J Shoulder Elbow Surg (2021) 30, e69–e75

ELSEVIER

Journal of Shoulder and Elbow Surgery

www.elsevier.com/locate/ymse

Chronic, persistent fungal shoulder arthropathy secondary to genetic mutation: a case report

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Keywords: Native shoulder; fungal infection; genetic mutation; chronic; infection; shoulder arthropathy; septic arthritis; Candida joint infection

Fungal musculoskeletal infections can be seen in immunocompromised as well as immunocompetent patients.[9] Septic arthritis due to fungal infection is extremely rare; its incidence is difficult to determine owing to its infrequent presentation and diagnostic shortcomings.[8,20] The most common fungal organism causing septic arthritis is *Candida albicans*; however, non-albicans *Candida* infections have been reported in the literature. Of all the joints affected, the knee is considered the most common, being involved in 75% of all cases. Moreover, prosthetic joint infections due to fungal infection represent <1% of all prosthetic joint infection cases, including the shoulder.[9,12,13,20] Modes of joint inoculation include hematogenous seeding, iatrogenic inoculation during surgical procedures or injections, or spread from a nearby contiguous infection.[19] In the immunocompromised group, patients at risk often have hematogenous malignancies, prolonged corticosteroid or antibiotic use, diabetes mellitus, and use of anti–tumor necrosis factor therapy.[4,6,16,22] Other risk factors include advanced age, the use of indwelling parenteral feeding or vascular catheters, the presence of prostheses, or the use of intra-articular joint injections.[7,8,15] There are very few reported cases of fungal infections involving the shoulder joint. Cases in native shoulder joints have included both immunocompetent and immunocompromised patients.[10,18] Diagnosing and treating a septic joint secondary to *Candida* is challenging most of the time because of the vague clinical and radiologic manifestations.[5]

We report the unique case of a 19-year-old, immunocompetent male patient with chronic fungal septic arthritis of the shoulder in the setting of synovial chondromatosis and a genetic predisposition to this type of infection. Informed consent was obtained from the patient for publication of this case report.

Case report

The patient was a right hand–dominant 19-year-old man referred from a community-based orthopedic surgeon. He immigrated to Canada from Iraq with his family. His parents were consanguineous (first cousins). When the patient arrived in Canada, he presented to a community surgeon with a several-month history of slowly progressing right shoulder pain. The shoulder pain was located anteriorly, as well as posteriorly across the shoulder girdle, exacerbated by overhead activities. On occasion, the patient noted crepitus throughout range of motion. There was no remarkable history of trauma, an infectious process, or surgical interventions on the involved upper extremity. The patient denied constitutional symptoms such as fever, rigor,

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

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1058-2746/$ - see front matter
https://doi.org/10.1016/j.jse.2020.09.004

or night sweats. He was not taking any oral analgesics, and he had not received any subacromial or glenohumeral injections. The patient was otherwise healthy and did not take any routine medications. He denied smoking, alcohol consumption, or the use of illicit drugs including intravenous drugs.

On initial physical examination, there were no clinical signs of swelling, erythema, or muscle atrophy. There was no single area of maximal tenderness on examination. The patient had full active and passive shoulder range of motion compared with the contralateral side. Rotator cuff muscle testing was 5 of 5 based on the Medical Research Council grading scale, and he had no signs of instability.[14] Examination of the cervical spine, elbow, wrist, and hand indicated they were non-contributory. The findings of the neurovascular examination were within normal limits.

Initial investigations ordered by the treating surgeon included plain radiographs, as well as a magnetic resonance arthrogram, of the affected shoulder. The glenohumeral joint space was well preserved; however, evidence of stippled calcifications surrounding the glenohumeral articulation was found on the plain radiograph. The magnetic resonance arthrogram confirmed the presence of several nodular projections from the surrounding synovium, as well as loose bodies within the joint. A provisional diagnosis of synovial osteochondromatosis was made, and the patient consented to undergo arthroscopic synovectomy and loose body excision. Intraoperatively, several synovial nodules and loose bodies were excised from the joint. Soft-tissue biopsy specimens from the synovium were submitted for pathologic as well as microbiological analysis. The analysis confirmed the presence of several hyaline cartilage nodules with varying degrees of calcification, confirming the diagnosis of synovial osteochondromatosis. The surgeon also noted some early, diffuse degenerative changes throughout the glenohumeral articulation, which were attributed to the presence of intra-articular loose bodies. There were no remarkable pathologic changes of the rotator cuff, labrum, long head of the biceps, and subacromial bursa at the time of arthroscopy.

