Septic arthritis of the hip in adults with sickle cell anemia

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Abstract

Although the presence of osteonecrotic bone is known to make joints more prone to infection, acute septic joint in hip osteonecrosis has not frequently been reported in adults with sickle cell disease. The clinical features at the time of admission, imaging findings suggesting the diagnosis, modes of treatment and sequelae of septic arthritis of twenty-four hip joints with osteonecrosis in patients with sickle cell disease were studied retrospectively over a 25-years period. This study evaluated also the complications, the efficiency and the risk of total hip arthroplasty in these patients. Most patients were in the third decade of life. Staphylococcus and Gram negative infection predominated. Treatment was first conservative but most of the patients needed surgery to treat infection and sequelae related to infection. A total hip arthroplasty was performed later in twenty joints. No deaths were observed, but complications occurred. Twenty of the patients in our study underwent delayed total hip arthroplasties following repeated aspirations of the joint and intravenous antibiotics. With an experienced surgical and medical team and multidisciplinary management of these patients undergoing total hip arthroplasty after hip infection, our rate of complications was acceptable.

Introduction

Sickle cell disease (SCD) is an autosomal-recessive disorder that produces hemolytic anemia related to abnormal hemoglobin and erythrocytes. Those who are homozygous for the sickle cell gene (hemoglobin SS) have a high risk of bone infection due to the association of recurrent episodes of sloughing of the intestinal mucosa resulting in enteric bacteremia and osteonecrosis caused by microvascular occlusion. This incidence is also high in patients with hemoglobin SC (compound heterozygotes for HbS- and HbC-producing alleles: SC) and in the various types of sickle-beta-thalassemia (Sthal) population and several studies have reported hip infections in children with SCD. Spontaneous septic arthritis of the adult hip is rarely reported and poorly defined. Many forms of chronic arthritis predispose the joint to bacterial infection, including rheumatoid arthritis, osteoarthritis, gout, and pseudo-gout.1 Bulmer2 and Kelly3 and Coventry presented the two largest series in the 1960s. These studies emphasized the typical delay in diagnosis and treatment that frequently required hip resection for disease control. However, since these studies were published, little emphasis has been placed on septic hip arthritis. Although the presence of osteonecrotic bone might be considered as making the joints more prone to bacterial infection, a review of the literature4-8 reveals only a small number of well-documented cases where osteonecrotic joints have become secondarily infected. In these series, only one child with osteonecrosis resulting from of sickle cell disease1 was shown to have an acutely septic hip joint superimposed upon a well-established osteonecrosis. We have an experience of twenty-four cases of pyogenic arthritis developing in osteonecrotic joints of adult patients with sickle cell disease. To our knowledge, before this report, there have been no series reporting of such a complication in adults. Based on the limited data available in the literature and our personal experience with twenty-four cases, we believe that it is important to report our data.

This study reviewed the incidence of hematogenous septic hip arthritis in sickle cell disease patients with osteonecrosis to define the factors at the time of admission and laboratory or imaging findings suggesting the diagnosis. Although clinical admission procedure has probably not changed since the 1960s, laboratory and imaging techniques available to aid the clinician in making a diagnosis have improved. However, it is unclear whether computed tomography (CT) or magnetic resonance imaging (MRI) are of assistance in early diagnosis and treatment in these cases. The outcome of these patients was examined and it was determined whether advanced imaging and surgical techniques diminished the sequelae of this disease process. We asked also whether total hip arthroplasty (THA) was a treatment for the sequelae and provided substantial long-term pain relief and improved function in this patient population.

Material and Methods

The authors of this study have experience in the management of more than 1500 patients with sickle cell disease undergoing orthopaedic procedures. These patients were homozygous for the sickle cell gene (haemoglobin SS), haemoglobin S/haemoglobin C, or had haemoglobin S associated with beta thalassemia. Among these patients, we retrospectively reviewed twenty-four consecutive patients with sickle cell disease who between the years of 1983 and 2003 developed septic hip arthritis on the site of a previous osteonecrosis. All the patients had osteonecrosis as an adult (average age, 25 years; range, 18 to 43 years). The diagnosis of osteonecrosis was known in fourteen patients before the diagnosis of infection and discovered at the same time as the infection in ten patients. There were sixteen female patients and eight male patients; the minimum follow-up (up to the latest clinical evaluation) was five years (mean, 13 years; range, 5 to 25 years). No patient was lost to follow-up.

