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Case Report

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Sickle Cell Trait: Is It Always Benign?

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Abstract

Sickle cell disease is a well-known homozygous inherited hemoglobinopathy that causes vaso-occlusive phenomena and chronic hemolysis. Vaso-occlusion results in sickle cell crisis and can eventually lead to complications involving multiple organ systems. However, the heterozygous counterpart, sickle cell trait (SCT) has less clinical significance as these patients are generally asymptomatic. This case series examines three unrelated patients with SCT ranging from the age of 27 to 61 years, who presented with pain in multiple long bones. Hemoglobin electrophoresis confirmed a diagnosis of SCT. Radiographic images of the affected sites showed osteonecrosis (ON). Interventions included pain management and bilateral hip replacement in two of the patients. Historically, vaso-occlusive disease in patients with SCT with no evidence of hemolysis or other hallmark findings of sickle cell disease is rare. There are limited reported cases of ON in SCT patients. Clinicians should explore other hemoglobinopathies not tested on routine hemoglobin electrophoresis and alternative risk factors for ON in these patients.

Keywords: Sickle cell trait; Osteonecrosis; Sickle cell disease

Introduction

Sickle cell trait (SCT) is a presumed benign condition, and the heterozygous status is most commonly used to discuss preconception counseling. Although rare, potential complications of SCT include urinary tract infections, hematuria, hyposthenuria, renal medullary carcinoma and potential for vaso-occlusion at high altitudes [1]. Unless SCT is coinherited with another hemoglobinopathy, the incidence of vaso-occlusive phenomena is low and not well documented. This case series presents three patients with SCT and osteonecrosis (ON) of multiple bones.

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Case Reports

Case 1

A 27-year-old African American female (body mass index (BMI) 27.47 kg/m^2), with a medical history of SCT and endometriosis diagnosed 3 years prior during infertility testing, presented to the clinic with atraumatic left hip pain for 3 years. The pain was worst with weight-bearing and mildly relieved with over-the-counter pain medication. Physical examination of the left hip at the initial encounter demonstrated tenderness in the lateral and anterior surfaces, abnormal external and internal rotation, abnormal abduction, adduction, and flexion, and positive FABER test. Based on outside records, the magnetic resonance imaging (MRI) showed early avascular necrosis of the left femur head. She was referred to orthopedics and treated with a one-time dose of intra-articular steroids. Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen provided minimal relief. She continued to have left hip pain and subsequently developed pain in her right hip and bilateral shoulders. She had a history of dislocation of the left shoulder 1 year prior to symptom onset with multiple subsequent dislocations of the same shoulder. Physical examination of the right shoulder was positive for glenohumeral joint crepitus, restricted forward flexion of 140°, and a positive impingement test. The left shoulder had tenderness to palpation over the anterior aspect of the shoulder, limited forward flexion of 120°, positive apprehension, cross arm, and impingement test. The right hip examination was positive for tenderness in the lateral and anterior surfaces with abnormal external and internal rotation. Prior to interventions, she was using a cane or walker to ambulate with a significant limp, and she was unable to lift her arms past her shoulders, dress or comb/wash her hair.

She underwent radiographic investigations including bilateral hip radiography and bilateral shoulder radiography. The hip radiographs showed bilateral femoral head collapse, subchondral cystic change, sclerosis, moderate left and mild right-sided joint space narrowing, and flattening of the acetabular roofs, consistent with grade 4 bilateral osteonecrosis of the femoral heads (ONFH) (Figs. 1, 2). Radiography of the left humerus originally showed chronic corticated fragments of the superior humeral head. Subsequent radiographs 4 years later showed avascular necrosis of bilateral humeral heads with left being classified as severe. Hemoglobin (Hb) electrophoresis showed 39.8% HbS, HbA 57.1%, 3.3% HbA2, and < 1.0% HbF. There was no evidence of spherocytes, sickle cells,