The patient was then referred to our clinic at 2 years postoperatively. He complained of marked posterior shoulder pain with range of motion, as well as nighttime pain when lying on the affected side. For the past 2 years, he had noticed a mass growing slowly over the posterior aspect of the shoulder girdle. His range of motion was progressively worsening in accordance with the growing mass. He denied any interim trauma to the shoulder and was not complaining of any constitutional symptoms. He had not received any subacromial or glenohumeral joint injections postoperatively. There was no remarkable change in the patient's health aside from taking acetaminophen on occasion for pain in his shoulder. He again denied any illicit drug use or recent travel history. We reviewed the patient's initial chart, including operative and pathology reports, which showed that some of the biopsied tissue from the aforementioned arthroscopic débridement identified fungal hyphae using special stains. The patient was unaware of this information.

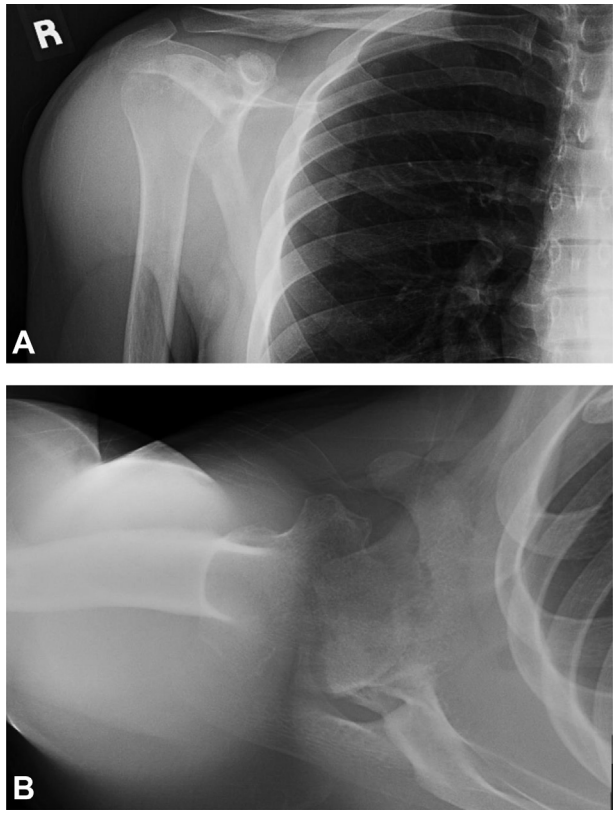

Figure 1 Radiographs of right *(R)* glenohumeral joint: anteroposterior view (**A**) and axillary view (**B**). One should note the substantial erosive and cystic changes throughout the humeral head, as well as glenoid erosion medial to the root of the coracoid.

Clinical examination revealed a very large fullness across the posterior aspect of the shoulder. There was no evidence of any skin changes or erythema overlying the shoulder. Palpation identified a nontender mass with discernible borders measuring approximately 10 × 10 cm. Assessment of active and passive range of motion showed forward elevation to 90°, abduction to 45°, external rotation to neutral, and internal rotation to the buttock. Throughout passive range of motion, the patient complained of posterior shoulder pain as well as crepitation. No sign of instability was noted. Supraspinatus and infraspinatus muscle power was graded 4 of 5, with no evidence of an external rotation lag sign. Distally, the elbow, wrist, hand, and neurovascular examination findings were normal. Initial investigations included plain radiography (Fig. 1). There was evidence of severe glenohumeral joint degeneration including humeral head subchondral cysts, irregularity of the humeral head articular surface, and destruction of the glenoid articular surface with medialization due to bony erosion. In light of the information revealed from the pathology reports, as well as clinical and radiographic

