

Prosthetic Joint Infections Due to *Histoplasma capsulatum*: A Report of 3 Cases

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Abstract

Histoplasma capsulatum causes pneumonia and multisystemic disease in humans. Musculoskeletal involvement in histoplasmosis is most often tenosynovitis and rarely septic arthritis. Even more uncommon is the involvement of prosthetic joints. Here, we report a series of 3 cases of prosthetic joint failures caused by infection due to *H capsulatum*. Together with a review of 4 previously reported cases, we summarize host characteristics, clinical presentation, surgical approaches, antifungal management, and outcomes of this rare orthopedic joint infection.

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Histoplasma capsulatum is a dimorphic fungus that is endemic throughout the Ohio and Mississippi river valleys and in certain pockets around the world. Although the fungus primarily causes lung infection, extrapulmonary histoplasmosis may involve the bone marrow, liver, brain, spleen, and the gastrointestinal tract.^{1,2} Osteomyelitis and septic arthritis are uncommon forms of histoplasmosis, while the involvement of joint prosthesis is even much more uncommon.^{2,3} In our review of the medical literature, we found only 4 cases of *H capsulatum* infection involving a prosthetic joint.⁴⁻⁶ Here, we present the clinical outcomes of 3 additional cases of prosthetic joint infection (PJI) due to *H capsulatum*.

CASE REPORT

Case 1

A 77-year-old diabetic woman from Wisconsin presented to our clinic in 2019 with a 2-day history of right knee pain. She was a recipient of a deceased donor kidney transplant for end-stage renal disease due to autosomal dominant polycystic kidney disease in 1991, followed by a living-related donor kidney transplant due to allograft failure from calcineurin inhibitor nephrotoxicity in 2009. She was receiving maintenance immunosuppression with tacrolimus, mycophenolate

mofetil, and prednisone. She also had bilateral total knee arthroplasties (TKAs) in 1998 (right) and 2012 (left) for degenerative joint disease. She did not have fever, chills, rigors, or other signs and symptoms of systemic illness. On physical examination, her right knee was erythematous, swollen, warm, and tender. Right knee synovial fluid analysis was suggestive of infection (Table). She had an elevated C-reactive protein level (23.1 mg/L; normal range, <8 mg/L). However, the synovial fluid cultures for bacteria were negative at 14 days.

She underwent irrigation and debridement of the right knee joint. Intraoperatively, the right knee joint and prosthesis did not look grossly infected, and because the components were well-seated, they were retained. Fifteen days later, multiple cultures of intraoperative tissue specimens grew *H capsulatum*. *Histoplasma* serology and urinary *Histoplasma* antigen were negative. The chest radiograph was normal. Oral itraconazole was initiated. The dose of mycophenolate mofetil was reduced. Twelve months later, she was tolerating itraconazole and she had a pain-free functional right knee joint. There were no symptoms of immune reconstitution inflammatory syndrome. Because of the retained components and her immunocompromised status, chronic long term itraconazole suppression is planned.

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Case 2

A 69-year-old woman from Iowa with rheumatoid arthritis taking etanercept and prednisone had multiple prosthetic joints implanted for painful destructive arthritis, including a left shoulder reverse arthroplasty in 2019. Eight months after her left shoulder arthroplasty, she complained of progressive lingering pain in her left shoulder. The C-reactive protein level was 13.8 mg/L. The radiograph of the shoulder revealed lucency about the glenoid component, which was suggestive of loosening. Left shoulder synovial fluid analysis revealed 3512 cells/ μ L with predominance of neutrophils. The culture of the synovial fluid was negative at 14 days.

Over concerns of underlying infection and component loosening, she underwent resection of left shoulder prosthesis. On histopathology, there was no evidence of acute inflammation. However, after 12 days of incubation, the intraoperative tissue cultures were positive for *H capsulatum*. The chest radiograph was normal. *Histoplasma* serology and urine antigen were negative. Oral itraconazole therapy was initiated. She has completed 7 months of itraconazole treatment before shoulder reimplantation. She continued receiving itraconazole treatment at the time of this report, with reassessment planned at 1 year. Despite not resuming etanercept treatment of her underlying rheumatoid arthritis, there were no symptoms related to immune reconstitution inflammatory syndrome.

