Case Report

Aspergillus Hip Arthritis in COVID-19 Era: Two Case Reports

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Abstract

Corticosteroids have been a mainstay in the treatment protocols and guidelines of COVID-19. However, its use in high dosage or for extended duration renders patients immunocompromised after COVID-19 recovery, and thus, susceptible to secondary opportunistic infections. We report the two cases of septic hip arthritis due to *Aspergillus* species in corticosteroid immunosuppressed post-COVID-19 patients. One patient recovered successfully from the arthritis and subsequently underwent total hip arthroplasty with good outcome. The second patient presented late to us in a critical condition and had two comorbid conditions along with, due to which, in spite of all measures, could not be revived and succumbed to death. We highlight the issue of the rare cause of fungal hip arthritis in immunosuppressed post-COVID-19 patients and stress the necessity to remain vigilant and identify the causative organisms correctly, especially fungal pathogens in such susceptible populations in the present COVID-19 era.

Keywords: Aspergillosis, *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus* infection, COVID-19, immunosuppression, infectious arthritis, post-COVID conditions, septic arthritis

Introduction

The rampant administration of high-dose systemic corticosteroids in COVID-19 patients in this pandemic roots from evidence that witnessed the benefits of glucocorticoids in severe COVID-19 requiring respiratory support, where its correct use may decrease fatal outcomes.[1,2] However, high corticosteroid dose or extended usage must be weighted with the risk and benefit of *primum non nocere*.[3] The overdrive of corticosteroids in the treatment of COVID-19 is largely accountable for the marked increase in opportunistic infections, especially patients with comorbidities and/or underlying disease conditions. Among the opportunistic infections, fungal infections account for the most case reports in COVID-19 patients.[4] Although COVID-19 associated pulmonary aspergillosis is widely reported and acknowledged as a complication,[4] osteo-articular manifestations of invasive aspergillosis are sparsely described in the literature.

Aspergillus septic arthritis is one such rare, severe, and in some cases, life-endangering variety of extrapulmonary invasive aspergillosis infection occurring mainly in immunocompromised patients.[5] No specific clinical manifestations can differentiate *Aspergillus* arthritis from septic arthritis due to bacteria or other pathogens. Early recognition plays a critical part in mortality and mortality, devolves on the identification of vulnerable immunosuppressed population with symptoms of fever, pain, joint tenderness, along with local signs of inflammation,[5] and warrants urgent further evaluation of septic etiology. We describe here two cases of *Aspergillus* septic arthritis of the hip occurring in immunosuppressed post-COVID-19 patients at a tertiary orthopedic center and review the relevant literature.

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Case Reports

Case 1

A 69-year-old male patient presented with complaints of severe pain, restriction of movements, and inability to bear weight on the left hip for the last 1.5 months. The symptoms were insidious in onset and progressive, with pain radiating to the ipsilateral

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knee. There was an associated history of low-grade fever and the presence of constitutional symptoms without any history of weight loss. There was no history of any preceding trauma or comorbidities. Past history of the patient elaborated on a history of repeated treatment with steroids due to severe COVID-19 infection 2.5 months and polymyositis 6 months before the onset of present complaints. The patient had been hospitalized for 10 days for severe COVID-19 infection when he had been administered intravenous (IV) steroids and subsequently discharged on the tapering dose of oral steroids. The patient had had a history of weakness of bilateral proximal thighs and arms when he was diagnosed with polymyositis and treated with tapering dose of oral steroids. Examination revealed body temperature 100.8°F, anterior hip point tenderness, mild joint swelling, and muscle spasm with global restriction of joint movement, without any erythema or local rise of temperature. X-ray showed features of septic arthritis [Figure 1]; laboratory results and synovial fluid analysis are shown in Table 1. As synovial fluid showed growth of *Aspergillus fumigatus*, urgent arthrotomy, debridement [Figure 2] with excision arthroplasty and gentamicin-loaded cement spacer for left hip was planned [Figure 3]. Tissue culture was also negative for any bacteria or *Mycobacterium tuberculosis* (MTB) and yielded growth of *A. fumigatus*. Computed tomography-scan chest did not show any foci of pulmonary invasive aspergillosis, and there was neither manifestation nor any history of cutaneous or any other source of primary Aspergillosis. The diagnosis was confirmed to be primary *Aspergillus* septic hip arthritis in a post-COVID-19 steroid immunosuppressed patient. After consultation with Infectious Disease Specialist Committee, the patient was started on oral posaconazole 300 mg twice daily on day 1, followed by 300 mg once daily. The patient was having uneventful and good recovery from *Aspergillus* arthritis when he suddenly developed acute decompensated heart failure 1.5 months thereafter. He was diagnosed with double-vessel coronary artery disease with severe left ventricular dysfunction; for which, coronary angiogram with percutaneous transluminal coronary angioplasty (PTCA) with stenting of proximal left coronary artery was done. The patient was continued on posaconazole prophylaxis for a total duration of 6 months. Left total hip arthroplasty (THA) was undertaken 6 months after PTCA after all clinical, radiological, and laboratory markers were normal. Intraoperative tissue cultures and biopsy did not yield any fungal organisms. The patient is doing well 1-year post-THA with painless free range of motion with no signs of recurrence. Follow-up X-rays are shown in Figure 4.

