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REVIEW ARTICLE

Part - A

Salmonella Osteomyelitis and Septic Arthritis in Children

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ABSTRACT

Salmonella infections of the bone and joints are very rare. They are common in hemoglobinopathies and immunocompromised children. The diaphysis and metaphysis of the long bones are common sites. The spine pelvis, ribs, and cranium are rare sites. The clinical course is indolent compared to acute osteomyelitis. Serological tests and culture can be used for the diagnosis. Radiographs are frequently negative early in the disease. CT scans and MRI scans can be used in certain cases. The majority of cases can be managed with antibiotics. In this review, we describe the etiology, clinical features, investigations, and management of Salmonella bone and joint infections. We have described the features of Salmonella bone and joint infections in normal and sickle disease patients. We also present an illustrative case of Salmonella septic arthritis of the shoulder in an immunocompetent infant one month after COVID-19 infection.

Keywords: Salmonella osteomyelitis; Salmonella septic arthritis; septic arthritis of infancy; septic arthritis of the shoulder

Introduction

Osteomyelitis is an infection of the cortex and medulla of the bone. Infection of the joints is called septic arthritis. In neonates and infants, septic arthritis and osteomyelitis can coexist. It is due to transphyseal vessels crossing the metaphysis and epiphysis. In older children, it is due to the metaphysis being intracapsular, such as the hip, shoulder, elbow, and ankle. The most common organism causing osteomyelitis/septic arthritis in children is *Staphylococcus aureus*. Group A streptococci, *E. coli*, *H. influenzae*, and *Streptococcus pneumoniae* are other organisms that cause osteomyelitis and septic arthritis [1].

Salmonella infections of the bone and joints are rare. They account for approximately 0.8% to 0.45% of all types of osteomyelitis. *Salmonella* infection can cause acute and chronic osteomyelitis [2, 3]. These infections are rare in healthy individuals but common in children with hemoglobinopathies [4]. *Salmonella* osteomyelitis is common in the metaphysis and diaphysis. Rarely, it can cause osteomyelitis in the vertebrae and pelvis [5, 6].

In this review, we describe the etiology, clinical features, investigations, and management of *Salmonella* bone and joint infections. We also present an illustrative case report.

Microbiology

Salmonella is a gram-negative bacilli. It is an enteropathogen. There are two species of *Salmonella*, *S. enterica*, and *S. bongori*. They are commonly associated with typhoid [7]. *Salmonella* can be divided into typhoidal and nontyphoidal species. *Salmonella enterica* subspecies cause the majority of nontyphoidal *Salmonella* infections. Enterica serotypes Enteritidis, *Salmonella typhimurium*, *S. Newport*, *S. Heidelberg*, and *S. Javiana* can cause bone and joint infections [8].

The organism reaches the human body by direct or indirect contact with many species of animals or food derived from them, their excreta, contaminated meat, milk, eggs, and water. Infected pets, turtles, and contaminated marijuana are other sources [9]. The mode of transmission is feco-oral. In developing countries, *Salmonella* infection is endemic. Children on exclusive breastfeeding are protected from this infection. Ingestion of cow's milk, meat, and meat products and fortified foods can cause *Salmonella* infections in infants on breastfeeding. It can spread from reptiles and amphibians [10].

Clinical features of osteomyelitis and septic arthritis

Salmonella infections are associated with one of the four clinical syndromes, namely, enteric fever, gastroenteritis, bacteremia, and asymptomatic carrier state. A total of 0.8% of *Salmonella* infections are osteomyelitis. Approximately 0.45% of all osteomyelitis is due to *Salmonella*. It is common in the diaphysis of long bones and the spine [11]. The incidence of *Salmonella* septic arthritis in healthy children is 0.1 to 0.2%. Hemoglobinopathies, liver diseases, malignancies, immunocompromised states such as connective tissue disorders, chronic steroid intake, diabetes mellitus, lymphoma, trauma, and extremes of ages are associated with an increased risk of *Salmonella* osteomyelitis [12, 13]. The frequent site of involvement of *Salmonella* infection is the diaphysis of long bones. The femur and humerus are the most common bones involved. There are reports of osteomyelitis involving the pelvis and spine [14, 15, 16, 17].