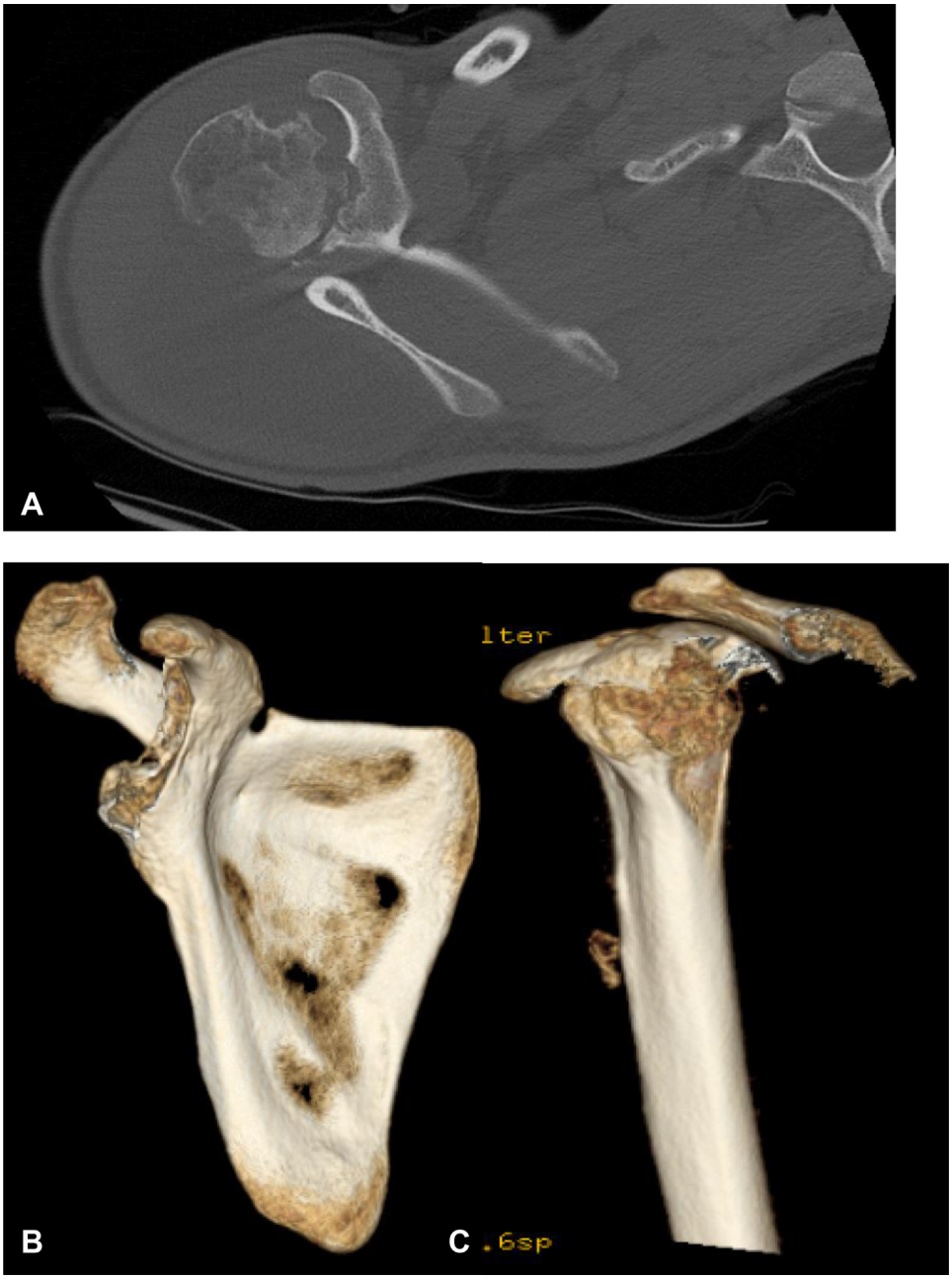

Figure 2 Two-dimensional axial computed tomography scan (**A**) and 3-dimensional computed tomography reconstructions with humeral subtraction *(left)* and scapular subtraction *(right)* (**B**) of right shoulder. The images verify the destructive changes throughout the humerus and glenoid seen on plain radiography.

findings, our new working diagnosis was chronic septic arthritis secondary to a glenohumeral fungal infection.