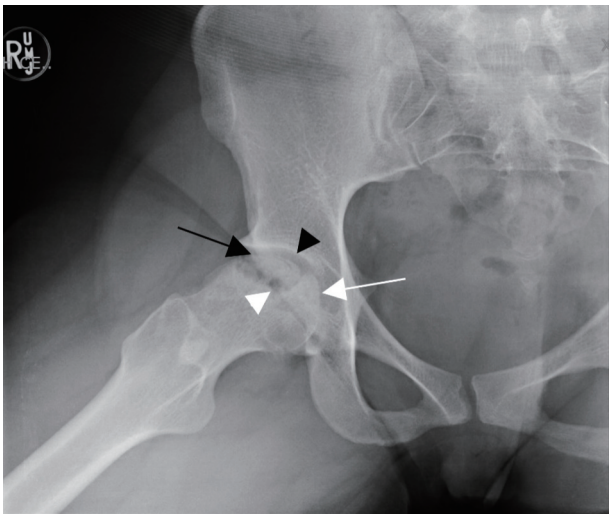

Figure 1. Right-sided femoral head collapse (white arrow) with subchondral cystic change (white arrowhead), sclerosis, mild joint space narrowing (black arrow), and flattening of the acetabular roofs (black arrowhead), consistent with grade 4 ONFH in case 1. ONFH: osteonecrosis of the femoral head.

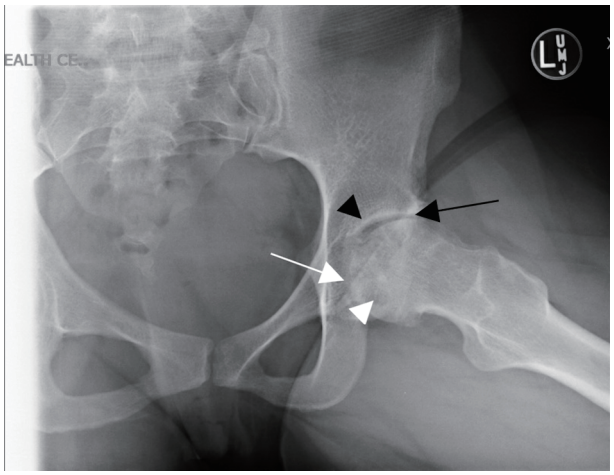

Figure 2. Left-sided femoral head collapse (white arrow), subchondral cystic change (white arrowhead), sclerosis, moderate joint space narrowing (black arrow), and flattening of the acetabular roofs (black arrowhead) (grade 4 ONFH in case 1). ONFH: osteonecrosis of the femoral head.

or schistocytes on peripheral smear. Autoimmune tests included antinuclear antibody (ANA), lupus anticoagulant, cardiolipin antibody, anti-double stranded DNA (anti-dsDNA), beta-2 glycoprotein, which were negative. Hemolytic anemia laboratory test included a retic count of 1.4%, Hb of 12.3 g/dL, mean corpuscular volume (MCV) 84 fL, lactate dehydrogenase (LDH) 164 U/L, haptoglobin 80 mg/dL, and total bilirubin 0.2 mg/dL, all within normal limits. Additional lab tests, including human immunodeficiency virus (HIV), hepatitis B, hepatitis C, rapid plasma reagin (RPR), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lipid panel, vitamin D, and drug test were non-contributory. Known family history was negative for sickle cell disease (SCD) or ON. Social history included less than 5 pack-years of tobacco use, occasional alcohol use, no recreational drug use, no recent pregnancies, no use of oral contraceptives, and residence in an urban community. Dual-energy X-ray absorptiometry (DEXA) scan of the spine and hip was normal. A Mayo Clinic sent out blood test called "Thalassemia and Hemoglobinopathy Evaluation", which test for thalassemia and other hemoglobinopathy was consistent with SCT with no other additional hemoglobinopathy.