Case 2

A critically ill 74-year-old male patient was referred to our center with complaints of fever, pain in the left hip, inability to bear weight on affected hip and rapid deterioration of health condition for 15 days, when he was admitted at a primary center and diagnosed with *Pseudomonas aeruginosa* septic hip arthritis, and treated with antibiotics. The patient was a known case of chronic liver disease (CLD) with portal hypertension and chronic kidney disease (CKD). The patient suffered from COVID-19 infection 3 months before the onset of present complaints. The patient was hospitalized for 22 days for COVID-19 treatment with noninvasive mechanical ventilation, steroids and IV antibiotics, when his CLD and CKD stages deteriorated. On examination, patient was drowsy, with Glasgow coma score $E_4M_6V_3$, with heart rate of 110 beats/min, SpO_2 92% room air, respiratory rate 20/min, temperature 101.2°F, pitting pedal edema, flapping tremor, bilateral basal lung crepitation, and splenomegaly with abdominal free fluid. Left hip examination revealed anterior hip point tenderness, joint swelling, localized rise of temperature, and global restriction of joint movement, without erythema. X-ray showed features of septic arthritis [Figure 5]. Laboratory results and synovial fluid analysis are shown in Table 1. Patient was diagnosed with Grade II hepatic encephalopathy associated with

Figure 1: X-ray pelvis with both hips-Anteroposterior view showing gross destruction and resorption of the left femoral head with superior migration of the proximal femur. The supero-lateral weight bearing portion of the left acetabulum shows osteolysis with ill-defined acetabular margin. Juxta-articular osteoporosis is noted around the left hip joint

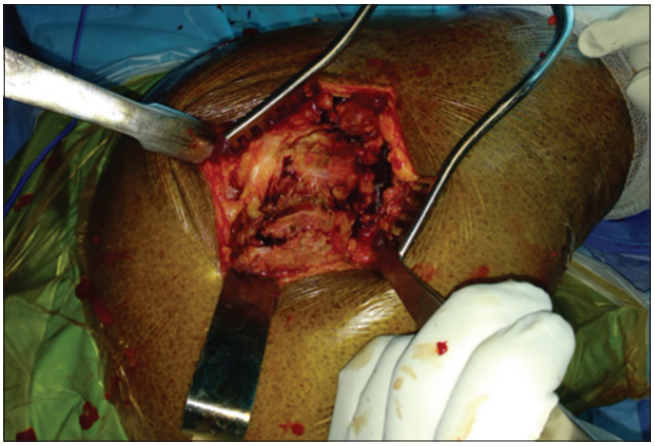

Figure 2: Intraoperative picture during debridement of the left hip. There was loss of soft-tissue planes. Capsule was adherent to the bone with surrounding unhealthy granulation tissue. There was no frank pus. Complete femoral head destruction and cavitary deformity with osseous destruction on weight-bearing surface in the acetabulum were observed

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Table 1: Laboratory findings of two *Aspergillus* septic hip arthritis patients