A computed tomography scan with 3-dimensional reconstructions of the shoulder confirmed the destructive changes seen on plain radiographs (Fig. 2). The scan also delineated the posterior mass as a complex fluid collection emanating from the glenohumeral joint with calcified margins similarly seen on the capsule medially. The collection was deep to the posterior fibers of the deltoid but superficial to the infraspinatus and teres minor musculature (Fig. 3). The initial blood work revealed a normal leukocyte count of 8.8×10^9 cells/L. Eosinophilia was present, with a concentration of 0.698×10^9 cells/L. The erythrocyte sedimentation rate and C-reactive protein level were 4 mm/h and 10.5 mg/L, respectively. Blood culture results were negative for bacteremia or fungemia. Hepatitis viral serology yielded negative findings, as did antibody screening for human immunodeficiency virus. On ultrasound-guided aspiration of the fluid collection, approximately 65 mL of brown-green fluid was withdrawn. Microbiology fluid culture analysis showed positive findings for *C albicans*. There was no evidence of any aerobes,

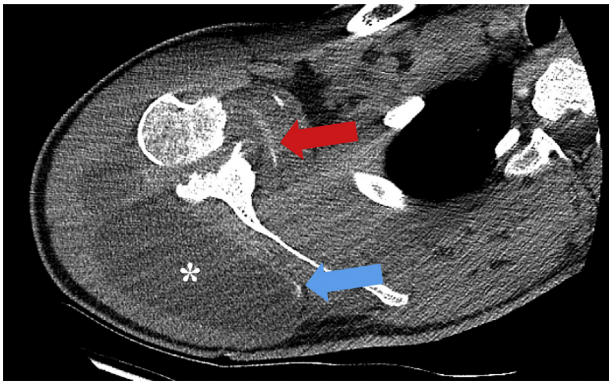

Figure 3 Axial computed tomography scan of the right shoulder girdle showing the large fluid collection *(*)* located posteriorly across the shoulder on clinical examination. The fluid collection was deep to the posterior deltoid and superficial to the infraspinatus and teres minor. The scan also delineates the calcified margins of the posterior mass *(⟸)*, as well as the capsule medially *(⟸)*, with communication to the glenohumeral joint.

anaerobes, or acid-fast bacilli. Moreover, there was no evidence of urate or calcium pyrophosphate crystals under polarized microscopy.

The patient consented to undergo irrigation and débridement of the right shoulder. He was placed in the left lateral decubitus position. A posterior curvilinear incision was made along the scapular spine, extending down the lateral border of the scapula. A full-thickness fasciocutaneous flap was raised medially. The fluid-filled capsule was incised, and over 100 mL of brown purulent fluid was evacuated from the wound. Excision of the fluid collection's capsule and gentle curettage of surrounding soft tissue were performed, followed by aggressive pulsed irrigation. A delto-trapezial flap was then raised off the scapular spine to expose the posterior glenohumeral joint. The infraspinatus was severely atrophic. The suprascapular nerve was exposed at the level of the spinoglenoid notch; a diminutive appearance was observed secondary to chronic compression from the fluid collection. Working through the interval between the infraspinatus and teres minor, we encountered the posterior joint capsule. We performed a longitudinal arthrotomy and encountered more brown purulent fluid. There appeared to be a tract connecting the joint to the extra-articular capsule in proximity of a former posterolateral arthroscopic portal. The glenoid and humeral head were completely devoid of hyaline cartilage, exhibiting erosive changes consistent with a chronic and aggressive arthropathy. There was no evidence of any tears or pathologic infiltration into the rotator cuff tendons. The soft-tissue planes and skin were closed in layers following aggressive pulsed irrigation. The synovium, as well as the excised capsule, was submitted for pathologic analysis. Grocott's methenamine silver- for Fungus (GMS-F) and periodic acid-Schiff (PAS) stains confirmed the presence of *Candida* spores and pseudohyphae. Giant cells and focal areas of necrosis were present throughout the synovium. Stains for acid-fast bacilli showed negative findings. There was no evidence of polarizable material or malignancy.

Postoperatively, the infectious disease team was consulted. The team advised 6 months of oral antifungal therapy as oral therapy permits excellent synovial penetration.[3] Itraconazole was recommended because of increasing resistance of the *Candida* species to fluconazole. The patient began early range-of-motion exercises and, eventually, strengthening as tolerated. Following the 6-month course of antifungals, the patient was constitutionally well and exhibited no concerning clinical signs of infection. He had minimal pain at rest; however, active and passive range of motion elicited shoulder pain. His range of motion showed improvement, with forward flexion to 90°, external rotation to 10°, and internal rotation to the sacrum. Normal findings were noted for the leukocyte count, at 5.7 $\times$ 10^9 cells/L; the eosinophil count, at 0.2 $\times$ 10^9 cells/L; and the C-reactive protein level, at 3.4 mg/L. Unfortunately, after a 3-month holiday from antifungal therapy, a recurrent fluctuant mass developed along the posterior aspect of the shoulder. The shoulder was re-aspirated under fluoroscopic guidance. Cultures confirmed the presence of *C albicans*. The patient consented to undergo repeated irrigation and débridement, as well as resection arthroplasty, to eradicate the infection (Fig. 4). Intraoperative cultures grew *C albicans*. The patient was prescribed fluconazole at the recommendation of the infectious disease specialists (a different team) at that time.