The diagnosis of bone and joint infections was based on the initial examination at the time of admission, laboratory values, blood cultures and joint aspiration. Patient charts were examined to identify clinical features at the time of admission; pertinent medical history, including risk factors, physical examination, radiographic and laboratory findings. All charts were reviewed for information regarding the symptoms at the time of admission (i.e., pain, fever, swelling, inability to walk, or limited joint motion). The presence or absence of specific findings in the physical examination was noted, including fever, location(s) of soreness, and location of swelling, range of joint motion, heat, erythema, and gait. Pertinent laboratory data at admission were leukocyte count, differential, C-reactive protein and erythrocyte sedimentation rate. Later results of blood or aspirate cultures also were noted.

A retrospective review of radiographs was performed. CT, MRI results, bacteriological findings, antibiotic treatment, management, and outcome were also evaluated.

MR imaging was performed in seventeen patients with a 1.5-T unit. The following imaging parameters were used: T1-weighted spin-echo imaging, T2-weighted fast spin-echo imaging, and gadolinium-enhanced T1-weighted spin-echo imaging. A fat suppression
Results

Age, sex and haemoglobin type

The age at onset of acute septic arthritis was average twenty-five years (range, 18 to 43 years). There were sixteen female patients and eight male patients. Nineteen patients were homozygous for the sickle cell gene (hemoglobin SS), four had haemoglobin S/S, and one had haemoglobin S/β-thalassemia.

 Associated conditions and pathogenesis

In seven patients (four with SS and three with SC), septic arthritis appeared to have been secondary to contiguous foci of osteomyelitis in the same femur. In these seven patients, the diagnosis of osteomyelitis in childhood and the diagnosis of osteonecrosis as adults were known before the hip infection. In the remaining seventeen patients, infection appeared to have been blood borne. In twelve patients, the sites of bone infection were related to osteomyelitis at a distance from the infected joints: the affected bones were the humerus (7 bones),ibia (3 bones) and femur (2 bones). Another source of bone infection was apparent in two patients with presumed haematogenous spread.

Twelve patients were anaemic with haemoglobin under 20%, while six others (5 with SS and 1 with SC) were severely anaemic with haemoglobin under 16%. General risk factors were present in eight patients and included diabetes mellitus (one patient), dental abscess (one patient), immunosuppressive therapy (two patients), lupus with corticosteroid treatment (one patient), presence of a permacath (three patients).

Clinical features

At the time of admission, the characteristics of the patients varied, although some common themes emerged. All patients suffered from high or groin pain and decreased motion of the affected area. Twelve out of twenty-four patients were unable to bear weight. Five patients (21%) had multifocal joint infection. This polyarticular sepsis was present in four of the nineteen patients with SS (21%) and in one of the four patients with haemoglobin SC (25%). The highest number of joints infected was five in one patient with haemoglobin SS.

The most frequent physical findings at the initial examination were temperature >38.2°C in 75% (18 out of 24 patients) and soreness over the affected area in 83% (20 out of 24 patients).

Most patients requested admission for treatment at a late stage. Only 11 (46%) patients were seen within a week of illness. Thirteen patients delayed for a month before requesting admission to the hospital: arthritis occurred later as a complication of septicaemia and/or osteomyelitis.

Those patients where arthritis was diagnosed on the first days after admission had a long history of osteonecrosis (longer than 1 year) and symptoms of increased pain and temperature occurred suddenly. Evidence of systemic disease was either absent or very mild. By contrast, those where the diagnosis of arthritis was delayed were often initially so desperately ill that the main objective of treatment was the preservation of life during the course of a systemic infection. Septic arthritis was often only first suspected when these very ill patients began to improve.