Laboratory investigation (normal reference range)	Value	
	Case 1	Case 2
Hemoglobin: 13-16 (g/dL)	11.7	9.2
WBC: 4000-11,000 (/mm^3)	14,660	20,810
Differential leukocyte count (%)		
Neutrophil: 45-75	78.80	92.70
Lymphocyte: 25-45	12.90	4.60
Eosinophil: 1-8	2.50	0.00
Basophil: 0-1	0.10	0.00
Monocyte: 0-10	5.70	2.70
Platelet: 1.5-4.5 (lakhs/mm^3)	2.54	1.06
ESR: 0-15 (mm at end of 1 h)	60	85
C-reactive protein: 0-6 (g/L)	40.8	102.7
Procalcitonin: <0.5: Low risk of severe sepsis, >0.5-<2.0: Moderate risk of severe sepsis, >2.0-<10: High risk of severe sepsis, >10.0: Severe sepsis/septic shock (ng/mL)	-	4.37
PT: 11.2-14.8 (s)	12.8	20.2
INR: 0.8-1.13	1.10	2.3
aPTT: 25.9-39.3 (s)	28.2	53.4
Rheumatoid factor	Negative	Negative
Anti-cyclic citrullinated peptide	Negative	Negative
Anti-nuclear antibody	Negative	Negative
Anti streptolysin O titer: 0-200 (IU/mL)	<200	<200
Synovial fluid analysis		
WBC	42,700	94,300
Neutrophils (%)	85.2	94.7
Gram stain	Occasional pus cells, no organism	Plenty pus cells, gram negative bacilli
AFB smear	Negative	Negative
Aerobic culture	No growth	*P. aeruginosa*
Anaerobic culture	No growth	No growth
Fungal culture	*A. fumigatus*	*A. flavus*
Semi-nested real time PCR	MTB not detected	MTB not detected
Blood culture	No growth	No growth
Serum galactomannan	Negative	Negative
Urine analysis		
Routine examination	Normal study	Occasional pus cells and epithelial cells albumin 1+
Culture	No growth	No growth
Renal function test		
Urea: 11-43 (mg/dL)	25.60	154.90
Creatinine: 0.66-1.25 (mg/dL)	0.85	1.70
Sodium: 135-145 (mmol/L)	137.00	139.00
Potassium: 3.5-5.1 (mmol/L)	3.90	4.90
Liver function test		
Total bilirubin: 0.2-1.3 (mg/dL)	0.80	3.00
Direct bilirubin: 0-0.3 (mg/dL)	0.20	1.20
Total protein: 6.3-8.2 (g/dL)	7.80	6.10
Albumin: 3.5-5 (g/dL)	4.20	2.20
ALT: 5-50 (U/L)	35.0	75.0
AST: 17-59 (U/L)	37.0	89.0
ALKP: 38-126 (U/L)	108	151
GGT: 15-73 (U/L)	18	71
Serum HIV-1,2 antibody	Nonreactive	Nonreactive
Serum HbsAg	Nonreactive	Nonreactive
Serum anti-HCV	Nonreactive	Nonreactive

WBC: While blood cell count, INR: International Normalized Ratio, PT: Prothombin time, aPTT: Activated partial thromboplastin time, ESR: Erythrocyte sedimentation rate, HCV: Hepatitis C virus, HbsAg: Hepatitis B surface antigen, PCR: Polymerase chain reaction, ALT: Alanine transaminase, AST: Aspartate transaminase, GGT: Gammaglutamyltransferase, ALKP: Alkaline phosphatase, MTB: *Mycobacterium tuberculosis, A. fumigatus: Aspergillus fumigatus, A. flavus: Aspergillus flavus, P. aeruginosa: Pseudomonas aeruginosa*

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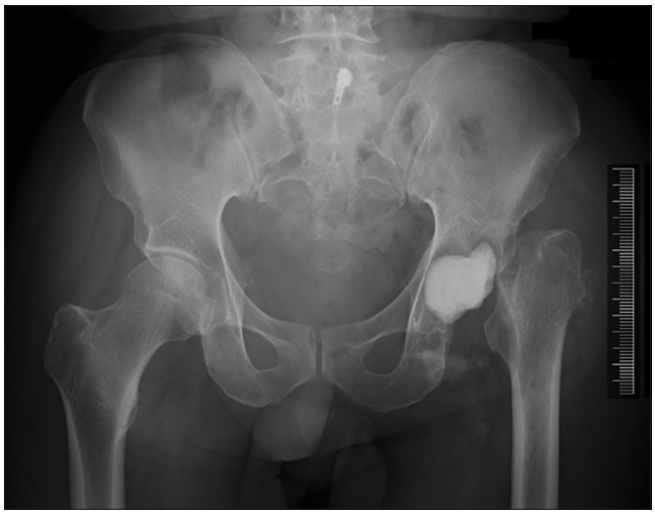

Figure 3: Immediate postoperative X-ray after debridement and excision arthroplasty with gentamicin cement spacer insertion. The entire diseased femoral head and neck was excised, along with the diseased portions of the acetabulum