Case 3

A 75-year-old man from Nebraska with hypertension underwent a right TKA in 2019 for degenerative joint disease at his local hospital. Two weeks later, he developed redness, swelling, and drainage of the surgical wound. He did not have a fever or other systemic symptoms of disseminated infection. During surgical debridement of the right knee, the wound was found to track deep into the knee joint prosthesis. Thus, resection TKA was performed. Multiple intraoperative tissue cultures grew *H capsulatum*. A computed tomography scan of the chest revealed mediastinal and hilar adenopathy. *Histoplasma* M band serology was positive, whereas urinary antigen was negative. Oral itraconazole therapy was initiated but later

complicated by congestive heart failure. His antifungal regimen was subsequently changed to posaconazole.

Three months after resection arthroplasty, he presented to our hospital because of recurrence of right knee pain. Radiographic studies revealed a fractured knee spacer. He underwent irrigation, debridement, and exchange of the spacer. Intraoperative cultures were negative. The chest radiograph was normal. *Histoplasma* serology and urine *Histoplasma* antigen were negative. He continued receiving posaconazole therapy to complete 1 year of antifungal treatment. Right TKA reimplantation was performed 10 months after initial resection arthroplasty.

DISCUSSION

Our case series of PJI due to *H capsulatum* add to 4 previously reported cases.⁴⁻⁷ The clinical details of all 7 cases are summarized in the Table. One common characteristic of these cases is the delayed growth of *H capsulatum* in cultures, which led to the initial use of broad-spectrum antibacterial therapy for presumed culture-negative PJI.^{8,9} About 7% to 10% of PJIs are culture-negative, which is most often due to the recent intake of antibiotics.^{8,9} However, as highlighted in this report, it may be due to an unusual organism such as fungi.¹⁰ To diagnose unusual infections, one may need to prolong culture incubation, use special culture medium, obtain serology, or perform molecular testing. In addition, one should consider unusual infection when there is a history of exposures, such as residence or travel to endemic areas. Our 3 cases reside in the Midwest United States and were at risk of histoplasmosis. In all the reported cases, *H capsulatum* eventually grew in cultures, albeit delayed (among the cases in which time to growth was reported [at least 12 days]).⁵ Notably, *Histoplasma* serology and urinary *Histoplasma* antigen were negative in all except 1 case in which the M band was positive, suggesting that cases were localized infections involving only joint arthroplasty. This finding is consistent with a study reporting that most bone and joint infections due to *H capsulatum* are localized.³ Our third case, however, could have been a component of a systemic disease because of the reported presence of mediastinal and hilar adenopathy

TABLE. Clinical Characteristics and Outcomes of 7 Cases of Prosthetic Joint Infection Due to *Histoplasma capsulatum*

Case number (author; patient location)	Age (y)/sex	Comorbidity	Presenting symptoms	Joint involvement	Synovial fluid cell count	Synovial fluid or tissue culture	Blood culture	Serology	Urine <i>Histoplasma</i> antigen	Surgical treatment	Antimicrobial treatment	Outcome
1 (Berbari; Wisconsin)	77/F	Kidney transplant	Right knee pain and swelling	Right knee joint	2530 cells (88% neutrophils)	<i>H capsulatum</i> on surgical culture after 15 d of incubation	Negative	Negative	Negative	Debridement and retention	Itraconazole (lifelong plan)	Good function at last follow-up (12 mo)
2 (Berbari; Iowa)	69/F	Rheumatoid arthritis, previous breast cancer	Left shoulder pain	Left shoulder joint	3512 cells (85% neutrophils)	<i>H capsulatum</i> on surgical cultures after 12 d of incubation	Negative	Negative	Negative	Resection arthroplasty	Itraconazole (ongoing)	Reimplanted at 7 mo after resection
3 (Berbari; Nebraska)	75/M	Hypertension	Right knee wound drainage	Right knee joint	Not done	<i>H capsulatum</i> on surgical cultures	Negative	Immunodiffusion M band positive	Negative	Resection arthroplasty	Itraconazole (heart failure) → posaconazole × 1 y	Reimplanted at 10 mo after the initiation of antifungal treatment
4 (Fowler; North Carolina)	84/F	Polymyalgia rheumatica	Sinus track over the left hip, pain and swelling	Left hip joint	192,500 cells (88% granulocytes)	<i>H capsulatum</i> on cultures 6 wk after surgery	Not reported	Not reported	Not reported	Debridement and retention	Itraconazole (lifelong plan)	Good function at the time of the last report (3 y)
5 (Meiyappan; travel to Ethiopia)	57/F	Vasculitis	Right knee pain and swelling	Right knee joint	1800 cells (31% neutrophils)	<i>Histoplasma capsulatum</i> on surgical and synovial fluid cultures	Not reported	Negative	Negative	Resection arthroplasty	Amphotericin B + posaconazole (prolonged)	Reimplanted at 11 mo; good function at 3.8 y
6 (Nowbakht; Wisconsin, Guatemala)	77/F	Cardiac disease, diabetes mellitus	Right knee pain	Right knee joint	Not reported	<i>H capsulatum</i> on synovial fluid culture	Negative	Not reported	Not reported	Resection arthroplasty	Itraconazole × 9 mo	Reimplanted at 9 mo; good function at 2 y
7 (Foo; Singapore)	68/M	End-stage renal disease receiving hemodialysis	Right knee pain and swelling	Right knee joint	9600 cells (56% neutrophils)	<i>H capsulatum</i> on tissue culture	Not reported	Not reported	Not reported	Revision with implantation of prosthesis	Itraconazole (ongoing at the time of the report)	No recurrence of symptoms at 8 mo

