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BRIEF REPORT

Prosthetic Joint Infection Due to *Histoplasma capsulatum* Complicating a Total Knee Arthroplasty

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Histoplasmosis is a common pathogen but rarely reported in prosthetic joint infections. We present a case of *Histoplasmosis capsulatum* prosthetic joint infection along with a literature review revealing no guidelines or consensus on surgical and antifungal management. We chose the 2-stage management with an antifungal spacer and systemic oral itraconazole.

Keywords. antifungal spacer; *Histoplasma capsulatum*; itraconazole; prosthetic joint infection; voriconazole.

Histoplasmosis, endemic in the Americas, is a common cause of infection in the United States with the highest rates in the Ohio and Mississippi River Valleys [1]. Cases reported in nonendemic areas have been seen, although less frequently, and often these patients were likely exposed while in an endemic area.

Clinical presentation depends on several factors, including the inoculum size, the patient's health, and the patient's immune status to *Histoplasmosis capsulatum* [1]. Common presentations include pulmonary syndromes, mediastinal syndromes, inflammatory syndromes, ocular histoplasmosis, and disseminated and local infection [1]. Unlike the African strain, *Histoplasma duboisii*, which has a tropism for bone, *H capsulatum* does not produce osteolytic lesions [1]. Bone marrow may be involved in disseminated histoplasmosis, particularly in immunocompromised patients [1]. Subacute or chronic solitary monoarthritis is a rare presentation in *H capsulatum* infection, especially in prosthetic joints. We report a case of prosthetic joint infection (PJI) from nonendemic *H capsulatum* complicating a total knee arthroplasty.

Received 25 March 2017; editorial decision 25 May 2017; accepted 5 June 2017.

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DOI: 10.1093/ofid/ofx118

CASE REPORT

In the fall of 2014, a 77-year-old man living in Milwaukee, Wisconsin presented with his second episode of right knee pain, which is post-total arthroplasty 13 years prior with revisions 9 and 7 years ago, for periprosthetic femur fractures. He had a history of coronary artery disease, well controlled diabetes mellitus (hemoglobin A1c 5.0), and osteoarthritis. He had no history of cancer or chemotherapy. Although he was originally born in Guatemala, he moved to the United States in 1969, with a brief trip back to Guatemala in 2008.

Two years prior, he developed right knee pain with a draining sinus tract. Aspiration was negative for bacteria, but he was treated with cephalexin for 1 week followed by doxycycline for 1 week with partial improvement, although ultimately returning with sepsis, bacteremia, and septic prosthetic knee. Repeat aspiration revealed pus with Gram-positive cocci in chains on Gram stain identified as group B streptococci (GBS). He underwent a 2-stage procedure with an antibiotic (vancomycin and gentamicin) spacer. Intraoperative fluid and tissue cultures grew GBS. He was treated with intravenous ceftriaxone daily for 4 weeks followed by 2 weeks of ciprofloxacin. Repeat right knee synovial aspirate was negative for bacteria, and he underwent reimplantation 3 months after initial presentation.

Now, 8 months later, he returns complaining of worsening knee pain. Joint aspiration was performed with negative Gram stain and cultures for bacteria. Initial fungal smear was negative; however, at day 6 of incubation, a mold was identified as *H capsulatum* on culture and confirmed on deoxyribonucleic acid probe testing. Fungal blood cultures remained sterile. Antibodies for *Coccidioides* and *Aspergillus* along with urine antigens for *Blastomyces* and *Histoplasma* were all negative; computed tomography of chest, abdomen, and lumbar spine revealed no evidence of disseminated histoplasmosis.

He underwent removal of the infected prosthesis with placement of a voriconazole-embedded spacer, and intraoperative cultures grew *H capsulatum*. He started 200 mg of itraconazole capsules twice daily, and at 9 months of therapy a surveillance arthrocentesis for culture was negative and he underwent reimplantation. At the time of this manuscript submission, the patient has been symptom- and infection-free for more than 24 months.