The clinical features of *Salmonella* osteomyelitis are indistinguishable from those of other bacterial osteomyelitis. It has an indolent course. Therefore, the diagnosis is often delayed. They often present with fever, local pain, and inability to move the limb. Local inflammatory signs, such as swelling, redness, and a local rise in temperature. The local signs are minimal compared to other bacterial infections. Irritability, pseudoparalysis, dehydration, and swelling occur in infants and young children [13, 18].

Septic arthritis is hematogenous in origin or contagious from an adjacent site of infection. In infants, there is direct communication between the metaphyseal and epiphyseal vessels, so metaphyseal osteomyelitis can produce septic arthritis. After the formation of physis, the infection can spread to a joint if the metaphysis is intraarticular. The hip and knee are the commonly affected joints. Septic arthritis of the shoulder is rare in children, especially with *Salmonella* [19]. The features of toxemia are rare. Most of the signs are localized, so patients present late, and diagnosis is usually delayed [20].

Why *Salmonella* infection is common in sickle cell disease

The incidence of osteomyelitis in sickle cell disease is between 1.5 and 12% [6]. Sickle cell disease and *Salmonella* infections are closely associated. Hodges and Holds and Lambotte-Légrand were the first to point out the relationship between *Salmonella* infection and sickle cell disease. There is an increased incidence of infection

with capsulated organisms due to autosplenectomy and defective complement pathways. There are many reasons for the increased incidence of Salmonella infections in sickle cell anemia. Large quantities of Kupffer cells containing breakdown products of red cells and cirrhosis in sickle cell anemia are associated with Salmonellosis. This is due to the liver failing to clear the organisms from the portal circulation. There is a failure of macrophages to clear bacteria. This is due to increased phagocytosis of the breakdown products of abnormal red blood cells. Due to frequent gallstones, these patients are chronic carriers of Salmonella. The abdominal crisis in these patients leads to intestinal ischemia. Capillary occlusion and gastrointestinal mucosa loss help the organism transduce through the mucosal wall and reach the bloodstream [21].

Bone infarcts are frequent in sickle cell disease. Persistent periosteal blood flow and poorly developed collateral circulation reduce medullary blood flow. The abnormal cells causing sluggish blood flow lead to thrombosis and infarction. The increased metabolic activity, high oxygen demand, and fibrosis of marrow due to infarcts all reduce the local resistance and increase the growth of infective organisms. Salmonella can remain dormant at the site of infarct for a long time. The proliferation and spread of these bacteria into the bloodstream usually follow a sickling crisis. Salmonella osteomyelitis is generally preceded by a sickling crisis [21,22]. After proper antimicrobial treatment, the fever decreases in two to three days in normal persons after Salmonella bacteremia. In sickle cell disease, the fever is prolonged after the initiation of treatment due to the slow apoptotic death of cells, which allows the bacteria to persist in the body for a long time. It can also be due to the high initial immune response triggered by bacteremia [23].

Clinical features in sickle cell disease

Salmonella osteomyelitis is common in children with sickle cell disease. Even then, Staphylococcus aureus is the most common organism producing osteomyelitis in sickle cell disease. It is common in early childhood. Involvement of the hand and feet is common in infancy and early childhood. Older children's long bones are frequently involved. Unlike other pyogenic infections, the diaphysis is the most common site. The upper end of the humerus, femur and sternocostal junctions are the common sites. Epiphysis involvement with septic arthritis is common in infancy. Abscess formation and sinuses are frequent. Multiple sites with symmetrical

involvement are also common. In neglected cases, pathological fractures can occur.

It is difficult to differentiate osteomyelitis from ischemic crisis because both have similar clinical features. High-grade fever, pronounced fever, local inflammatory signs, and features of toxemia are more in favor of infection. In the case of osteomyelitis, children fail to respond to measures such as rest, hydration, analgesics, and alkalis. The majority of cases can be managed as outpatients. However, failure to outpatient management, toxemia, operative debridement, pathological fractures, extensive involvement, and toxemia are indications for inpatient care [21, 24, 25]. Early recognition and treatment of osteomyelitis in sickle cell disease is essential to prevent recurrent relapses and chronic osteomyelitis [25]

Septic arthritis in sickle cell disease

The incidence of Salmonella septic arthritis in healthy children is 0.1 to 0.2%. Septic arthritis due to Salmonella is rare. Preexisting enteric fever is a rare occurrence in Salmonella septic arthritis. Many children develop reactive Salmonella arthritis following diarrheal disease and enteric fever. It is common in sickle cell anemia patients. Rarely, it is reported in immunocompetent children without hemoglobinopathies. Most of the reports are from countries such as India, where enteric fever is common. The shoulder, hip, and elbow are the common sites. The knee joint is the second most common site of Salmonella septic arthritis. The presence of transphyseal capillaries connecting the metaphysis and epiphysis is the reason for their predilection. The metaphyseal osteomyelitis can directly spread to the epiphysis. The synovium is a favored site of metastasis in Salmonella bacteremia [26, 27]. Dislocation of the joint can occur as a complication [28].