Figure 5: X-ray pelvis with both hips-Anteroposterior view showing gross destruction and resorption of the left femoral head with superior migration of the proximal femur. The supero-lateral weight bearing portion of the left acetabulum shows osteolysis with ill-defined acetabular margin. Juxta-articular osteoporosis is noted around the left hip joint

decompensated CLD, acute on CKD, and left hip septic arthritis. Urgent arthrotomy, debridement [Figure 6] with excision arthroplasty, and gentamicin spacer insertion were done for left hip [Figure 7]. Tissue culture analysis showed scanty growth of *P. aeruginosa*. In addition, fungal culture showed growth of *Aspergillus flavus*. Primary foci of Aspergillosis could not be ascertained; so it was diagnosed with a primary pseudomonas with *Aspergillus* septic hip arthritis. Infectious Disease Specialist Committee Consultation was taken and patient was started on sensitive drugs-IV Meropenem 1 g IV q8 h along with oral posaconazole 300 mg twice daily on day 1, followed by 300 mg once daily. However, the patient continued to deteriorate in spite of treatment and succumbed to death after 16 days due to deterioration of liver and kidney status.

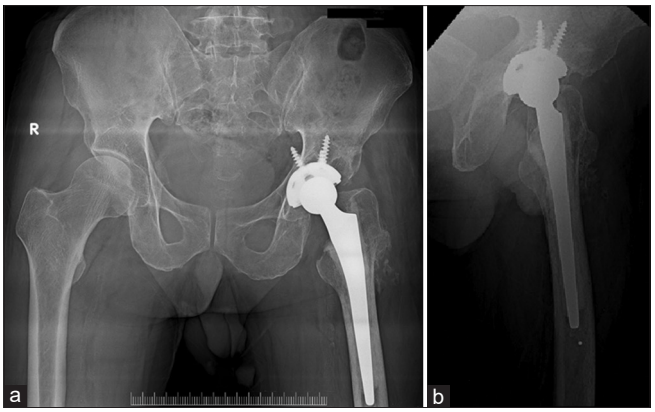

Figure 4: X-ray of the pelvis with both hips-Anteroposterior view (a) and X-ray left hip-lateral view (b) at 1 year follow-up after left total hip arthroplasty of the patient showing good alignment, positioning, and fixation of the components

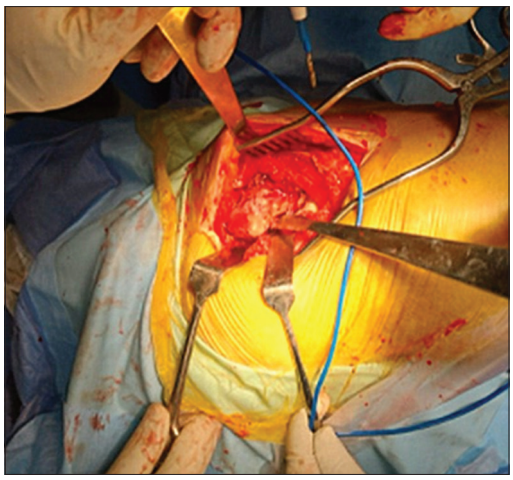

Figure 6: Intraoperative picture during debridement of the left hip. There was loss of soft-tissue planes. Capsule was adherent to the bone with lot of infected granulation tissue. There were the pockets of seropurulent pus. Complete femoral head destruction and cavitary deformity with osseous destruction on weight bearing surface in the acetabulum were observed. All the bones were osteoporotic

Discussion

Invasive fungal infection has been progressively attributed as a late sequelae of COVID-19.[6] High levels of pro-inflammatory (interleukin-1, 2, 6, and tumor necrosis factor-alpha) and anti-inflammatory (interleukin-4, 10) cytokines, less CD4 interferon-gamma expression, and fewer CD4 and CD8 cells which makes them vulnerable to opportunistic fungal infections.[7] An exponential increase in the incidence and mortality rates of invasive fungal infections is reported among COVID-19 survivors, especially whoever received immunosuppressive therapies or who had underlying conditions.[6,8-11] Although *Aspergillus* is the most common fungus isolated from COVID-19-infected patients,[10] there is no literature about COVID-19 associated *Aspergillus* septic hip arthritis till date. This is the first report of primary *Aspergillus* septic hip arthritis in immunosuppressed post-COVID-19 patients.