Her treatment plan/goals were to relieve pain and postpone joint replacement due to her age on presentation. Conservative management with opioids, injections of intra-articular steroids, and platelet plasma injections were administered. After 5 years of pain medications, non-weight-bearing crutches and physical therapy, she underwent bilateral hip decompression. She continued to experience pain and ultimately underwent a total hip replacement (THA).

Case 2

A 58-year-old African American male (BMI 26.24 kg/m^2) with history of hypertension, gastritis, spontaneous pneumothorax, self-reported SCD, and osteoarthritis with avascular necrosis of bilateral hips and bilateral knees presented to the hematology clinic to establish care after relocating from the out-of-state. The patient underwent bilateral THA surgery 11 years prior as a result of grade 4 avascular necrosis. He had chronic arthralgia in his left shoulder, back and bilateral knees, and no reported hospitalizations for sickle cell pain crisis. The physical exam showed limited range of motion of the shoulders, back, hips, and knees due to pain.

Radiography of bilateral hips showed bilateral total hip arthroplasty with no evidence of failure or loosening. Bilateral shoulder radiography showed osteopenia, muscle atrophy, and acromioclavicular joint arthritis. Bilateral knee radiography showed generalized osteopenia, muscle atrophy, and avascular necrosis of the distal femurs and proximal tibias without subchondral fracture. Hb electrophoresis which was repeated showed HbA of 56%, HbS 40%, HbA2 2.8%, HbF < 1%. Autoimmune tests included ANA, rheumatoid factor (RF), myeloperoxidase antibody, all negative. The hemolytic anemia laboratory test included retic count of 1.5%, Hb of 12.7 g/dL, MCV 86 fL, platelet count 254 × 10^3/µL, LDH 184 U/L, haptoglobin 60 mg/dL, and total bilirubin 0.2 mg/dL, all within normal limits. Additional lab tests including HIV, hepatitis B, hepatitis C, ESR, CRP, lipid panel, vitamin D, and drug test were non-contributory. Social history included 20 pack-years, no alcohol or recreational drug use, and residence in an urban community. Due to the severe avascular necrosis on multiple radiographic images, bone biopsies were performed which showed extensive necrosis and no evidence of Erdheim-Chester disease. The Mayo Clinic "Thalassemia and Hemoglobinopathy Evaluation" was consistent with SCT with no other additional hemoglobinopathy.

The patient continues to struggle with chronic pain despite surgical intervention. He is on oral opioids and skeletal muscle relaxant. He is also being followed by pain management and has had sympathetic blocks.