At the patient's regular follow-up visit 2 weeks after the second shoulder operation, he had begun experiencing progressive swelling in the right ankle. Clinical and radiographic investigations including magnetic resonance imaging of the ankle revealed a similar process to what was occurring in the right shoulder. The patient's ankle condition prompted genetic testing. He was seen by our colleagues in foot and ankle surgery, who arthroscopically irrigated and débrided the ankle and confirmed our suspicion. This occurred 1 month after the second shoulder operation while the patient was receiving oral fluconazole. The infectious disease specialists recommended the continuation of oral fluconazole for 1 year after the surgical procedures, given the septic arthritis of multiple joints. For the same reason, they arranged for genetic testing to investigate for a genetic predilection for invasive, recurrent Candidiasis, specifically *CARD9* (caspase recruitment domain-containing protein 9) deficiency. It is interesting to note that the genetic testing effectively revealed a homozygous frameshift mutation involving the *CARD9* gene. This gene represents a primary immunodeficiency, associated with eosinophilia, and confers a selective defect against fighting fungal infections.[2,21]

At the latest follow-up, 18 months from the last shoulder operation (repeated irrigation, débridement, and resection arthroplasty), the patient could flex to about 70°. Abduction was limited to 60°-70°, with external rotation to 20° and

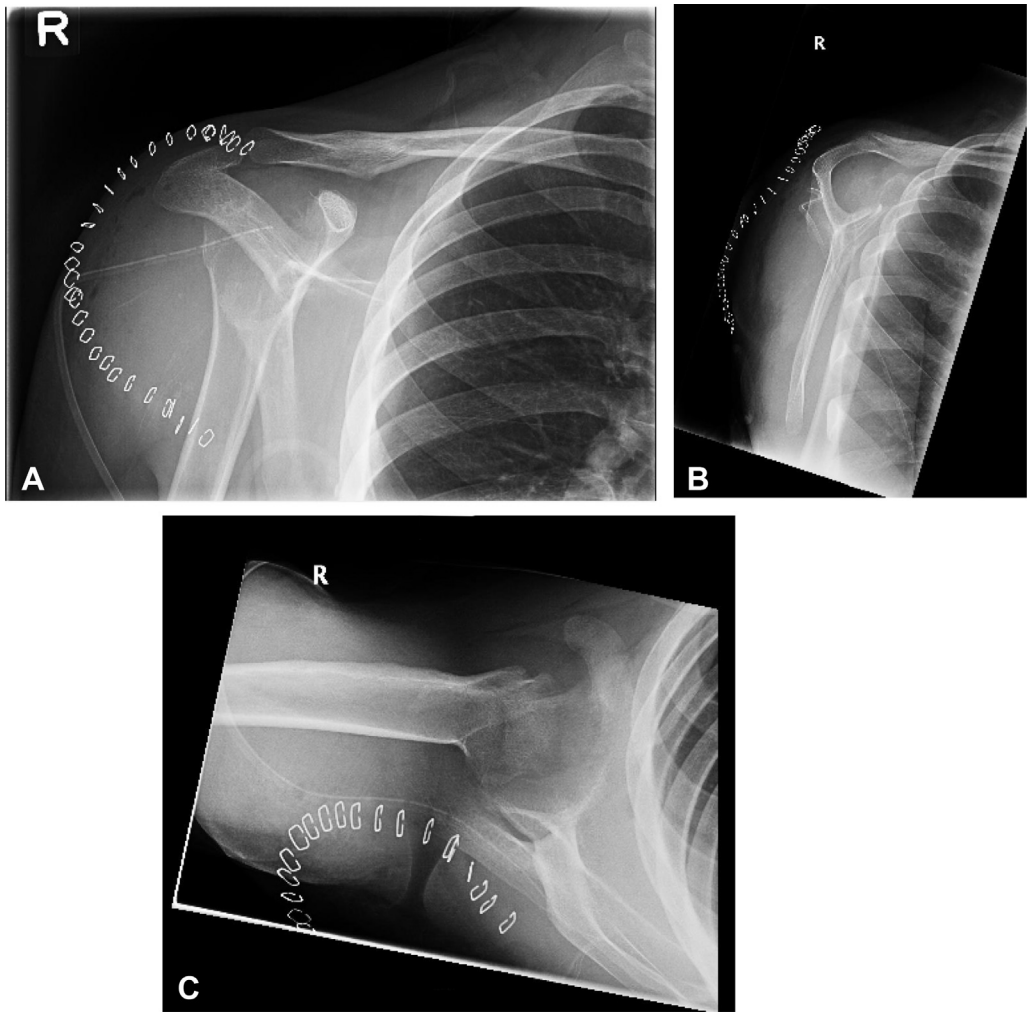

Figure 4 Anteroposterior (**A**), trans-scapular (**B**), and axillary (**C**) views of right *(R)* shoulder. The radiographs show resection of the humeral head and partial resection of the glenoid after repeated irrigation and débridement for recurrent fungal septic arthritis.