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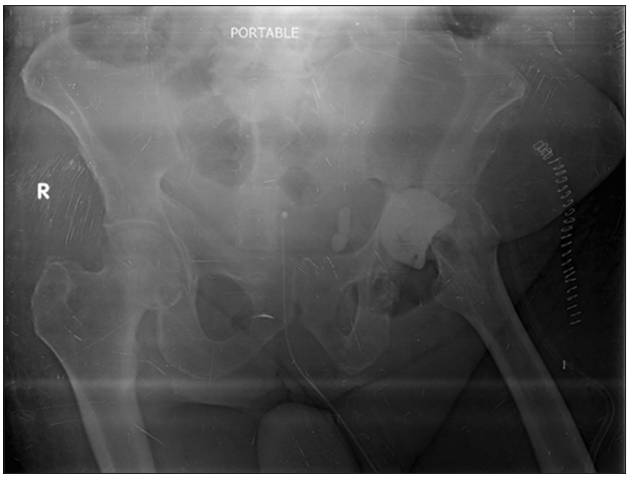

Figure 7: Immediate postoperative X-ray after debridement and excision arthroplasty with gentamicin cement spacer insertion. The entire diseased femoral head and neck was excised, along with the diseased portions of the acetabulum

Aspergillus species have ubiquitous distribution, affecting males predominantly and are commonly associated with immunosuppression, debilitating conditions such as chronic granulomatous disease, solid organ or bone marrow transplantation, chemotherapy, IV drug use, diabetes mellitus, or malnutrition.[12,13] It also occurs in patients undergoing surgical interventions,[12,13] immunocompetent individuals,[14] and also in co-infection with tuberculosis (TB).[15] *Aspergillus* infection spreads hematogenously, by contiguous infective foci, and by inoculation in the case of surgeries or trauma.[12,13] There has been a steady rise in Aspergillosis with >200,000 life-threatening infections due to invasive aspergillosis happening worldwide per year.[16] However, osteo-articular complications of invasive aspergillosis are still not well understood because of the scarcity of *Aspergillus* septic arthritis cases reported so far in the literature.[5,13,17] A total of 35 cases from 29 patients suffering from *Aspergillus* species arthritis of native joints were identified from PubMed and MEDLINE databases between the years 1976 and 2021.[5] *A. fumigatus* was the most common organism isolated, followed by *A. flavus*, *Aspergillus terreus* and not further specified.[5] Our literature search revealed only four cases of *Aspergillus* septic hip arthritis till date[14,15,18,19] [Table 2]. Diagnostic methods and technical and management guidelines are hence based on limited information.[5]

Swelling, pain, and tenderness of involved joint in *Aspergillus* arthritis are the most common clinical manifestations; fever, edema, erythema, and decreased range of motion are less common findings.[12,13] In septic arthritis where culture is negative for bacteria, substantial clinical acumen for fungal pathogens must be present, particularly for immunocompromised patients. Because of the rarity, orthopedicians must be trained to diagnose these infections through studies featuring their symptoms, severity, treatment, and outcome.[5]

Arthrocentesis and open biopsy are the most common tools for definite diagnosis of *Aspergillus* arthritis as fluid culture detects all cases; peri-articular culture of bone tissue is also highly sensitive.[13] Synovial fluid can be clear, turbid, or serosanguineous. Inflammatory markers may be elevated.[20] Even in positive fungal culture, TB must always be ruled out for TB-endemic countries.[15]

Treatment strategy is multidisciplinary based upon a combination of surgical drainage of joints, debridement of the necrotic bone and cartilage to reduce the fungal burden, and systemically active extended antifungal treatment.[21] Surgical irrigation and debridement is almost always mandatory.[12] We used local low-pressure pulsatile suction-irrigation using 4 l 0.9% normal saline, followed by 100 ml of 3% hydrogen peroxide, 100 ml of 10% povidone-iodine, and finally 2 l 0.9% normal saline after surgical debridement for both the cases because a combination of pulsatile lavage, hydrogen peroxide, and povidone-iodine is more effective in reducing the microbial count.

2016 practice guidelines for the diagnosis and management of Aspergillosis recommend voriconazole for the primary treatment of *Aspergillus* septic arthritis.[22] In a double-blind, double-dummy, Randomized Control Trial (RCT) in 2021, Maertens *et al*. concludes that posaconazole is noninferior to voriconazole for the treatment of invasive Aspergillosis and has significantly fewer treatment-related adverse events.[23] Posaconazole is a very potential drug for the treatment of *Aspergillus* arthritis and is even susceptible and suitable for *Aspergillus* species which demonstrate resistance to Amphotericin B, Itraconazole, and Voriconazole.[24,25] Posaconazole is generally well-tolerated, widely distributed in the body, undergoes liver metabolization with no significant renal effects. Adverse events are generally mild.[26] Posaconazole is even appropriate for patients unable to tolerate long-term therapy with other antifungals.[27] We also found very satisfactory results with the use of Posaconazole for the treatment of *Aspergillus* septic arthritis and propose further research for the validation of the same.