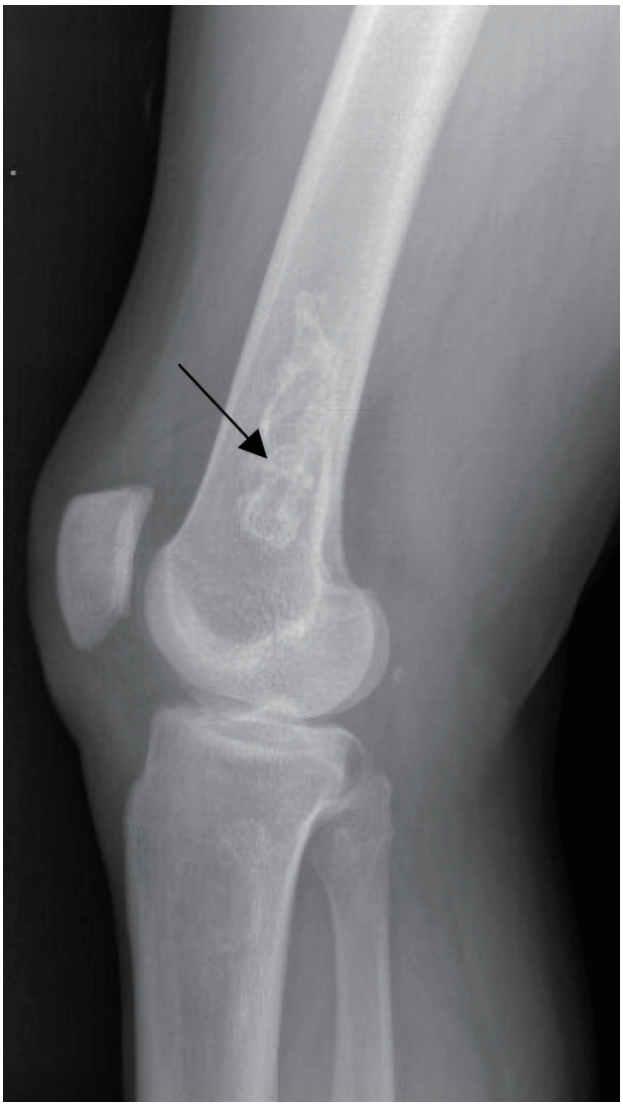

Figure 3. Osteonecrosis of the right femur and tibial diaphysis in case 3. Plain radiograph revealing irregular intramedullary sclerosis (arrow) in the distal femur.

Case 3

A 61-year-old African American male (BMI 32.8 kg/m^2) with a medical history of cerebrovascular accident, multiple transient ischemic attacks, diabetes mellitus, vitamin D deficiency, degenerative joint disease, hyperlipidemia, and hypertension, presented to hematology clinic after he was referred from primary care physician due to sickling noted on peripheral smear. He had chronic knee, ankle, and severe lower back pain which had progressively worsened over the past 3 years. He has a family history of SCT in parents and sickle cell anemia in his sister. Physical examination showed tenderness and decreased range of motion in bilateral knees, ankles, and back.

Radiographs of knee showed osteoarthritis and ON of the bilateral femoral and tibial diaphysis (Fig. 3). MRI knee showed degenerative changes with meniscal tears and bone infarct involving the distal femur and proximal tibia. Hb electrophoresis showed HbA of 56.4%, HbS 39.3%, HbA2 3.4% and HbF < 1.0 %. Blood counts showed Hb of 13.8 g/dL, MCV 93.6 fL, white blood cell (WBC) 4.81 × 10^3/µL, platelets 256 × 10^3/µL, with no evidence of hemolysis (total bilirubin 0.1 mg/dL, retic count 1%). Autoimmune disease labs including ANA, anti-dsDNA, antineutrophil cytoplasmic antibodies (C-ANCA), perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA), RF, antiphospholipid, and myeloperoxidase antibody were negative. ESR, CRP, and lipid panel were elevated. Additional lab tests including HIV, hepatitis B, hepatitis C, and drug test were non-contributory. The Mayo Clinic "Thalassemia and Hemoglobinopathy Evaluation" was consistent with SCT with no other additional hemoglobinopathy. Social history included 44 pack-years, occasional alcohol use, no recreational drug use, and residence in an urban community.

His pain is primarily being controlled by pain management and he has undergone multiple epidural steroid injections, platelet plasma injections, and nerve blocks to the spine, shoulders, and knees. He takes over-the-counter analgesics for breakthrough pain.

Discussion

The normal constitution of adult Hb is a tetramer of two alpha chains and two beta chains. Many mutations to the Hb gene have been discovered and their associated clinical findings described. One mutation well studied is the formation of HbS via a point mutation. This HbS can be inherited in a heterozygous or homozygous pattern. SCD constitutes homozygous inheritance of HbS or any hemoglobinopathy in which the sickle mutation is inherited in combination with another globin gene mutation. Some common examples of genetic hemoglobinopathies that present as SCD is: HbSS, HbSC, HbSβ+Th, HbSβ0Th, etc. [1]. These inherited genotypes are clinically relevant as they cause hemolysis and vaso-occlusive events. In contrast, SCT is a heterozygous inheritance of HbS with HbA greater than 50% and HbS less than 50%. Because SCT has more HbA, the incidence of hemolytic anemia and vaso-occlusive episodes are rare. This case series presented three cases of avascular necrosis in patients with SCT.

