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Nontyphoidal *Salmonella* Osteomyelitis in an Immunocompetent Adult Without Preceding Symptoms

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Abstract: A 23-year-old man presented with a painful swelling of his left shin approximately 5 weeks after a very mild trauma. He had not experienced fever, abdominal pain, or diarrhea. Magnetic resonance images were compatible with chronic osteomyelitis. The cultures of the bone biopsy showed growth of *Salmonella enterica* serovar Enteritidis. Blood cultures remained sterile, there were no signs of a carrier state, and no immune deficiency could be found. After surgical debridement, the patient was treated with ceftriaxone and co-trimoxazole and later ciprofloxacin because of an allergic reaction. Nontyphoidal *Salmonella* osteomyelitis is rare in immunocompetent adults without a hemoglobinopathy. The treatment consists of surgical debridement and prolonged antibiotics.

Key Words: *Salmonella*, nontyphoidal, osteomyelitis

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CASE

In August 2018, a 23-year-old White man presented because of a painful swelling on the anterior side of his left lower extremity, which had emerged 3 days earlier. Two weeks before presentation, he had returned from Suriname where he had been living for 4.5 months in the capital, Paramaribo. Six weeks before presentation, he had tripped and fell during a jungle trekking, hurting his left shin. It was a minimal trauma, the skin remained intact, and he did not have any pain or discomfort afterward. He had no previous medical history, and he did not recall having had fever, chills, abdominal pain, or diarrhea in the past years. His dietary history did not reveal an obvious source for a possible asymptomatic foodborne infection. On physical examination, there was a painful swelling of 2 × 3 centimeters on the anterior side of his left shin. His general practitioner had already ordered an ultrasound of his left leg, which showed a cortical lesion of the tibia with periosteal thickening and edema. Erythrocyte sedimentation rate, leukocyte count, and C-reactive protein were within normal ranges. Magnetic resonance imaging (MRI) revealed bone and marrow edema of the diaphysis of the left proximal tibia in addition to a microabscess and fistula to the marrow (Fig. 1). Histopathological examination of a bone biopsy revealed chronic, active, and granulating inflammation. The bone biopsy was cultured and revealed growth of a pansensitive strain of *Salmonella enterica* serovar Enteritidis (*Salmonella* Enteritidis). Two sets of blood cultures did not show growth of bacteria. Because of the relative small size of the lesion and in an effort to avoid surgical intervention, he initially started with monotherapy of 2 weeks of ceftriaxone intravenously, followed by a 4-week course of oral co-trimoxazole. In the meantime, he tested negative for HIV and immunophenotyping of a peripheral blood sample was normal. Tests for sickle cell anemia or thalassemia were not performed because of the normal blood

count and his White race. To investigate whether he was an asymptomatic carrier, an abdominal ultrasound to look for gallstones was conducted, but this was negative as was the polymerase chain reaction for *Salmonella* species in his stool. After antibiotic treatment, the MRI was repeated and showed a slight increase of the osteomyelitis. Therefore, a surgical debridement was performed after which the patient received 2 weeks of intravenous ceftriaxone followed again by oral co-trimoxazole (Fig. 2). After 2 days of taking co-trimoxazole, he experienced swelling of his lips and diffuse urticaria. Because of a suspected allergic reaction to ceftriaxone or co-trimoxazole, we switched to oral ciprofloxacin for the remainder of his treatment, which was 4 weeks in total of oral antibiotics. The swelling and urticaria subsided within 2 days. Per-operative blood and bone cultures remained negative. On his last follow-up 3 months after surgery, the patient was doing well and the painful swelling had completely subsided.