Laboratory values varied widely. Nearly all patients had an increased white blood cell count. Ninety-six percent (23 out of 24 patients) had a white cell count exceeding 15,000/mm³ (range, 7,900-32,300/mm³). White cell differentials averaged 77±4% polymorphonuclear leukocytes. The Westergren sedimentation rate had values ranging from 24 to 89 mm/h (mean=52). C-reactive protein was higher than 20 mg/L in all patients with a mean of 48 mg/L (range 22 to 126 mg/L).

Bacteriological findings

Joint aspiration was performed in all patients. The diagnosis of osteoarticular infection was made by aspiration of pus from the joint. The numbers and types of other cultures varied for our patient population: blood culture, or tissue biopsy. There were eighteen patients with blood cultures, twenty-four with joint aspirate, and twenty with tissue cultures. Blood cultures were positive in 55% (10 out of 18 patients), tissue biopsy cultures positive in 60% (12 out of 20 patients) and aspiration in 96% (23 out of 24 patients). The most sensitive culture proved to be joint aspiration. At gross analysis, the joint fluid was turbid in twelve, purulent in eight patients, serosanguineous in four patients.

The pathogen was identified in twenty-three out of twenty-four patients for a positive identification rate of 96%. In only one patient the pathogen could not be identified: the infection was however confirmed by the histology. Staphylococcus aureus was the most common isolate (17 cases). For the remaining cases, Streptococcus pneumoniae (1 case), Haemophilus influenza (1 case) and Escherichia...
coli/Enterococcus (4 cases) were cultured. Salmonella was not found.

Radiological and imaging findings

Imaging data from plain radiographs, CT scan and MRI were reviewed for indications of infection. Radiographs (pelvis, hip joint with AP and lateral views) were obtained in all patients and were abnormal in only thirteen patients at the time of diagnosis. Characteristic findings included narrowed joint space (4 hips), destruction of the femoral head (6 hips), evident avascular necrosis of the femoral head (10 hips), lytic changes of the femoral neck (1 hip), cortical erosion of the acetabulum (12 hips), osteomyelitis of the proximal femur (7 hips), soft-tissue gas in the hip and buttock (1 hip), and femoral neck osteolysis extending into the intertrochanter (1 hip). Eight patients had subluxation. Radiographs appeared normal in eleven patients at the time of diagnosis.

The diagnosis of hip osteonecrosis was known before infection in thirteen hips and discovered at the time of admission with hip pain and temperature in the eleven patients with normal radiographs. The amount of joint fluid in each affected hip was not considered as sufficiently abnormal to suspect infection since it is frequently associated with osteonecrosis. MRI was useful in suspecting the diagnosis of infection in all the seventeen patients with MRI: the abnormal findings associated with the usual osteonecrosis signs were a thicker synovial membrane, signal intensity alterations in the soft tissues around the hip joint and abnormal signal intensity in the bone marrow at a distance from the osteonecrosis. An enhancing rim of inflamed synovial membrane could be differentiated from the hypointense joint fluid on contrast-enhanced images in seventeen patients. Signal intensity alterations in the soft tissue around the affected hip joint were present in seventeen patients and enhanced after administration of contrast medium.

Fat-suppressed gadolinium-enhanced T1-weighted spin-echo images were more sensitive in the detection of signal intensity alterations in soft tissue than were fat-suppressed T2-weighted fast spin-echo images. These signal intensity alterations in soft tissue were located within the muscles and surrounding fascial planes just lateral to the femoral head on higher sections and around the femoral neck on lower sections. These signal intensity alterations tended to be confined to the pericapsular regions except in the seven cases of septic arthritis and coexistent contiguous osteomyelitis, in which more extensive signal intensity alterations in soft tissue were noted at a distance from the joint with sometimes (2 cases) complicated soft-tissue abscess. Signal intensity alterations in the bone marrow of the affected hip joint were present in ten patients. However, such signal intensity alterations, when only present on the femoral head, were not useful for the diagnosis of infection because of associated osteonecrosis. These signal intensity alterations were more useful when located in the acetabulum and adjacent to the articular surfaces (five cases). In two patients, extensive signal intensity alterations involved the femoral metaphysis. At surgery, these signal intensity alterations were confirmed to be coexistent osteomyelitis.

