suggestive of osteomyelitis.

Presumptive diagnosis of acute on chronic osteomyelitis of the right femur was made and cortical window with decompression surgery was planned. Cortical window was made with osteotome and blood-tinged pus was found in-between muscle planes and inside intramedullary cavity. Postoperatively, intravenous (IV) cefuroxime was given.

Pus from knee joint cavity, muscle plane, and intramedullary cavity showed growth of *S. enterica* subspecies *enterica* serovar Typhi identified by conventional methods and serotyping using antisera (Difco, Becton and Dickinson, New Jersey, USA). The isolate was sensitive to ampicillin, cotrimoxazole, ofloxacin, ciprofloxacin, ceftriaxone, and cefotaxime by Kirby–Bauer disk diffusion method. Aerobic blood culture was found to be sterile. The patient showed remarkable improvement postoperatively and was discharged while still on treatment with IV Ceftriaxone 2 g BD for 2 weeks.

## Discussion

Enteric fever is caused by facultative intracellular organisms – *Salmonella* Typhi and *Salmonella* Paratyphi A and B. It is more common among people traveling to or residing in developing countries like India where sanitation is poor and there is fecal contamination of food

and water.<sup>[9]</sup> Enteric fever usually presents as acute febrile illness along with headache, diarrhea or constipation, relative bradycardia, splenomegaly, and leukopenia. Rarely, extraintestinal complications involving skeletal, cardiovascular, pulmonary, hepatobiliary, genitourinary, and central nervous systems are seen.<sup>[10]</sup>

*Salmonella* osteomyelitis is a rare presentation documented in hospitals, constituting 0.8% of all *Salmonella* infections and only 0.45% of all types of osteomyelitis occurring especially in sickle cell disease patients and caused usually by nontyphoidal *Salmonellae*.<sup>[11]</sup> In sickle cell patients, capillary occlusion secondary to intravascular sickling may devitalize and infarct the gut, permitting *Salmonella* bloodstream invasion thereby increasing the chances of osteomyelitis. Complement system and impaired opsonization have also been suggested to play a role.<sup>[12,13]</sup>

Incidence of *Salmonella* osteomyelitis or arthritis is very rare in apparently healthy individuals with no predisposing factors. Cumulative records of *Salmonella* osteomyelitis cases in healthy adults (since 2010) from various parts of India have been enlisted in Table 1. Most of these cases have been reported from the southern part of the country. *Salmonella* osteomyelitis cases in healthy adults from other countries of the world (since 2010) have also been depicted in Table 2.

At our center, 35 culture-proven cases of enteric fever and 3 cases of extraintestinal salmonellosis (osteomyelitis) caused by *Salmonella* Typhi were reported during the year 2017–2018, and in India, owing to its endemicity unlike other countries, Typhi is the main cause of *Salmonella* osteomyelitis.

First, these cases are unique owing to the rarity with which they occur. Second, three cases of *Salmonella* osteomyelitis from a tertiary care center in a year indicate



**Figure 5:** Anteroposterior and lateral views of X-ray showing ill-defined irregular intramedullary radiolucency over distal two-third of the right femur suggestive of osteolytic lesions



**Figure 6:** Magnetic resonance imaging showing large intramedullary collection with sclerotic bone fragments at the distal end of the right femur

toward some indigenous risk factors predisposing to these extraintestinal manifestations in this region. The *Salmonellae* surviving in aberrant sites and persisting thereafter *in vivo* might be due to the insufficient treatment given for enteric fever. Inadequate dosage prescribed by quacks or other conventional treatment modalities may lead to the subsiding of symptoms but not complete cure (as was noted on careful history taking of these three cases), leading to persisting infection.

“Persisters” are defined as quiescent bacterial cells that survive lethal antibiotics or stresses but can regrow under appropriate conditions. These organisms are primarily responsible for latent infections, extraintestinal infections, and posttreatment relapse, posing significant challenges

for the treating physicians. Ying Zhang proposed a Yin–Yang model to describe the heterogeneous nature of persisters. A number of genes and pathways have been discovered which are as follows: toxin–antitoxin modules, stringent response, DNA repair or protection, phosphate metabolism, alternative energy production, efflux, antioxidative defense, and macromolecule degradation. Therefore, symptoms abate for some time with or without antibiotic treatment. Complications encountered at a later stage maybe due to the bacteria persisting inside body having adapted themselves to lesser-known niches.<sup>[40,41]</sup>

*Salmonella* osteomyelitis can be diagnosed by isolation of *Salmonella* species from the affected site. Simultaneous isolation of *Salmonella* spp. from blood and affected musculoskeletal site substantiates the diagnosis of disseminated *Salmonella* infection as seen in Case 2. Inability to isolate *Salmonella* spp. from blood samples in suspected cases of osteomyelitis as seen in Cases 1 and 3, respectively, can possibly be explained by the fact that inappropriate and inadequate antibiotic treatment usually results in chronic persistent infections which may exhibit the phenomenon of intermittent bacteremia. This issue can to some extent be addressed by obtaining adequate volumes of repeat blood samples from different sites at regular time intervals. Negative stool culture result in Case 1 can be explained by intermittent shedding of the bacterium in stool samples of infected patients. Insignificant Widal test results in the same case which could possibly be due to early and inadvertent administration of antibiotics (although a clear-cut past medical and treatment history was not available) and waning humoral immune response.