DISCUSSION

Salmonella Enteritidis together with *S. enterica* serovar Typhimurium is the most frequently occurring serotype causing nontyphoidal *Salmonella* (NTS) infections in the world, typically a gastroenteritis. However, like the typhoidal *Salmonella* serotypes, *Salmonella* Typhi, and *Salmonella* Paratyphi, NTS serotypes can also cause invasive infections.¹ Infection in humans occurs mostly through contaminated food or milk. The reported incidence of Salmonellosis in Suriname was 14 per 100,000 inhabitants in 2016 and zero in 2018.²

Approximately 5% of the NTS infections are complicated by a bacteremia leading to sequelae like endocarditis, mycotic aneurysm, and meningitis in 40% of the cases.¹ These extraintestinal manifestations are strongly associated with immune suppression.³ In 0.8% of all *Salmonella*-infected patients, an osteomyelitis will develop.⁴ There is growing evidence that NTS infections, just like (para)typhoid fever, can result in an asymptomatic carrier state. The incidence in the case of NTS is an estimated 0.15%.⁵ In the case of typhoid fever, it is estimated that 25% of these carriers did not have symptoms fitting a *Salmonella* infection or cannot remember the initial infection.⁶ Not only gallstones but also gallbladder epithelial cells, enterocytes and hepatocytes can function as a reservoir for *Salmonella* species.^{5,6} Intermittent periods of bacterial shedding are alternated with months in which the patient remains culture negative.⁵ Besides, it is possible for *Salmonella* species to survive in antigen presenting cells. Probably, it is the macrophages in the reticuloendothelial system that play the most substantial role for (prolonged) survival.⁷ All of this explains how some patients can develop complications of an invasive *Salmonella* infection months to years after the initial infection or without prior symptoms.⁸

In only 0.45% of all cases of osteomyelitis, *Salmonella* species are the causative pathogen and then often it is a nontyphoidal serotype.^{4,8} It is most prevalent in children and adults with sickle cell anemia.⁹ Functional asplenia and vaso-occlusive events leading to micro bone infarctions make sickle cell patients more vulnerable to osteomyelitis. When translated to this case, it is possible that

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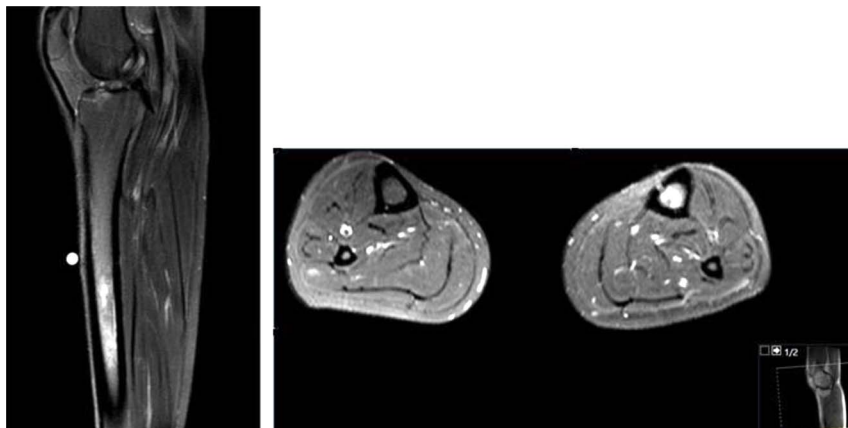


FIGURE 1. T2-weighted MRI of the left tibia showing bone and marrow edema, microabscess, and a fistula.

the trauma of the tibia led to a localized area of vaso-occlusion and eventually a necrotic bone fragment susceptible to infection. The patient then acquired a *Salmonella* Enteritidis infection at a later point in time or was an asymptomatic carrier, and by hematogenous dissemination, the necrotic bone fragment was infected.

More predisposing factors for *Salmonella* osteomyelitis are the use of corticosteroids, lymphoma, autoimmune diseases, diabetes mellitus, chronic granulomatous disease, and immune deficiency.^{3,8,10}

The typical localization of a hematogenous osteomyelitis in adults is a vertebra. *Salmonella* osteomyelitis, on the other hand, seems to occur more often in the diaphysis of the long bones.^{4,8,10–12} This is of importance because most primary bone tumors tend to originate from the metaphysis and can be an important differential diagnosis.^{8,13}

There is a distinction between an acute and chronic osteomyelitis. Classically, it is thought that the acute manifestation can be treated without a surgical intervention and with antibiotics alone. However, this is also depending on how extensive the lesion is and the presence of necrosis.¹⁴ In a chronic infection, there is seldom fever, often mild complaints, a slow gradual course, and normal inflammation parameters.¹⁴ That is the reason why sometimes, it can be difficult to make the distinction with a bone malignancy.⁸