internal rotation to the sacrum. He was still experiencing a painful arc. However, he was able to go to the gym and work out with some weights below the belt level (Fig. 5). Recently (6 years after the initial shoulder irrigation and débridement surgical procedure), the patient was still following up with our infectious disease colleagues. Since he was prescribed fluconazole permanently following the ankle operation, he never required any further surgical irrigation and débridement of any joint. He was generally doing well; however, he noted increased shoulder pain when he missed several doses of fluconazole. The final recommendation was that he will require oral fluconazole for life, and the decision for definitive surgery on the shoulder in the context of arthroplasty is unlikely given the ongoing process.

Discussion

Fungal arthropathy of the shoulder is a very rare entity. In this case, the etiology and timing of inoculation were unclear. There could have been direct inoculation at the index arthroscopic shoulder operation. However, the presence of hyphae in the biopsy specimen taken at the time of the initial shoulder arthroscopy suggests that a potential secondary hematogenous spread is possible. In this condition, the synovial osteochondromatosis was likely an incidental finding. *Candida* species are part of the natural flora of the human skin; thus, direct inoculation can occur. However, it is rare for spontaneous Candidiasis to develop in patients, unless they are immunocompromised.[21] In this case, the patient had a confirmed primary immunodeficiency in the form of a *CARD9* mutation. To our knowledge, this is the first reported case of a patient with fungal arthropathy of the shoulder with this specific mutation. This case demonstrates the severity of periarticular and articular destruction caused by fungal septic arthritis, as well as failed and delayed diagnosis, and the resultant patient morbidity. The difficulty in eradicating these infections despite aggressive surgical and pharmacotherapeutic intervention is exemplified. *Candida* species have the ability to

