



Culture-negative septic glenohumeral arthritis identified with plasma microbial cell-free DNA sequencing: a case report



Michael Scheidt, MD^a, Krishin Shivdasani, MD, MPH^{a,b,*}, Andrew Gaetano, BS^c, Ryan Leduc, MD^a, Amanda Harrington, PhD^d, Nickolas Garbis, MD^a, Dane Salazar, MD, MBA^a

^aDepartment of Orthopaedic Surgery and Rehabilitation, Loyola University Medical Center, Maywood, IL, USA

^bCarle Illinois College of Medicine, University of Illinois Urbana Champaign, Champaign, IL, USA

^cStritch School of Medicine, Loyola University Health System, Maywood, IL, USA

^dDepartment of Pathology and Laboratory Medicine, Loyola Medicine, Maywood, IL, USA

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Septic arthritis of the glenohumeral (GH) joint is a relatively uncommon diagnosis which is often difficult to diagnose, particularly in immunocompromised patients. Common symptoms include constitutional symptoms such as fever and chills, pain localized to the shoulder upon palpation and with active and passive range of motion, erythema, effusion, and warmth. Septic arthritis commonly results from either direct inoculation or hematogenous dissemination of the organism. Standard of care for diagnosis requires aspiration of joint fluid focused on synovial white blood cell (WBC) count, percentage of presence of polymorphonuclear (PMN) cells, presence of crystals, Gram staining, and culture. Typically, the presence of synovial WBC >50,000 cells per microliter and percent PMN >90% stands as highly suggestive of presumed septic arthritis; definitive diagnosis of causative agents and further guidance of antibiotic therapy relies on organism identification through Gram staining and culture.¹⁰

The etiology of culture-negative septic arthritis may be factorial, including presampling antibiotics, intracellular or fastidious pathogens, and inadequate sampling techniques. In cases of negative cultures and high clinical suspicion, for example, a febrile patient

with monoarticular arthritis, erythema, effusion, pain upon palpation, and active and passive range of motion, significantly elevated erythrocyte sedimentation rate, C-reactive protein, and synovial WBC count, it is important for physicians to understand not only the limitations of culture-based diagnostics but also to understand the availability of supplementary diagnostic modalities to establish an appropriate diagnosis to guide further clinical care.

In this report, we present a case of septic arthritis of the GH joint in an immunocompromised patient with prior heart transplantation and negative preoperative and intraoperative cultures. Diagnosis was established as *Rothia dentocariosa* following next generation sequencing (NGS) of microbial cell-free DNA samples using the Karius assay (Karius, Redwood, CA, USA) test.

Case report

Given that this was a case report of a single patient, institutional review board approval of this study was waived. The patient provided consent for participation and publication.

A 72-year-old right-hand dominant female with a complex past medical history including viral myocarditis ultimately resulting in heart transplant several years prior initially presented to an outside institution with acute hypoxic respiratory failure, where she was found to have a large saddle pulmonary embolism for which she was intubated and underwent mechanical thrombectomy. The patient was on chronic immunosuppressant therapy, including

Institutional review board approval was not required for this case report.

*Corresponding author: Krishin Shivdasani, MD, MPH, Department of Orthopaedic Surgery and Rehabilitation, Loyola University Health System, 2160 First Avenue, Maywood, IL 60153, USA.

E-mail address: krishin.shivdasani001@luhs.org (K. Shivdasani).

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mycophenolate and tacrolimus, due to her transplant history. Her course was then complicated by colitis with unknown cause, altered mental status, and leukocytosis that began at the outside institution. She was transferred to our institution, a large, tertiary care academic center, where she was admitted under the care of the transplant service. Her colitis of unknown cause, altered mental status, and leukocytosis resolved over the course of the next 2 and a half weeks. She subsequently developed acute-onset right shoulder pain with activity, 24 days after her initial admission. She remained afebrile without leukocytosis.

Anterior-posterior (AP) and axillary views of the right shoulder were obtained, which were unremarkable (Fig. 1). Her physical examination was not notable for any signs of infection overlying the right shoulder, such as joint effusion or erythema. One nonspecific sign of potential systemic infection, albeit improving, was her altered mental status upon presentation to our institution. Additionally, she did have pain with attempted range of motion of the shoulder, with passive range of motion to 80° of forward flexion and 10° of external rotation measured at 0° of abduction causing pain. Given these examination findings, as well as an elevated erythrocyte sedimentation rate and C-reactive protein of 96 mm/hr and 128.6 mg/L, respectively, an ultrasound-guided aspiration of the shoulder was performed under ultrasound guidance. Initial ultrasonography demonstrated a fluid collection at the anterior subdeltoid bursa with intermittent internal low-level echoes and perimeter hyperemia, nonspecific for inflammatory or infectious processes (Fig. 2). The procedure obtained 7 cc of cloudy fluid in the subacromial/subdeltoid space. This was sent for cell count, crystal analysis, Gram stain, and cultures. The cell count demonstrated 54,000 WBCs per microliter with 93% PMN cells, consistent with a diagnosis of a septic joint (WBC >50k cells per microliter and PMN >90%). Given the low plausibility of an isolated septic subacromial bursitis, we discussed obtaining a magnetic resonance imaging to evaluate the integrity of the rotator cuff, as a full thickness rotator cuff tear would indicate that the subacromial space was in communication with the GH joint. However, due to implantable devices, the patient was unable to have a magnetic resonance imaging; therefore, an ultrasound of the shoulder was obtained. Repeat diagnostic ultrasonography of the right shoulder demonstrated a full-thickness tear of the supraspinatus/infraspinatus tendons with fluid communication between the GH joint and subacromial space (Fig. 3), consistent with pyogenic arthritis of the GH joint.