Avascular necrosis occurs due to decreased blood flow to the bones. The four mechanisms which may contribute are mechanical disruption of vascular supply due to trauma, intravascular thrombosis or embolism, intraosseous extravascular compression from lipocyte hypertrophy or Gaucher cells, or increased venular pressure exceeding arteriolar pressure [2, 3]. Most experts believe that it is the result of the combined effects of genetic predisposition, metabolic factors, and local factors affecting blood supply [3]. Direct and indirect factors such as fractures, dislocations, rapidly progressive osteoarthritis, SCD, corticosteroids, autoimmune disease, caisson disease, viral infections, hypercoagulable disorders, hyperlipidemia, tobacco use, alcohol use, bisphosphates, male gender, cancer, and marrow-replacing diseases are known accelerants for the development of ON [4]. The case series presents three patients with SCT and severe ON of multiple bones. Evaluation of their

risk factors showed no evidence of autoimmune disease, long-term use of glucocorticoids, radiation, leukemia, HIV infection, hepatitis, or alcohol use abuse. Obesity and hyperlipemia was present in only one of the patients. Although none of the patients had a comprehensive thrombophilia workup, medical history was negative for venous thromboembolism. All three patients have a tobacco use history with a current pack-year ranging from 5 to 44. These three patients differ in age range as well as comorbidities. One meta-analysis of the incidence of ON in cigarette smokers showed a dose-dependent risk. When classified by pack-years, heavy smokers (> 20 pack-years) were at a higher risk of ONFH (odds ratio (OR): 2.26; 95% confidence interval (CI): 1.24 - 4.13), but no significant difference in risk was identified in light smokers (< 20 pack-years) (OR: 1.81; 95% CI: 0.88 - 3.71) when compared with non-smokers [5]. Two of the patients in this case series developed ON with less than 20 pack-years. The major non-traumatic risk factor for ONFH has been related to corticosteroid use, 40% [6], mostly with prolonged and high doses. There have been instances in literature where low-dose and even single-dose corticosteroids have been attributed to destructive ON [7]. Two of the patients in this case series have a history of intra-articular steroids usage but the first dose was administered following diagnosis of ONFH. Trauma was present in all three patients. The 27-year-old one had multiple shoulder dislocations to her left glenohumeral joint, and the remaining patients had mild degenerative joint disease. Although trauma was present, it does not explain the development of ON in the bilateral femurs or right humerus of the 27-year-old patient. In the setting of osteoarthritis present in the 57-year-old and 61-year-old patients, we cannot definitively say if the ON caused the osteoarthritis or *vice versa*.