DISCUSSION

We describe a patient with first bacterial and then fungal PJI in a nonendemic region. It is interesting to note that in the year preceding the positive fungal culture for *H capsulatum*, 2 separate fungal cultures from that joint were negative. Historically,

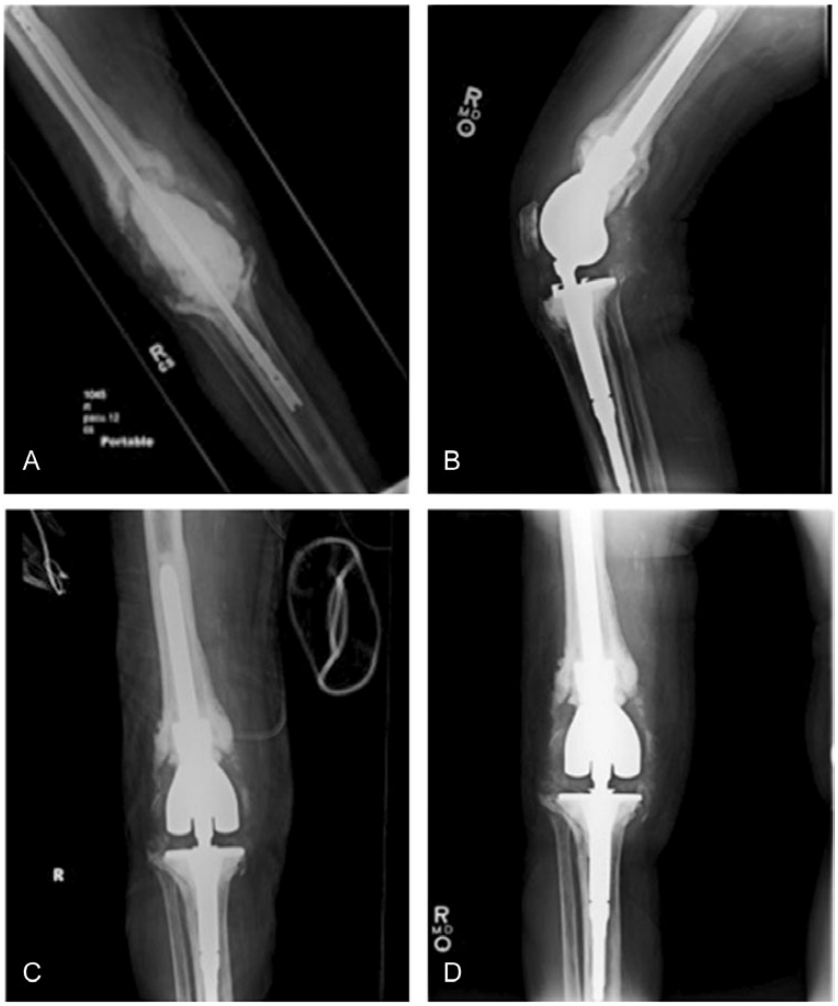

Figure 1. Antifungal spacer placed with 4 "batches of cement" impregnated with 800 mg of voriconazole (A). Knee prosthesis placed at second stage, cemented with standard techniques (B–D).

culture of periprosthetic tissue has been the gold standard for diagnosis of PJI, which our patient fulfilled with multiple periprosthetic cultures [2].

The patient did travel once to a *Histoplasma*-endemic region since initially moving in 1969. However, there was no travel history between negative and positive cultures. Reactivation of dormant organisms after many years in patients who become immunosuppressed is known to occur, including in people who have moved from endemic to nonendemic regions [1].

In a MEDLINE review of English and Spanish literature, our case represents the first instance of total knee arthroplasty complicated by *H capsulatum* infection and the second case of *H capsulatum* infecting a prosthetic joint. In 1998, Fowler et al [3] described the first reported case of PJI due to *H capsulatum* infecting a total hip arthroplasty. That patient was unable to undergo prosthetic joint removal and was prescribed lifelong itraconazole suppressive therapy [3]. Our search revealed 16 reports of *H capsulatum* infecting joints; most of these case reports include tenosynovitis. The knee is the most common site of monoarticular manifestation [4]. Four case reports involved native knee joints [5–8] and 1 prosthetic hip joint [3]. Of these patients with knee involvement, 1 had leukemia [5], 1 had diabetes mellitus, polymyositis, and pulmonary interstitial disease [6], 1 had disseminated histoplasmosis [7], and 1 was on immunosuppression for polymyalgia rheumatica [8]. Our patient's risk factors included diabetes mellitus, joint trauma (presence of joint prosthesis), and osteoarthritis. A questionable risk factor is the intra-articular aspirations in the year preceding the *H capsulatum* infection.

Most of the literature regarding fungal PJI implicates *Candida*, usually *albicans* [9–11]. Recommendations for treatment of rare fungal infections, such as *H capsulatum*, is extrapolated from experience with *Candida* infections. In 2009, Azzam et al [12] published the first large-scale multicenter study on PJI caused by fungal pathogens, which again demonstrated *Candida* as the most causative and thus most studied pathogen (42 of 46

patients in literature review and 28 of 31 patients in retrospective chart review).