After obtaining informed consent, the patient was taken to the operating room, where an arthroscopic irrigation and débridement was performed. Cultures were again taken from the shoulder. She was noted to have fibrinous fluid in the joint and several small loose pieces of cartilage and biceps tendinopathy. There were multiple fibrinous adhesions in the joint that were débrided. The subacromial space was also irrigated and débrided arthroscopically at the time of surgery.

However, both initial aspirate and intraoperative cultures remained with no growth of any organisms postoperatively at final result. Initially, the patient was placed on broad spectrum antibiotics, cefepime and vancomycin, due to the high clinical suspicion of septic arthritis. With a lack of diagnostic organism for guided antibiotic therapy, a Karius blood test, assessing plasma for cell-free microbial DNA, was sent per recommendations of the infectious disease physician, which detected *Rothia dentocariosa*.

Postoperatively, the patient had an unremarkable recovery. The patient was placed on meropenem for 6 weeks per infectious disease recommendations and progressed to normal activity by 3 months. At 1 year postinfection, the patient has remained infection-free and without reoperation. She reports a pain intensity of 1/10 and has remained off of narcotic medication. Her reported American Shoulder and Elbow Surgeons score on a scale from

0 (poor) to 100 (excellent) was 85, notable for minimal difficulties with putting on a coat, washing her back, putting on a bra, reaching a high shelf, and lifting 10 pounds above her head.

Discussion

Septic arthritis represents an orthopedic emergency due to the irreversible damage that may ensue without prompt diagnosis and treatment. Most commonly, septic arthritis of the shoulder is as result of a bloodstream-borne infection with hematogenous seeding of the shoulder joint, however, can be result of direct inoculation through traumatic arthrotomy, prior operative treatment, or joint arthrocentesis. In immunocompromised patients, the patient's overall immune response to pyogenic arthritis can be muddled, resulting in delays for diagnosis and appropriate treatment.¹⁷

Most commonly, septic arthritis of the native shoulder in adults is the result of *Staphylococcal aureus*, while Gram-negative bacilli or other skin flora account for a smaller amount of infections.⁹ Contrarily, *Rothia* species, a commensal Gram-positive coccobacilli often found in the oropharynx, rarely manifest in clinical infections with most cases often occurring in patients with established central venous access, on immunosuppressive medications, and those with neutropenia.¹³ While rare cases of bacteremia with septic shoulder arthritis due to *Rothia aeria* and chronic hip arthroplasty infection of *Rothia mucilaginosa* have been reported, *Rothia* species are commonly more implicated in bacteremia and endocarditis associated with immunocompromised patients.^{2,7,11–13} Diagnosis is generally established on standard bacterial cultures, with immunocompromised patients generally having more than 1 positive culture in more than 76% of cases.¹³

Contrarily, a treatment dilemma presents in cases of culture-negative septic arthritis. Poorly directed broad spectrum antibiotic treatment for unidentified organisms may lead to recalcitrant septic arthritis following initial irrigation and débridement, requiring subsequent surgeries, increased morbidity, decreased quality of life, and increased healthcare costs.¹⁸ In these cases, polymerase chain reaction (PCR) analysis, traditional Sanger sequencing, and NGS may be used with clinical benefit. Targeted PCR demonstrates high sensitivity but is limited to the detection of targeted gene sequences for specific organisms and often may not provide a diagnostic advantage in comparison to standard cultures.^{5,16,19} Broad range PCR and traditional Sanger sequencing performed directly on operative or aspirate samples target the 16S rRNA gene which is highly conserved among bacteria and allow for microbial identification of organisms; however, it cannot resolve infections that are polymicrobial and is often not more sensitive than standard culture techniques.^{14,15} NGS, and specifically shotgun metagenomic sequencing—DNA is subsequently sheared into tiny fragments that are independently sequenced and analyzed—demonstrates several advantages over traditional methods. In addition to identification of organisms that may not be recovered using standard techniques, it can also detect common antibiotic resistance genes to allow for more specific treatment modalities.⁴ One commercially available assay, Karius (Karius, Redwood, CA, USA), has been marketed as a less invasive NGS test to potentially identify deep infections through the detection of microbial cell-free DNA in plasma.⁸ These metagenomic approaches for identification of microorganisms, however, are currently limited to a small number of commercial laboratories and large academic medical centers, where testing may only be performed for research and development purposes.^{8,14} One important caveat with this approach is that, while sensitivity of these tests has been described from 80%–90%, it is not uncommon that nonclinically relevant