Another classification of osteomyelitis is based on the mechanism in which an infection disseminates, either hematogenous or nonhematogenous. In almost all reported cases of *Salmonella* osteomyelitis, dissemination occurred through hematogenous spread.^{8,12,13,15} The treatment of the osteomyelitis itself is independent of the underlying mechanism.¹⁵

In the cases where there is a slow gradual course of the infection without a clear prior episode of fever or illness, it can take weeks, months, or even up to years before the diagnosis of chronic osteomyelitis is made.¹¹ This is also likely with a *Salmonella* osteomyelitis because it is not uncommon that there is not a history of abdominal pain, diarrhea, or fever and blood and stool cultures can be negative.^{8,10,15,16} During the diagnostic workup, a conventional x-ray will often be made as a starting point and to exclude other pathology, like osteoarthritis. The preferred imaging modality is MRI, which has a sensitivity of 78% to 90% and specificity of 60% to 90% and gives the most detail of the local extension of the infection.¹⁴ The diagnosis, however, is made by microbiology and/or histopathology. Positive cultures of the bone biopsy are considered the criterion standard. If these are negative, a diagnosis can still be made if there is a high suspicion based on clinical and radiology findings, and there are positive blood cultures growing a fitting pathogen.¹⁴ It is discouraged to take superficial wound cultures. The microorganisms that grow in these cultures only match

with bone biopsy cultures in one third of the cases.¹⁷ In the case of *Salmonella* osteomyelitis, there is an indication to investigate carrier state, which includes looking for gallstones and checking for *Salmonella* presence in the stool. Clinicians have to realize that even if the tests are negative, the patient can still be a chronic carrier through the mechanism of intermittent shedding discussed earlier. Furthermore, it is warranted that the patient is tested for immune deficiencies and hemoglobinopathy (depending on the ancestry of the patient).

Monotherapy consisting of only antibiotics is possible if the lesion is small, but most often, a combination of antibiotics and surgical debridement is necessary.^{8,10–12,14–16} When there is an abscess or fistula, surgery is virtually inevitable.¹⁵ The choice of an antibiotic is based on the susceptibility of the cultured strain but also on how well the drug can penetrate into bone. The duration of treatment is a minimum of 6 weeks with at least 2 weeks of intravenous therapy.¹⁴ *Salmonella* osteomyelitis, however, tends to be refractory and chronic in nature. This makes the treatment difficult, which often consists of multiple surgical interventions and long-lasting antibiotic therapy.^{10,18–20} Furthermore, a growing increase of resistance to ciprofloxacin and co-trimoxazole in many parts of the world challenges (oral) treatment of NTS osteomyelitis.

CONCLUSIONS

Nontyphoidal *Salmonella* osteomyelitis, especially without preceding symptoms of an infection, is very rare in an immunocompetent

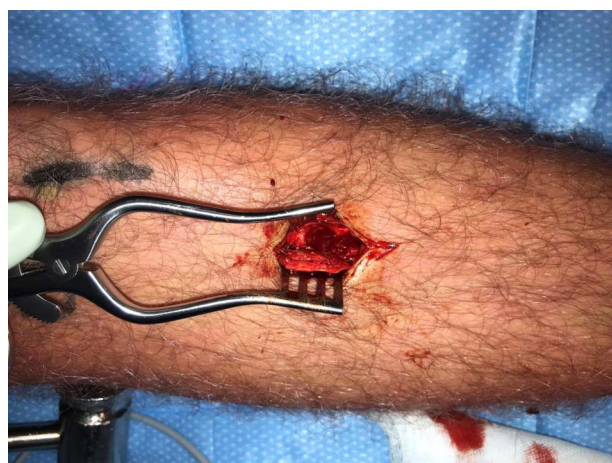


FIGURE 2. Intraoperative photograph of osteomyelitis of the left tibia.

adult without a hemoglobinopathy.^{8,15,16,18} It is not uncommon for *Salmonella* osteomyelitis to develop months or years after the initial infection without even clear gastrointestinal symptoms or fever. It is recommended to investigate for carrier state in any patient and to search for immunosuppression and a hemoglobinopathy in otherwise healthy patients. Treatment typically consists of a combination of surgical debridement and antibiotics but can be complicated and long-lasting.

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