Computed tomography was used as the third modality of imaging. No patient on whom CT was performed had normal findings. Bone scans were consistent for osteomyelitis in seven patients. Specific findings of infection included cortical erosion of the acetabulum, subchondral cyst formation in the acetabulum (5 cases) and gas in the hip (3 cases). Fluid was present in the hip of all patients. CT scan was useful for joint aspiration and to evaluate the recurrence of fluid in the joint.

Treatment and complications during treatment

We observed medical complications in relation with the transfusions needed by these patients. Minor complications from transfusions were observed in 6 cases and major complications in 2 cases. Febrile, nonhemolytic reaction was a frequent complication of red blood-cell transfusion even with leukodepleted red blood cells. This was observed at a rate of 25% (6 cases) and was associated with symptoms such as fever and pain complicating subsequent management and increasing the number of days of hospitalization. Major transfusion reactions (severe alloimmunization) were encountered in two cases (8%) despite the use of extended Ag-matched blood. These two patients developed massive intravascular hemolysis seven days after transfusion.

There were eight septic dislocations of the hip despite traction and joint aspiration. Twelve other patients had joint destruction at three months follow-up since the diagnosis. So, twenty patients were treated with femoral head resection and later THA. Two patients had arthroscopy and drainage performed without resection of necrotic tissue and had later joint space narrowing indicative of articular cartilage damage. The remaining two patients who did not undergo surgery were ambulatory at discharge (without a narrowed joint space on radiographs). Therefore, only two of twenty-four patients had an acceptable outcome in which they were ambulatory and had no radiographic evidence of joint space narrowing at discharge.

Of the patients who required THA, at the time of femoral head resection, positive culture was present in seven of the twenty hips despite the treatment with adapted antibiotics. The other thirteen hips appeared to have been sterilized by the treatment despite joint destruction. Patients underwent THA within an average period of 12 months (range 6 to 24 months) after femoral head resection, which improved their functional status. Technical difficulties on the acetabulum were related to bone that was usually soft. When acetabulum destruction by infection was present, an acetabular ring with a cemented cup was used to improve the fixation of the prosthetic cup (4 cases).

We observed orthopaedic complications in 2 cases (8%). The excessive intraoperative blood loss contributed to an increased incidence of wound hematoma and prolonged drainage (more than 15 days) in one patient who received thromboembolic prophylaxis with warfarin. Another patient had postoperative transient peroneal nerve palsy (3 months) with foot drop relating to hematoma.

Following THA, patients improved in terms of relief of pain, function, and range of motion. The average score for pain was 1.5 points (range, 1 to 3 points) preoperatively and 5.8 points (range, 5 to 6 points) postoperatively. After the operation, 16 of the 20 hips were entirely free of pain and the remainder had only occasional discomfort. The score for function averaged 1 point (range, 1 to 3 points) preoperatively and 5.1 points (range, 4 to 6) postoperatively, since most of the patients were able to walk more than 1 km. The score for the cumulative range of motion of the hip averaged 2.1 points (range, 1 to 3 points) preoperatively and 4.6 points (range, 4 to 5 points) postoperatively.

No immediate postoperative infection occurred in the 24 patients, but late infection occurred in 3 hips. None of these patients had positive intraoperative cultures at the time of THA implantation. The average time to revision for infection was 4 years (range, 2-6 years). The organisms cultured at the time of revision for infection were the same as at the time of arthritis (Staphylococcus aureus). Revision for infection was performed with the “two-stage technique,” performed 45 days after removal of the primary arthroplasty. At the most recent follow-up (average 13 years, range 5 to 25 years) 2 of these 3 hips were without infection and one still had recurrence of infection.