Literature about joint reconstruction after fungal septic arthritis is exceedingly sparse; and thus, no protocol has been developed for joint arthroplasty after fungal infections.[20] Two stage joint reconstruction with antibiotic-loaded cement spacer technique is a familiar and acclaimed protocol in periprosthetic joint infection management and is presently also acquiring evidence for the treatment of septic arthritis. It also benefits candidates with advanced joint degeneration before infection. Patients treated with a staged antibiotic-loaded cement spacer before joint arthroplasty report decreased re-infection rates, lesser contractures due to head and neck resection, and superior leg length maintenance and functional scores.[28,29] The final stage of joint arthroplasty also becomes simpler with lesser intraoperative blood loss.[30] Most studies recommend proceeding with final arthroplasty when the wound is completely healed and C-reactive protein is normalized.[31]

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Table 2: Case reports of *Aspergillus* septic hip arthritis described in English literature

Year	Authors	Gender/age (years)	*Aspergillus* species	Joint affected	Immunosuppressive conditions/medications	Other site of *Aspergillosis*	Symptoms	Treatment
1990	Lagier[18] (Histological study)	Male/64	*Aspergillus* species	Right hip	Nil	Nil	Painful stiffness	Total hip replacement
2012	Figue`res *et al*.[19]	Male/43	*A. fumigatus*	Left hip	Pancreas-kidney transplantation for type 1 diabetic nephropathy Maintenance therapy: Tacrolimus (5 mg bid) and mycophenolate mofetil (500 mg bid)	Nil	-	Oral Voriconazole 200 mg bid, 50% reduction of tacrolimus dose Hip replacement after 6 months of initiation of Voriconazole
2015	Yoon *et al*.[14]	Female/49	*A. fumigatus*	Right hip	Nil	Undiagnosed recurrent pulmonary *Aspergillosis*	Pain, limited range of motion	Intravenous amphotericin B for 2 weeks, followed by Oral Voriconazole for 6 months THA after 9 months
2016	Kumar *et al*.[15]	Male/60	*A. flavus*, MTB	Right hip, right knee	Angioplasty, type 2 diabetes mellitus	Nil	Pain right hip and gluteal region, fever, low back pain	Intravenous Voriconazole 200 mg bid 2 weeks followed by Oral Voriconazole 200 mg bid Daily regimen anti-TB treatment

MTB: *Mycobacterium tuberculosis, A. fumigatus: Aspergillus fumigatus, A. flavus: Aspergillus flavus*, TB: Tuberculosis, THA: Total hip arthroplasty

In our opinion, modern two stage hip reconstruction with cement spacer is safe and effective in *Aspergillus* septic hip arthritis. Final stage THA can be carried out once the infection is cleared clinically, hematologic and biochemical marks are normal and if the patient has persistent pain and/or other symptoms of arthritis. We found a good outcome with THA in our patient, similar to the previous reports.[14,19] [Table 2] which report favorably for hip replacement in *Aspergillus* arthritis sequelae.

Conclusion

Immunosuppression is a very important clinical entity in the present post COVID-19 pandemic era, and it should be kept in mind while evaluating post COVID-19 patients in orthopedics. The use of corticosteroids and various other immunosuppressant drugs for COVID-19 treatment renders patients susceptible to various secondary invasive opportunistic infections. *Aspergillus* septic arthritis of the hip is a very rare condition that may develop *de novo* or as a superadded entity in immunosuppressed patients who had a prior history of COVID-19 infection. These cases emphasize the necessity of being vigilant about opportunistic fungal infections and stress upon performing fungal cultures routinely in septic arthritis in immunosuppressed patients. Prompt diagnosis and intensive management in the form of surgical debridement along with systemically active prolonged antifungal therapy with serial monitoring are prerequisite for a successful outcome. Posaconazole can be an alternative to voriconazole in the treatment of *Aspergillus* arthritis. Two-stage joint reconstruction with cement spacer is safe and effective in the treatment of *Aspergillus* septic hip arthritis. THA can be carried out in such patients after proper control of infection and carries good result.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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