**Table 1: Cumulative records (since 2010) of *Salmonella* osteomyelitis cases in healthy adults from different parts of India<sup>[7,8,14-24]</sup>**

Zone	Site of involvement	Isolate	References
North	Dorsolumbar vertebra	<i>Salmonella</i> Typhi	Mohanty <i>et al.</i>
	Knee joint	<i>Salmonella</i> Typhi	Gupta <i>et al.</i>
	Hip joint	<i>Salmonella</i> Typhi	Gupta <i>et al.</i>
West	Sacroiliac joint	<i>Salmonella</i> Typhi	Phadke <i>et al.</i>
Central	Thoracic spine vertebra	<i>Salmonella</i> Typhi	Gupta <i>et al.</i>
South	Lumbar vertebrae	<i>Salmonella</i> Typhi	Banerjee <i>et al.</i>
	Thoracic spine	<i>Salmonella enteritidis</i>	Lakshmi <i>et al.</i>
	5 cases of osteomyelitis of unspecified sites	<i>Salmonella</i> Typhi	Sudhakaran <i>et al.</i>
	Distal femur	<i>Salmonella</i> Typhi	Ranjith <i>et al.</i>
	Rib	<i>Salmonella</i> Typhi	Mathuram A <i>et al.</i>
	Hip joint	<i>Salmonella</i> Typhi	Shanthi <i>et al.</i>
	Right acetabulum	<i>Salmonella</i> Typhi	Faseela <i>et al.</i>
	Cranial vault	<i>Salmonella</i> Typhi	Bhooshan <i>et al.</i>

**Table 2: Cumulative records of *Salmonella* osteomyelitis cases in healthy adults from other countries of world since 2010<sup>[25-39]</sup>**

Country	Site of involvement	Isolate	References
<b>Developed countries</b>			
Greece	Thoracic spine	<i>S. enteritidis</i>	Papaioannou <i>et al.</i>
United States	Spondylitis	Nontyphoidal <i>Salmonella</i> (not specified)	Zaid <i>et al.</i>
	Thoracic vertebra	<i>Salmonella</i> Typhi	Shrestha <i>et al.</i>
Singapore	Vertebral osteomyelitis	<i>Salmonella</i> Typhi	Khoo <i>et al.</i>
Japan	Vertebra	<i>S. enteritidis</i>	Oki <i>et al.</i>
	Distal radius	<i>Salmonella</i> spp. (not specified)	Tonogai <i>et al.</i>
United Kingdom	Rib	<i>S. Typhimurium</i>	Scarci <i>et al.</i>
	Sacroiliac joint	<i>Salmonella</i> Mbandaka	Le Doare <i>et al.</i>
Korea	Femoral diaphysis	Nontyphoidal <i>Salmonella</i> (not specified)	Kim <i>et al.</i>
Spain	Tibial diaphysis	<i>Salmonella</i> spp. (not specified)	Martínez-Serrano <i>et al.</i>
Germany	Knee joint	<i>S. enteritidis</i>	Salem <i>et al.</i>
Turkey	Knee joint	<i>S. enteritidis</i>	Uygur <i>et al.</i>
<b>Developing countries</b>			
Saudi Arab	Hip arthritis	<i>Salmonella</i> (not specified)	Alhazzazi <i>et al.</i>
Kenya	Distal radius (left forearm)	<i>Salmonella</i> Paratyphi A	Ayeni <i>et al.</i>
China	Pelvis	<i>Salmonella</i> Typhi	Angela <i>et al.</i>

*S. enteritidis*=*Salmonella enteritidis*, *S. Typhimurium*=*Salmonella Typhimurium*

In all the three cases we are reporting, *Salmonella* osteomyelitis was not initially suspected, and no identifiable risk factors were noted. Since this entity is clinically as well as radiographically similar to osteomyelitis caused by other pyogenic agents, it is essential to diagnose and treat such cases accordingly. Bone tumors such as Ewing's sarcoma and fibrous dysplasia are also important differential diagnosis of pyogenic osteomyelitis and they may have very similar clinical presentations.

To conclude, clinicians should keep the possibility of *Salmonella* as an etiological agent in patients with osteomyelitis, especially in those giving a history of preceding fever with or without gastrointestinal manifestations even in the absence of underlying comorbidities like hemoglobinopathies. Furthermore, healthcare practitioners should ensure that each enteric fever patient receives appropriate antibiotics in the correct dose and for the right duration. In addition, antibiotic susceptibility test results of *Salmonella* isolates should be used to guide proper therapy. Restriction of indiscriminate use of antibiotics in these cases would further prevent emergence and spread of multidrug resistance.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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