CASE REPORT

Salmonella osteomyelitis in an immunocompromized patient presenting as a primary lymphoma of the bone

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Summary During the past few decades, an increasing number of immunosuppressive drugs have been developed to treat autoimmune and rheumatic diseases, as well as post-transplant patients. In parallel, the incidence of immunocompromized patients in the general population has risen, for example, patients who are HIV positive, undergoing hemodialysis or suffering from diabetes mellitus. In such predisposed patients, infections with organisms of even reduced invasive potential can result in atypical invasive manifestations.

In industrialized countries, an increase in the number of human non-typhoid Salmonella infections was observed in the 1980–1990 s [Shimoni Z, Pitlik S, Leibovici L, Samra Z, Konigsberger H, Drucker M, et al. Nontyphoid Salmonella bacteremia: age-related differences in clinical presentation, bacteriology, and outcome. Clin Infect Dis 1999;28:822–7]. Beyond the main clinical manifestation of gastroenteritis, there is an increasing prevalence of extra-intestinal infections by this pathogen. We report a patient with acute osteomyelitis due to Salmonella typhimurium without any previous signs of gastroenteritis.

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Case report

A 63-year-old male was referred from a district hospital with the diagnosis of lymphoma of the right femur associated with periosteal abscess formation (Figure 1). Painful swelling of the calf had developed, leading to significant function loss of the leg during the previous eight weeks. These symptoms were accompanied by three episodes of fever up to 38.9 °C and shivering. The patient had a medical history of arterial hypertension, diabetes mellitus controlled by oral antidiabetics, and pulmonary fibrosis treated with oral cortisone (8 mg/day) and azathioprine (100 mg/day) for several years. Deep venous thrombosis had been excluded by duplex sonography. An MRI scan showed an infiltrating intramedullary process replacing normal bone marrow within the right femur, compatible with lymphoma and accompanied by massive myositis. A chest X-ray suggested a polycyclic tumorous enlargement of the left lung hilus. These symptoms had been interpreted as a malignant lymphoma of the femur and...
mediastinal lymph nodes, accompanied by B symptoms. Antibiotic therapy with clindamycin had been started in the referring hospital.

The patient was in a reduced physical condition, but blood pressure, heart rate and abdomen did not show any abnormalities. The right knee, calf and thigh were swollen and tender, with elevated temperature and livid color of the overlying skin. WBC count was 19.5 x 10^9 cells/l and C-reactive protein was 47 mg/l (normal < 5 mg/l). Other blood chemistry was within normal limits. Plain radiographs of the right knee revealed no destruction of bony structures. A CT scan of the thorax confirmed pulmonary fibrosis, but revealed no tumorous lymph nodes. 99mTc bone scintiscan showed accumulation of activity at the right femur and thoracic vertebrae 7 and 8. A CT-guided biopsy of the soft tissue process and the femur corticalis revealed non-specific myositis and acute destructive osteomyelitis without signs of malignancy. The microbiological workup resulted in Salmonella typhimurium. Sequestrotomy, lavage, local antibiotic treatment and drainage were performed. Consequently, local symptoms improved. However, on the fifth post-operative day, the patient developed septicemia with cardiocirculatory and respiratory insufficiency, to which he finally succumbed on day nine. Autopsy revealed severe pseudomembranous colitis.

Discussion

Infections with non-typhoid Salmonella species are most frequently acquired through consumption of contaminated food, in particular uncooked eggs, poultry and meat products. Usually, the incubation period is 7 hours to 2 days, and the infection presents as self-limiting gastroenteritis. Salmonella serotypes typhimurium and enteritidis account for 83% of infections, leading to diarrhea, vomiting, abdominal cramps and low-grade fever. Temperatures return to normal within 48–72 hours and diarrhea resolves within 10 days. Specific antibiotic treatment is not warranted, but fluid and electrolyte replacement might be necessary in elderly patients or those with underlying disease. Hospital admission is required in 13–29% of cases. Less than 6% of immunocompetent patients were reported to be bacteremic. Focal infections of various organs occur during septicemia and can involve almost all organ systems.