Discussion

Although the association between osteonecrosis and septic arthritis can be readily explained, the paucity of documented cases suggests that this association may be rare and in this situation early recognition of pyogenic hip arthritis is mandatory. Cases of septic
arthritides superimposed on osteonecrosis in patients with sickle cell disease were difficult to diagnose unless there was a high index of suspicion. Patients with sickle cell disease frequently have systemic illnesses\(^{16}\) and their symptoms of sepsis may be attributed to sites other than their joints. For example in one patient, persistent sepsis was considered to be due to bacterial endocarditis despite adequate antibiotic therapy and the hip was only diagnosed as a source of infection 6 weeks later.

The clinical features of septic arthritis and an exacerbation of osteonecrosis may be very similar. A thorough history with particular emphasis on predisposing risk factors and laboratory and imaging findings in favour of infection will guide the clinician to consider the diagnosis of septic hip arthritis. Routine radiographs are generally not useful in identifying early septic arthritis. In a series of thirty-five patients without sickle-cell disease, magnetic resonance imaging was shown to be 92% sensitive and 96% specific for the diagnosis of acute osteomyelitis.\(^{15}\) However, other articles on patients with sickle-cell disease concluded that the distinction between acute infarction septic arthritis and osteomyelitis is difficult.\(^{12,14}\)

Many of our patients with septic arthritis demonstrated signal intensity alterations in the soft tissue around the affected hip joint, a finding that probably represented reactive soft-tissue oedema. In addition to joint effusions, intense enhancement and hypertrophy of synovial membrane were consistently encountered in hip joints affected by septic arthritis in our study.

The value of laboratory studies in the differential diagnosis of osteoarticular infections and bone infarction in children with sickle cell disease is controversial\(^{22,23}\) and no data are available in adults. Our patients with documented articular infections had white blood cell counts ranging from 7,900 to 32,300/mm\(^3\). There was a trend in patients with infections of white blood cell counts exceeding 15,000 mm\(^3\) in 96%. Westergren sedimentation rates exceeded normal values in 100% of our articular infection group. But, in bone infarction related to sickle cell disease, the results (of the Westergren sedimentation rates) are variable during a long period and have been reported to exceed normal values in 75%. Creatine reactive protein levels should be obtained initially. Typically, it is the first marker elevated and the first to respond to treatment. In our experience, the CRP is normal in hip osteonecrosis without infection. It exceeded normal values in 100% of our infection group. Positive findings in these tests, when combined with the appropriate clinical findings (i.e., high fever, acute, and pain) increase the suspicion for arthritis.

If the diagnosis of infection is suspected or made, these patients should be subjected to articular punction. Following these guidelines, the diagnosis of infection and identification of a pathogen when present, can be made appropriately in over 90% of cases as documented by our study. However, once the bacterial invasion of the joint has commenced even with adopted antibiotics, direct and indirect factors can lead to joint destruction.\(^{24}\) The inflammatory cascade is ignited and despite its role in alleviation of the infection, it has a negative effect on the articular surfaces. Proteolytic enzymes degrade the proteoglycan matrix of collagen and cartilage ground substance compromising the ability of the articular surfaces to resist mechanical wear even if the patient is treated with traction. Infection occurring in necrotic tissue raises the question of whether in some cases the infected, necrotic tissue must be removed as part of the treatment, since antibiotics would likely have poor penetration into areas of necrosis where circulation is impaired. The reported cases of our series were all initially treated by repeated aspirations of the joint and intravenous antibiotics without resection of the necrotic tissue. But twenty-two patients needed surgical intervention, with two patients having arthroscopy and drainage performed without resection of necrotic tissue and twenty patients having their femoral heads excised. In some patients, it appears unlikely that the hip could be sterilized without resection of the infected necrotic tissue. The presence of positive culture in the resected femoral head in spite of appropriate intravenous antibiotics indicates that the hip infection is difficult to treat perhaps because of osteonecrotic tissue. In other patients, the hip appeared to be sterilized with joint aspiration and antibiotics but this treatment associated with traction was not sufficient to avoid cartilage destruction probably because the cartilage had a decreased resistance to wear. So joint destruction did not always mean persistence of infection and could be observed in a sterilized joint. Conflicting data are present in the literature about how rarely osteoarticular infection occurs in patients with sickle cell disease. A study by Keeley and Buchanan\(^{25}\) suggested that acute long-bone infarction would occur at least 50 times more commonly than bacterial osteomyelitis in sickle cell disease. Early studies by Golding et al.\(^{26}\) and Engh et al.\(^{17}\) concluded that osteomyelitis appeared commonly in sickle cell anemia. More recent reports from Saudi Arabia and Nigeria\(^{27}\) documented an incidence of osteomyelitis in sickle cell patients who had extremity complaints. Estimates of the prevalence of osteoarticular infection in children with sickle cell anemia have ranged from 0.2% (Epps et al.)\(^{18}\) to 5.4% (Barrett-Connor). To our knowledge, no estimation has been reported in adult patients. During the same period, we have treated about 1200 hip osteonecroses with sickle cell disease. So the risk may be about 24/1200 (2%) in patients with hip osteonecrosis. In our patients, systemic risk factors\(^{28,29}\) in the development of bacterial arthritis included diabetes and glucocorticoids. Another cause of increased risk of late infection in patients may be immunoparesis related to medical treatment by hydroxyurea. Two patients in our series had infection and medical treatment by hydroxyurea. Host microbial interactions play an important role in the pathogenesis of septic arthritis. Most bacteremias do not result in septic arthritis in these patients. However, it is well known that devitalized tissue\(^{22,28}\) enhances the development of sepsis, and it is likely that the presence of osteonecrotic tissue provides favourable conditions for localization of the circulating infective organisms. In our review, we noted that most of the patients with documented osteoarticular infections were homozygous SS, which has been shown by others in children to be most commonly associated with an increased proneness to bone and joint infections.