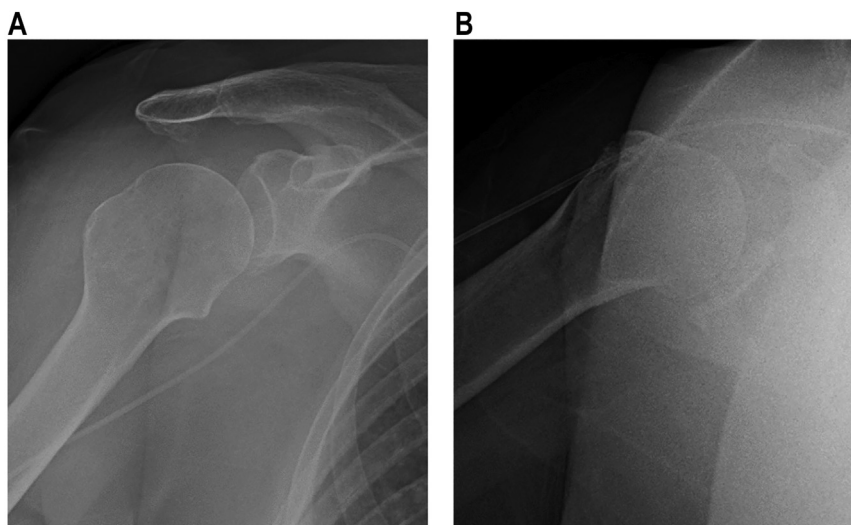


Figure 1 Anterior-posterior (AP) and axillary views of the right shoulder demonstrating no acute osseous findings, mild degenerative changes of the glenohumeral joint.

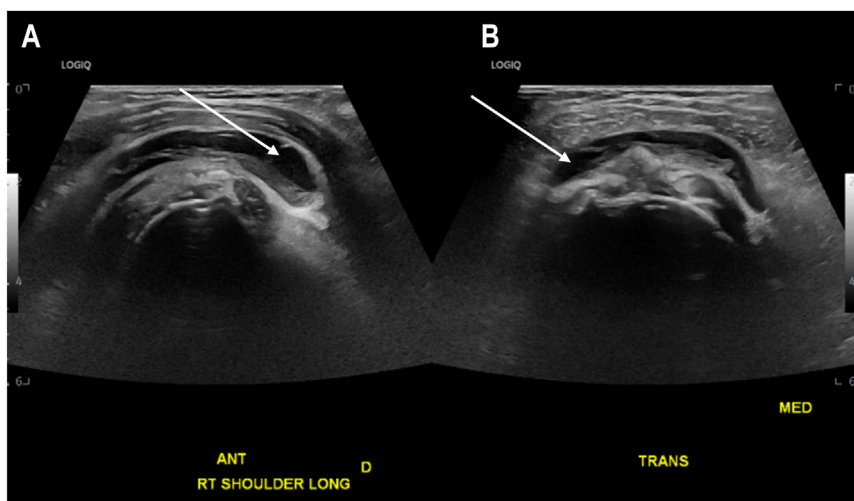


Figure 2 Right shoulder longitudinal and transverse views under ultrasonography demonstrating a fluid collection at the anterior subdeltoid bursa (white arrows) with intermittent internal low-level echoes and perimeter hyperemia. Imaging demonstrated nonspecific findings that may represent inflammatory or infectious processes.

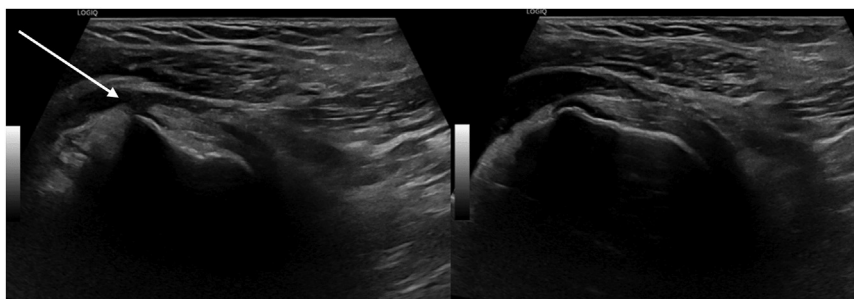


Figure 3 Transverse ultrasonography of the right shoulder demonstrating a full thickness tear of the supraspinatus/infraspinatus tendon with communication of fluid from the glenohumeral joint to the subacromial space (white arrows).

organisms or transient colonizing microbiota to be identified.^{1,3,8} Additionally, the main limitation of cell-free DNA sequencing tests in the inability to test susceptibility to antibiotics, prompting the need for infectious disease consultation for appropriate interpretation and management.⁶

Conclusion

NGS in orthopedic infections presents as a promising tool in cases of culture-negative infections. In this case, we describe a patient with culture-negative septic arthritis of the GH joint with

pathogen diagnosis obtained through plasma cell-free DNA sequencing. In these cases, cross-specialty collaboration is important to ensure timely identification and treatment of septic arthritis to maximally salvage joint tissue and functional capacity.

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