Evaluation for genetic changes is always important when exploring the cause of SCD presentation in SCT. Hematology has uncovered many Hb variations and associated clinical findings. Most of these variations can be explored at "A Database of Human Hemoglobin Variants and Thalassemia mutations" HbVar database [8]. Basic electrophoresis can diagnose the most common Hb mutations. For SCT HbA is between 50-60%, HbS 35-45%, and HbA2 < 3.5%. There have been a limited number of reported cases of SCD-related complications in patients with SCT and an additional rare mutation. One study found sickling of red blood cells and pain crisis in a patient with SCT and Antilles trait. HbS Antilles trait, alpha 2 beta 2, has the same electrophoretic mobility as HbS, and a low oxygen affinity and solubility. The erythrocytes were found to sickle at O_2 partial pressures similar to HbSC disease [9]. There is also a reported case of conversion of inherited SCT to SCD by uniparental disomy (UPD) resulting in mosaicism for SS and AS erythrocytes [10]. Hemogram variables like Hb/hematocrit (HCT) > 0.33 and lower fetal Hb levels have also been associated with an increased risk for ON [11, 12]. To test for other hemoglobinopathies, each patient in this case series had blood work sent to Mayo Clinic for "Thalassemia and Hemoglobinopathy Evaluation." A hematopathologist expert in these disorders evaluates the case and performs the appropriate tests. This blood test is Hb electrophoresis with reflex genetic testing. The test can identify rare Hb variants, the most common thalassemias, and rare thalassemia variants such as beta-cluster locus large deletions and duplications, delta-beta, delta-delta thalassemias, gamma-delta-beta, and epsilon-gamma-delta-beta thalassemias, large deletional alpha thalassemias and alpha-gene duplications, alpha-chain variants and non-deletional alpha thalassemias, and gamma-chain variants and non-deletional hereditary persistence of fetal hemoglobin (HPFH) (gamma-globin full gene sequencing). If variants are identified, reflex genetic testing is completed. In this case series, all three patients were found to have HbAS and no variants that require reflex genetic testing. In addition to the negative thalassemia and hemoglobinopathy lab, the absence of sickle cells on peripheral smear, normal Hb, normal MCV, and no evidence of hemolysis decreases the likelihood of an undiagnosed hemoglobinopathy as the cause of ON.

Additional genetic variables previously linked to ON include, the impact of the *BMP6* (bone morphogenetic protein) gene and polymorphism of nitric oxide-producing endothelial enzyme (eNOS), which catalyzes the conversion of L-arginine to L-citrulline, and nitric oxide [13]. Pyruvate kinase deficiency has notably been linked to acute sickling in a SCT case report. The patient presented with anemia, sickle cell pain crisis, recurrent leg ulcers, and occasional sickle cells on peripheral smear. The authors uncovered a coexisting SCT and pyruvate kinase deficiency as the cause of sickle cell crisis [14]. Other coinheritance genetic variants reported in SCT patients that present clinically as SCD are hereditary spherocytosis and glucoe-6-phosphate dehydrogenase deficiency. In these reported cases the presentation was sickling of the red blood cells and splenic infract [15]. Potential environmental causes of ON should similarly be acknowledged and explored. Interestingly, a Chinese study in 2015 found a higher prevalence of ONFH based on male gender, region of the country (North China; female: 0.62%, male: 1.19%, P = 0.0003), and urban residence (female: 0.59%, male: 1.14%, P = 0.0003) as compared to rural (female: 0.41%, male: 0.90%, P = 0.0003) and South China (female: 0.40%; male: 0.87%, P = 0.0003) [16]. As all three patients live in urban regions, unknown environmental causes could be an additional factor. Although a definitive cause for ONFH in these SCT patients is likely multifactorial, we believe the association should be recognized in the literature. Due to their unique clinical presentation and chronic pain management, they are followed every month.

Conclusions

There have been scarce reports of ON in patients with SCT in the literature. Although rare, this case series demonstrates that severe complications of SCD can present in patients with SCT. This may be due to other hemoglobinopathies that are not normally tested on routine electrophoresis, other biochemical changes that affect the red blood cells, or certain environmental factors. This case series further highlights the question if SCT is always benign. More database and prospective research focused on SCT patients should be conducted to investigate this phenomenon. Clinicians should keep in mind that although SCT is considered a benign disease, some of these rare complications can occur and must be recognized quickly and treated appropriately.

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None to declare.

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We claim to have no known competing financial interest or personal relationships that could have appeared to influence the work reported in this paper.

Conflict of Interest

We have no conflict of interest to disclose.

Informed Consent

The patients gave permission for the case series and images to be published.

Author Contributions

Tyiesha Sharron Brown: literature review and writing of the original draft. Rachaita Lakra: literature review and editing of original draft. Samip Master: supervision, writing review, and editing. Poornima Ramadas: conceptualization, supervision, writing review, and editing. All authors reviewed the results and approved the final version of the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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