Bacterial arthritis was hematogenously acquired in seventeen patients and in the majority of cases of septic arthritis in osteonecrotic joints (19 cases) there was a primary focus of bone infection at a distance from or contiguous to the hip. The causative organisms identified in our patients were Staphylococcus aureus, beta hemolytic Streptococcus, Hemophilus influenza and enterococcus. The unique susceptibility of sickle cell patients to Salmonella osteomyelitis was first fully appreciated by Hodges and Holt in 1951\(^{31}\) and has been confirmed by multiple subsequent authors.\(^{2,24}\) It is postulated that bone infarction, a common sequelae of sickle cell disease, combined with sluggish microcirculation and impaired opsonization causes Salmonella bacteremia to “almost invariably localize to bone”. However the incidence of septic arthritis in sickle cell disease with salmonella is more poorly defined. A review of the reported organisms from all the series show salmonella has not been reported as a pathogen in joint infection in sickle cell disease patients. Our review of recent literature reveals no strong predisposition to a particular pathogen in septic arthritis, although Staphylococcus has been prevalent in some series. Twenty of the patients in our study underwent delayed total hip arthroplasties following repeated aspirations of the joint and intravenous antibiotics. Although it was previously felt that insertion of a total hip prosthesis in the presence of current or previous infection is never warranted,\(^{32,33}\) recent studies have shown that results of total hip arthroplasty under those circumstances compare favourably\(^{34,35}\) with cure rates that have been reported for infections treated by resection arthroplasty,\(^{28}\) with the former group having far better functional results. We also recommend...
that patients with sickle cell disease who have advanced sequelae of septic arthritis of one hip should have a total hip arthroplasty rather than an arthrodhesis or a resection arthroplasty. With an experienced surgical and medical team and multidisciplinary management of these patients undergoing THA after hip infection, our rate of complications was acceptable. However, our data do not indicate complete safety of THA in this patient population and in this situation, but the risk-to benefit ratio appears reasonable.

We feel that our cases emphasize the importance of osteonecrosis as a risk factor in the development of septic arthritis as in rheumatoid disease. This is particularly important in those patients with osteonecrosis who are considered for total hip arthroplasty. As in children, infection should be suspected in any patient with osteonecrosis who is admitted with an acute exacerbation of an existing hip problem or evidence of a septicemia. Patients with such characteristics at the time of admission should be carefully evaluated for evidence of joint sepsis, and should have a diagnostic joint aspiration before total hip arthroplasty.

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