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Case report

Clostridium paraputrificum: An atypical and rare case of septic arthritis mimicking an acute sickle cell crisis

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ABSTRACT

Clostridium paraputrificum is an extremely rare species and constitutes only 1% of all clostridium infections in literature. Septic arthritis from *Clostridium paraputrificum* is even less documented, and currently there is only one known case report. Specifically, patients with sickle cell disease have a well-documented and increased susceptibility to infections with *Salmonella, Streptococcus pneumoniae, Hemophilius influenzae*, and *Enterobacter-klebsiella*. *Clostridium* infection in sickle cell patients has been less studied and described. Here we present a case of septic arthritis from *Clostridium paraputrificum* in a sickle cell disease patient likely provoked by underlying avascular necrosis of the right shoulder.

Introduction

The genus *Clostridium* consists of various pathogens which are gram-positive and anaerobic bacilli [1]. The genus consists of an abundance of diverse *Clostridium* species, some including *Clostridium perfringens, Clostridium botulinum, Clostridium tetani* and *Clostridium difficile* which can cause clinical syndromes in humans. *Clostridium* can be difficult to treat due to their ability to produce resistant endospores [2]. They are ubiquitously found in soil and water sources as well as in the intestinal tract of humans [3]. Infection with *Clostridium* species occurs at a rate of 1.8 per 100,000 persons per year [5]. Proper identification and treatment of these infections are of uttermost importance as they are frequently found in immunocompromised individuals and associated with underlying medical conditions such as occult malignancy, acquired immunodeficiency and inflammatory conditions [4].

Clostridium paraputrificum is a rare isolate and has been estimated to consist of only 1 percent of all clostridium cases [4,5]. It is rarely identified as a cause of human infections which is thought to be due to underreporting and inadequate anaerobic biochemical testing.[1] *Clostridium paraputrificum* has been known to affect adults and newborns, presenting as bacteremia, necrotizing enterocolitis, septic arthritis and cyst formation [3,6]. Risk factors that have been associated with bacteremia are alcohol abuse, diabetes, AIDS and sickle cell anemia [7].

Infection in sickle cell disease is an important and leading cause of mortality. As a population, they have an increased susceptibility to encapsulated organisms due to underlying functional asplenia, genetic factors and defects in complement activation.[8] *Clostridium paraputrificum* is seldom isolated as a source of sepsis and mortality in sickle cell disease. To our knowledge, we present the second known case of septic arthritis due to *Clostridium paraputrificum* and the first documented case provoked by underlying avascular necrosis.

Case presentation

A 47-year-old African American female with past medical history significant for sickle cell disease, thalassemia and recent pulmonary embolism presented to the emergency hospital for right shoulder pain. She described the pain as sharp in nature and 10/10 in severity but denied motor weakness or sensory loss. Due to the severity of pain, there was an associated significant decreased range of motion in her right shoulder in both adduction and abduction. She denied any trauma, fever, chest pain or shortness of breath. She did not have a history of shoulder injections or previous orthopedic surgeries. Of note, one month prior to presentation, she was admitted to a neighboring hospital institution and was diagnosed with COVID-19 pneumonia which subsequently resulted in small peripheral pulmonary emboli and a provoked sickle cell crisis. She improved over the course of one week and was discharged on Eliquis with appropriate outpatient follow up with her primary care physician.

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On admission in the emergency room she was febrile with temperature 100.4 F, heart rate 103 bpm, blood pressure stable at 120/60 and her oxygen saturation was 98 percent on room air. Initial lab work displayed a neutrophil predominate leukocytosis of 14.44, thrombocytosis with platelets measuring 631, and microcytic anemia with hemoglobin 8.4 which was near baseline. Normal kidney and liver function were noted. Other laboratory values included CRP 12.5, lactic acid 2.1, LDH 348 and reticulocyte count 8. Repeat COVID19 testing returned negative. Blood cultures on admission were drawn and did not display any growth. Peripheral smear on admission displayed microcytic normochromic red blood cells with occasional target and sickled cells. White blood cells appeared normal in morphology and thrombocytosis was present. Due to pain in her right shoulder, an X-ray was completed which displayed moderate glenohumeral joint degenerative changes with superimposed avascular necrosis. The X-ray was compared to imaging during her prior admission and no significant changes were evident.

The pain in her right shoulder was similar in nature and location to previous sickle cell crisis. On average she has two episodes of vaso-occlusive sickle cell crisis per year however has never required a red blood cell exchange or has had history of acute chest syndrome. After review of laboratory and imaging results, she was initially treated with pain control and intravenous fluids for suspected acute sickle cell crisis. However, after three days her pain and range of motion of the right shoulder did not resolve. A subsequent MRI or right shoulder displayed known avascular necrosis of the superior medial humeral head articular surface with a large joint effusion and associated synovitis (Fig. 1). Due to the large effusion and now worsening febrile illness, interventional radiology was consulted for aspiration of synovial fluid for suspected underlying septic arthritis. An ultrasound guided aspiration was attempted but due to viscosity of fluid, aspiration was unsuccessful. Orthopedic surgery completed a right shoulder arthroscopy with debridement and aspirate was described as purulent in appearance. Synovial fluid analysis returned and displayed a total RBC 24775, WBC 975, PMN 95, lymphocyte 4, monocyte 1 and total cell count of 25750. Although the synovial fluid did not fulfill criteria for septic arthritis, with the described purulent findings on examination during arthroscopy, she was prophylactically treated with antibiotics. Prior to the arthroscopy intervention and cultures, she had not been on antibiotics to blunt any immune response. She was initiated on broad spectrum coverage with vancomycin while cultures were pending final results. Initial cultures did not show any growth however within four days the anaerobic culture grew *Clostridium paraputrificum.*

She was started on flagyl 500 mg every eight hours and repeat blood cultures were drawn. The patient's pain drastically improved with an increasing range of motion of right shoulder and her fever had resided. Repeat blood cultures returned negative and she was discharged home with a 4-week course of antibiotics and appropriate follow up with hematology, infectious disease and orthopedic surgery.