F = female; M = male.
From references 4-7.

on the chest computed tomography scan. *Histoplasma* M band serology was also positive, although urine antigen and blood cultures were negative in this case. A detailed review of this third case did not identify unusual exposures that could have predisposed him to acquire a high burden of infection.

Overall, PJI due to fungi is extremely rare.¹¹ All fungi accounted for only 1% of 3525 PJI cases at Mayo Clinic during 1996 to 2014, and most are due to *Candida* species.¹¹ As mentioned, bone and joint infections due to *H capsulatum* are rare.^{3,12} None of the fungal PJIs in our institution from 1996 to 2014 were due to *H capsulatum*.¹¹ In a review of 222 osteoarticular infections due to dimorphic fungi from 1970 to 2012, only 18 cases of *H capsulatum* were observed.³ Most cases of osteoarticular infections due to *H capsulatum* (89%) were described as a solitary bone lesion or joint infection.³ The clinical presentation in our cases is consistent with this report—PJI due to *H capsulatum* appear to be mostly isolated without other active focus of infection.

Factors that predispose patients to develop PJI due to *H capsulatum* is unknown. Although many of the cases are residents in endemic regions, there are no unifying host characteristics in the 7 patients. Although the infection has occurred in immunocompetent patients, it is possible that an underlying immunosuppression may predispose a patient to develop PJI due to *H capsulatum*.⁵ However, in a case-control study of immunocompromised transplant patients with PJI, no case of histoplasmosis was reported.¹³ In another report on 152 transplant patients with histoplasmosis, none involved bones or joints.¹⁴ In addition, the time to infection in relation to initial joint implantation was highly variable (from weeks to many years), suggesting that there is no unifying factor that predisposes to this rare orthopedic infection.

The antifungal treatment of histoplasmosis depends on the immune status and disease severity.¹⁵ Because of the localized nature of joint infection in our patients, oral itraconazole alone was used. In one of the previously reported cases, amphotericin B was also used over concerns of disseminated histoplasmosis, although this was not conclusively proven. The duration of treatment of PJI due to *H capsulatum* is not clear; however, all cases were treated with more than 7 months of antifungal

therapy after resection arthroplasty. Longer (anticipated lifelong) courses were given to 2 immunocompromised individuals with retained joint components.

In general, a 2-stage exchange surgery (in which the infected joint prosthesis is removed during debridement, followed by antimicrobial treatment, and implantation of new prosthesis once the infection has cleared) is the recommended curative therapy for PJI.¹⁶ Because *H capsulatum* is efficient in forming a biofilm,¹⁷ a 2-stage exchange approach may also be needed for the complete eradication of PJI due to *H capsulatum*. Resection arthroplasty was used in 5 cases in this report, but the time to prosthesis reimplantation was highly variable. In addition to microbial and pharmacological factors, the decision on the timing of reimplantation considers host and social considerations, such as the desire to resume activities of daily living and the availability of caretakers during the debilitating periods related to surgical joint explantation. In 2 immunocompromised patients, resection arthroplasties were not performed because prostheses were well fixed and patients were functional without pain. Because of retained prostheses, both patients were receiving maintenance indefinite itraconazole suppression.⁵

CONCLUSION

Histoplasma capsulatum is a rare cause of PJI. The diagnosis of histoplasmosis was initially not suspected, and most patients were receiving antibacterial therapy for presumed culture-negative PJI until cultures surprisingly grew *H capsulatum*. Resection arthroplasty was performed in 5 of 7 cases, whereas debridement and retention strategy was used in 2 immunocompromised cases. All the cases were treated initially or fully with itraconazole for prolonged durations; one was also given amphotericin B over concerns of disseminated infection, while another one was transitioned to posaconazole after he developed heart failure attributed to itraconazole therapy.

Abbreviations and Acronyms: PJI = prosthetic joint infection; TKA = total knee arthroplasty

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