Septic arthritis due to Salmonella is monoarticular [27]. In children with sickle cell disease, there is recurrent vaso-occlusion with intestinal infarction leading to necrosis and increased gut permeability. This helps enteric Salmonella reach the systemic circulation and cause infection at different sites. The infarction of the bone in sickle cell disease is another factor favoring Salmonella osteomyelitis [23]. Salmonella typhimurium, Salmonella Paratyphi B, and Salmonella Enteritidis are common species associated with osteomyelitis [29].

Investigations

The workup of a child with Salmonella osteomyelitis begins with a routine hemogram.

There will be a moderate increase in total leukocyte count and C-reactive protein. Aspirate from the joint shows an increase in neutrophils. An ultrasound scan will show joint effusion with particulate material. The radiographs show no bony abnormality initially. Distension of the capsule and loss of soft tissue planes may be seen. Later, localized areas of lysis with sclerosis may be seen mimicking bone tumors [30]. An MRI scan is useful to visualize the abscess and surrounding osteomyelitis in early cases. The culture of the specimen shows gram-negative bacilli that grow in the McConkey agar. They also agglutinate with Salmonella O antigen. The biopsy is consistent with features of acute infection and osteomyelitis. The treatment of septic arthritis usually involves arthrotomy and splinting of the joint. Sensitive antibiotics are given parenterally initially followed by oral medication for three to five weeks [31, 32, 33].

Salmonella vertebral osteomyelitis

Salmonella infections of the vertebra are very rare. In the majority of cases, this follows an intestinal infection. Gibney (1899) reported four cases of typhoid spine following enteric fever [34]. They are more common in persons who are predisposed to Salmonella infections than in the general population. The infection spread to the vertebra through the hematogenous route. Contiguous spread from adjacent sites and contamination after invasive diagnostic and therapeutic interventions can rarely occur [35]. The most frequent site is the lumbar spine (50%), the dorsal spine (20%), and the rest in multiple sites [35, 36].

It is difficult to clinically differentiate between pyogenic and Salmonella spondylodiscitis. Back pain, neck pain, and fever are the common presenting symptoms. However, the diagnosis of this condition is difficult in afebrile patients presenting with back pain only [36]. Spondylodiscitis is associated with spinal and intracranial epidural abscesses [37, 38].

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Investigations revealed anemia, leucocytosis, or leukopenia. The erythrocyte sedimentation rate may be raised. Culture and serological tests of blood, urine, stool, and bone marrow may yield a positive result. CT scans and MRI scans show the destruction of vertebrae with paravertebral or epidural abscesses [39].

Treatment of Salmonella infections of the bone and joints

Most cases can be treated conservatively. On the suspicion of osteomyelitis, we can start the child on empirical antibiotics. After obtaining a positive culture of Salmonella, we have to rule out any predisposing factors, such as sickle cell anemia or other immunodeficiency states. Meantime sensitive antibiotics can be started intravenously for two to three weeks followed by oral antibiotics for four to six weeks. Most cases are sensitive to ceftazidime and ciprofloxacin. Ciprofloxacin should be avoided in children. Ampicillin, oxacillin, and cotrimoxazole are also effective. Third-generation cephalosporins such as ceftriaxone and cefotaxime can be used. The development of resistance to the above drugs is also noted. Follow-up using erythrocyte sedimentation rate and C-reactive protein can be used [26, 40]. Surgical treatments such as arthrotomy and incision and drainage of abscesses can be performed in certain cases. Spinal infections may need decompression and stabilization in indicated cases.

Conclusion

Salmonella infections of the bone and joints are rare. They are common in sickle cell disease and immunodeficiency. Even though the pathogenesis of disease in sickle cell and nonsickle cell disease are different, both respond to nonsurgical treatment. The prognosis is good if identified and treated early.

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