Prosthetic Joint Infection From Dimorphic Fungi

We reviewed reports of bone and joint infections caused by dimorphic fungi published from 1970 to 2012. Underlying conditions, microbiological features, histological characteristics, clinical manifestations, antifungal therapy, and outcomes were analyzed in 222 evaluable cases. Among these 222 (median age 41 years; interquartile range [IQR], 26–57), 73% had no predisposing condition. Histopathology performed in 128 (57%) and cultures in 170 confirmed diagnosis in 63% and 98% of cases. Diagnosis was obtained from an extra-osteoarticular site in 16 cases. The median diagnostic time was 175 days (IQR, 60–365), and dissemination was reported in 123 (55%) cases. *Sporotrix schenckii* was the most frequent (n = 84), followed by *Coccidiodes immitis* (n = 47), *Blastomyces dermatitidis* (n = 44), *H capsulatum* (n = 18), *Paracoccidiodes brasiliensis* (n = 16), and lastly, *Penicillium marneffei* (n = 13). Arthritis occurred in 87 (58%) cases and osteomyelitis in 64 (42%), including 19 vertebral osteomyelitis events.

Systemic antifungal agents were used in 216 (97%) patients and in combination with surgery in 129 (60%). Following the Infectious Diseases, a successful initial medical strategy was observed in 97 of 116 (84%) evaluable cases. Overall mortality was 6% and was highest for *P marneffei* (38.5%). This study demonstrates that dimorphic osteoarticular infections have distinctive clinical presentations, occur in immunocompetent patients, develop often during disseminated disease, and may require surgical intervention [13].

Currently, no randomized clinical trials addressing the selection of a curative surgical procedure for fungal PJI exist. The 2-stage protocol is effective for bacterial PJI and has been translated to fungal PJI. In addition, literature review supports that 2-stage reimplantation provides the best chance at success [9–12]. Debridement and prosthesis retention with or without antifungal therapy should only be used in acute infections, a rare presentation of fungal PJI [9, 12]. No consensus exists on the timeline of reimplantation, which has varied in previous studies [10–12]. Despite the lack of recommendations, the cornerstone of determining an optimal time to reimplantation is confirmation of an infection-free period after the initial surgery [11].

Why Voriconazole Over Itraconazole or Fluconazole for the Spacer?

Using an "antibiotic spacer" in the first stage of a "two-stage" revision has become commonplace for treatment of PJI, especially with biofilm forming organisms. The use of antibiotic-impregnated cement involves using an antibiotic that is heat-stable during the exothermic reaction of methylmethacrylate and has the most desirable elution based on its use with the particular methacrylate. Furthermore, the antimicrobial needs to be mechanically equally mixed in the "powder" before the monomer being mixed. Because of its properties, voriconazole is superior to fluconazole and itraconazole for use in antifungal spacers. No consensus exists on which antifungal is used; however, by extrapolating the properties needed for the antibiotic spacers, voriconazole is the most reliable. In a large, multicenter trial, voriconazole was as effective as amphotericin B and obtained a concentration above the minimum inhibitory concentration $(MIC)_{90}$ for *Candida albicans* [14]. Evidence suggests that higher concentrations of antimicrobials can be delivered locally by approximately 1000-fold, which would not be deliverable systemically given the side effects [15].

When using the published data to form an antifungal spacer, especially in patients with considerable bone loss, concentrations are based on a MIC extrapolated from the data available as well as the antifungal's elution properties. The antifungal spacer (Figure 1) was formulated with 4 "batches" of cement, each with 200 mg of voriconazole.

Oral itraconazole was selected for this patient given its proven efficacy against *H capsulatum*. Fluconazole is moderately effective for histoplasmosis and induces resistance during therapy causing treatment failure [1]. The duration of treatment of 6–12 months was based on expert opinion.

CONCLUSIONS

This case emphasizes the difficulty in diagnosing culture-negative septic arthritis and warns clinicians and surgeons not to negate the chance of fungal septic arthritis in otherwise low-risk patients. It also highlights the difficulty in determining the optimal time to consider reimplantation and further supports delayed reimplantation.

Acknowledgments

We acknowledge Drs. Amar Safdar and Joseph Wheat for providing helpful advice.

Potential conflicts of interest. J. E. received speaking fees from Allergan Speakers Bureau. L. O.-Z. received consulting fees and research grants from Astellas, speaking fees and research grants from Pfizer, consulting fees and speaking fees from Merck, consulting fees from Cidara, consulting fees and research grants from Scynexis, speaking fees and research grants from T2 Biosystems, and research grants from Immuntecis. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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