Salmonella arthritis and osteomyelitis occur with a frequency of less than 1%, and clinical signs of recent gastrointestinal infection cannot always be seen. Clinical signs of osteomyelitis include fever, bone pain, soft tissue swelling and leukocytosis, and are not indicative of the causative agent. Diaphysis and epiphysis of femur, tibia and humerus, as well as lumbar vertebrae, represent the most affected sites. S. typhimurium and S. enteritidis are the most common serotypes of human non-typhoid Salmonella infections, but recently other serotypes have been observed significantly more frequently. Immunity to Salmonella infection requires interplay between the innate and the adaptive immune systems. After ingestion, passage of Salmonella occurs via the epithelial M cells overlying Peyer’s patches, invasion of enterocytes or shuttling by cells that physiologically breach the epithelial layer, for example, dendritic cells (DCs). The presence of Salmonella on the basal site of enterocytes leads to the secretion of chemokines (IL-8, MIP-3α, MIP-2 and TNF-α), attracting cells of the innate immune system (neutrophils, macrophages, DCs and natural killer [NK] T cells). The expression of co-stimulatory molecules is upregulated soon after

Figure 1  MRI scan of the femur, showing (A) the extent of Salmonella osteomyelitis within the distal femur, and (B) periosteal and submuscular abscess formation.
infection and a myriad of cytokines are secreted (IFN-γ, IL-12, TNF-α and others). These cytokines are essential for the recruitment and activation of cells of the adaptive immune system, resulting in an efficient B- and T-cell response. Experiments in mice deficient in MHC class I, MHC class II or B cells have shown that CD4+ cells have a pivotal role in immunity to Salmonella, but CD8+ T cells and B cells play important contributory roles.

Translocation of Salmonella from the intestinal lumen to the submucosa, mesenteric lymph nodes and distant organs requires disruption of the mucosal barrier and suppression of the aforementioned host immune defense mechanisms. In our case, the patient had been treated with steroids and azathioprine for years, and received antacid treatment with omeprazole, increasing his susceptibility to Salmonella infection. The effects of glucocorticoids and azathioprine on the innate and adaptive immune response are summarized in Table 1. Most importantly, secretion of TNF-α and IFN-γ, which is essential in the initiation of the anti-Salmonella immune response, is significantly downregulated by glucocorticoids, and DCs are reduced in number and show diminished allostimulatory capacity. These mechanisms severely impede the induction of an effective specific immune response, which is further hampered by the direct action of glucocorticoids on T and B cells. Azathioprine contributes to the suppression of the adaptive immune response by inducing T-cell apoptosis through interference with the CD28 co-stimulatory signaling cascade. Treatment with glucocorticoids also influences the barrier function of the gut. The histopathology of the gut-associated lymphatic tissue (GALT) in corticosteroid-treated animals demonstrates changes in the dome epithelium of the Peyer’s patches and a significantly reduced number of M cells. Levels of secreted IgA are dramatically reduced, resulting in an increase in bacterial adhesion to the mucosa and translocation to mesenteric lymph nodes. In our patient, pre-existing diabetes and treatment with the proton pump inhibitor omeprazole might have acted synergistically with immunosuppressive therapy, as both were identified as risk factors for Salmonella infection.

In immunocompromized patients, diagnosis of infections can be delayed because of the absence of overt clinical signs. In our case, the presence of a hilar mass in the initial chest X-ray had pointed the diagnosis towards a malignant lymphoma, rather than towards infection. Patients under long-term treatment with thiopurines (azathioprine and 6-mercaptopurine) are exposed to an increased risk of lymphoma in the context of autoimmune disease. Primary lymphoma of the bone occurs at age 50—60 and accounts for 3—4% of all malignant bone tumors. The femur is most commonly involved, and the main symptoms are pain, swelling and pathological fracture. B symptoms are rarely present and few patients present with symptoms of systemic disease. Radiological finding are usually discrete with conventional techniques and, although MRI might show changes of intramedullary tumor infiltration, none of these findings is pathognomonic.

In conclusion, an infectious process with atypical or comensal bacteria should definitely be included in the differential diagnosis for immunocompromized patients. In the described case, multiple risk factors for systemic infection with food-borne pathogens were present. Early CT-guided or open biopsy should have resulted in earlier diagnosis and appropriate treatment.

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References