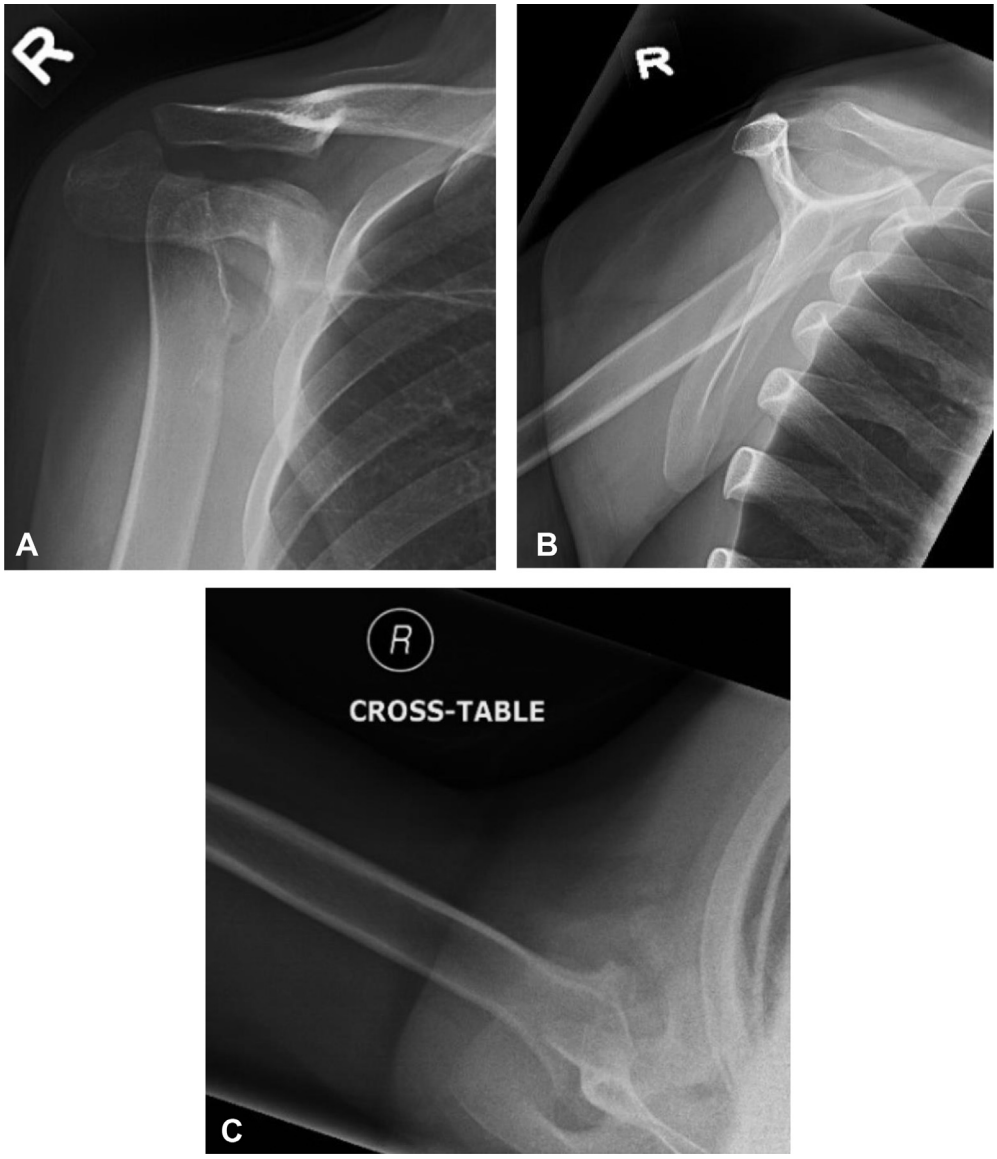

Figure 5 Anteroposterior (**A**), trans-scapular (**B**), and axillary (**C**) views of right *(R)* shoulder 2 years after last shoulder operation (these images were obtained by another service after the patient's last follow-up with us). The radiographs show the previously mentioned resection arthroplasty of the right shoulder.

form a biofilm similar to many virulent bacterial species. This can make eradication particularly difficult, especially in the setting of a periprosthetic infection.[2]

The diagnosis of fungal septic arthritis can be challenging. Patients may present with classic signs of septic arthritis (fever, chills, erythema, progressively worsening pain, joint effusion, and pain with range of motion) or lack classic clinical or radiographic signs.[21] Chronic, indolent cases are particularly challenging, as symptoms are often mild. Inflammatory biomarkers may or may not be elevated, and blood culture results are often negative for fungemia.[1] It is critical to consider patient risk factors that may contribute to the development of a fungal infection, as outlined earlier.

The recommended treatment regimen for septic arthritis and osteomyelitis caused by *C albicans* is limited to case series in the literature. Current recommendations include aggressive surgical débridement, followed by a 6-week course of fluconazole (6 mg/kg daily), or amphotericin B (3-5 mg/kg daily) for 2 weeks, followed by fluconazole. Other considerations include other azoles, as well as echinocandins. Osteomyelitis requires a longer course of therapy, typically between 6 and 12 months. Treatment failures can occur and are related to inadequate débridement or a drug-resistant organism.[17] Finally, there is a paucity of treatment recommendations in the setting of a *CARD9* mutation and musculoskeletal fungal infection. One case report of hip

osteomyelitis caused by Candidiasis suggested lifelong prophylaxis with fluconazole.[11]

Conclusion

A septic joint secondary to *Candida* is rare, especially in the shoulder. Diagnosing as well as treating such pathology is challenging most of the time because of the vague clinical and radiologic manifestations. The severity of periarticular and articular destruction caused by such an infection can result in significant morbidity if not recognized soon enough. A persistent fungal infection despite proper surgical débridement and pharmacotherapeutic intervention should raise the suspicion of possible immunopathology such as *CARD9* deficiency. Ongoing studies in immunomodulation and immunotherapy are undoubtedly necessary to formulate therapies in the setting of an immunocompromised host.

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