Discussion

Clostridium paraputrificum is an extremely rare cause of septic arthritis and is infrequently the etiology of sepsis in sickle cell disease patients. Due to colonization of *Clostridium paraputrificum* on the skin and in the gastrointestinal system, intraarticular injections, trauma or disseminated gastrointestinal disease can lead to introduction and seeding of bacteria. Our patient declined history of previous surgical interventions or abdominal complaints. Her only identified risk factors were sickle cell disease and associated avascular necrosis.

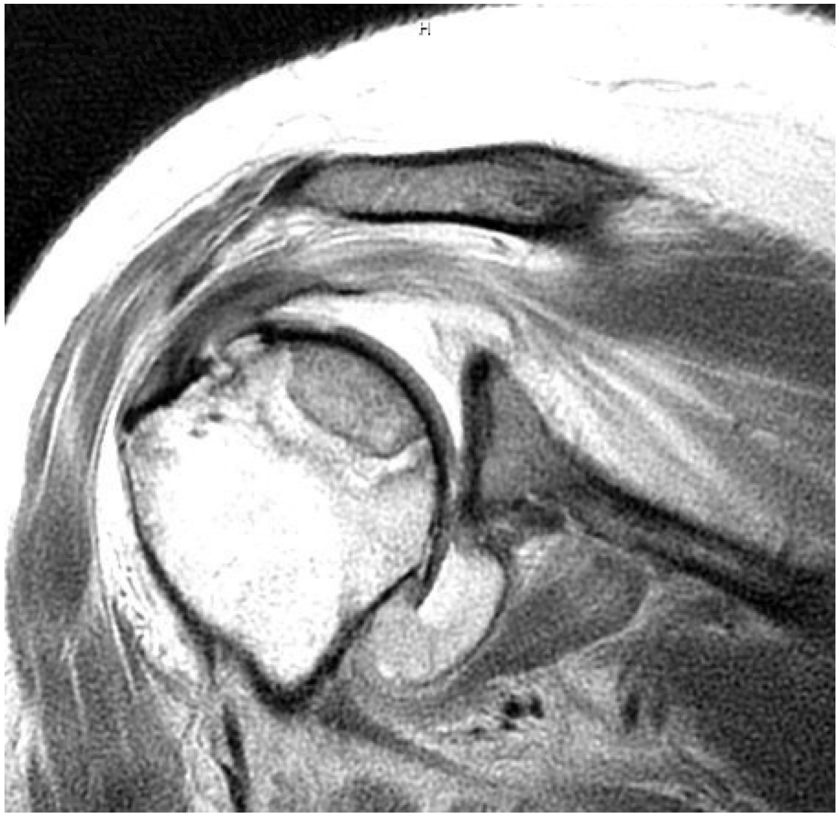

Fig. 1. MRI of right shoulder displaying avascular necrosis of the superior medial humeral head articular surface and associated joint effusion.

One of the largest contributors to morbidity in sickle cell disease is infection. Possessing the sickle cell gene leads to pathophysiological changes which increases susceptibility to infection. Impaired splenic function is one of many mechanisms which leads to increased bacterial infections. Due to sickled cells causing decreased circulation throughout the spleen, there is suboptimal clearance of pathogens by macrophages resulting in insufficient removal of encapsulated organisms [8]. Additionally, sickle cell disease patients also possess a defect in the process of complement activation which is thought to be largely due to faulty leukocyte function leading to decreased neutrophil killing potential [8].

Moreover, not only are sickle cell patients immunocompromised, but there are innate mechanisms in *Clostridium paraputrificum* which increases its infectious potential. Specifically, this organism forms terminal spores which can be metabolically dormant which leads to resistance to antibiotics, relapses and an increase in horizontal transmission [9]. Due to the scarcity of this organism, standard treatment protocols are limited. In a small study by Brazier et al. six strains of *Clostridium paraputrificum* were tested and they discovered that 4 were resistant to clindamycin, 1 was resistant to penicillin and 6 were susceptible to erythromycin, tetracycline, chloramphenicol, ampicillin/sulbactam and metronidazole [10].

In conclusion, the low incidence and difficulty in identification and isolation of this species has created limited knowledge on the overall prognosis, appropriate management, and understanding of risk factors in these individuals. Additionally, the lack of immune response to serious infection makes the diagnosis of septic arthritis in the sickle cell disease population especially difficult. This case highlights the importance of keeping a broad differential in persistent sickle cell arthritic pain as well as suggests avascular necrosis as a potential risk factor for *Clostridium paraputrificum* infections. Further studies are needed to help understand the disease spectrum as well as understand risk factors associated with invasive and severe infections in immunocompromised hosts.

CRediT authorship contribution statement

Jordan Ciuro: Writing - original draft. **Tania Little:** Writing - review & editing. **Evan Hiner:** Writing - review & editing. **Cynthia Vakhariya:** Writing - review & editing.

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