2019

Histoplasma capsulatum periprosthetic knee infection complicated by autoimmune-mediated systemic inflammatory response syndrome

Juan Carlos Suarez
Baptist Health Orthopedic Institute, juansu@baptisthealth.net

Case report

Histoplasma capsulatum periprosthetic knee infection complicated by autoimmune-mediated systemic inflammatory response syndrome

Arjun Meiyappan, MD [a], Jesus M. Villa, MD [a], Vani J. Sabesan, MD [a, *],
Preetesh D. Patel, MD [a], Juan C. Suarez, MD [b]

[a] *Cleveland Clinic Florida, Weston, FL, USA*
[b] *Miami Orthopedics and Sports Medicine Institute, Baptist Health South Florida, Kendall, FL, USA*

ABSTRACT

Histoplasma capsulatum periprosthetic knee infection has rarely been reported in the literature due to its low frequency. Notwithstanding, it is important to keep it among the differential diagnoses to avoid delays in treatment. The current report presents the case of infectious knee monoarthritis in an immunocompetent patient after unicompartmental knee arthroplasty. The joint infection was accompanied by disseminated histoplasmosis, which initiated an autoimmune reaction, ensuing a systemic inflammatory response syndrome. The management protocol used in this case was successful and included staged arthroplasty reconstruction combined with chronic antifungal and steroid pharmacotherapy. Approximately 4 years after total knee arthroplasty revision, there were no clinical signs of localized or systemic infection.
© 2019 Published by Elsevier Inc. on behalf of The American Association of Hip and Knee Surgeons. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Histoplasma capsulatum is a dimorphic fungus endemic in many countries. Within the United States, it is most prevalent in the Mississippi and Ohio River valleys. Other endemic regions are located in Latin America, Asia, and Africa [1,2]. It is usually asymptomatic in immunocompetent hosts, but it can manifest with florid symptoms in immunocompromised patients.

Isolation of *Histoplasma capsulatum* can be achieved using fungal specific special media such as Sabouraud agar. Incubation at 25°C for 6-12 weeks is usually required. A definitive diagnosis requires visualization of *Histoplasma capsulatum* microscopically in its yeast phase after transformation from its initial mold phase. This conversion is achieved by using enriched media (blood agar or brain heart infusion agar) with cysteine incubated at 35°C-37°C.

Culture using these specific media is only performed if there is a high suspicion of fungal infection.

There have been a handful of case reports on periprosthetic joint infection (PJI) due to *Histoplasma capsulatum* [3-5]. In the current article, we review the rare occurrence of an immune-mediated systemic inflammatory response syndrome (SIRS) caused by *Histoplasma capsulatum* knee PJI. Particularly, we address the challenges and pitfalls during the medical and surgical management of this atypical joint infection.

Case history

Patient's consent was obtained for the purpose of publishing this report. A 57-year-old immunocompetent white male underwent a right medial unicompartmental knee arthroplasty in 2002. The patient presented to our institution in October 2010 with acute knee pain and swelling, which had progressively worsened over the past months (Fig. 1). The patient had a past medical history of kidney stones and vasculitis, as well as a past surgical history of left ankle surgery, bilateral inguinal hernia repair, navel hernia repair, kidney stone removal, and rectal fistula. The pain was accompanied by fevers and a diffuse erythematous rash. The appearance of the symptoms followed a visit to Ethiopia where the patient suffered an illness associated with significant diarrhea, weight loss, fever, and

Figure 1. Anteroposterior and lateral radiograph of the right knee taken in 2010 (approximately 8 years after implantation) demonstrating unicompartmental knee arthroplasty with radiolucency around the tibial component and varus collapse, in addition to a radiolucent area around the femoral component suggesting loosening of the components.

skin rashes. The patient underwent knee joint aspiration, and the culture of the sample obtained was positive for *Histoplasma capsulatum*. Inflammatory markers were notably elevated: the erythrocyte sedimentation rate (ESR) was 106 mm/h (the normal value according to the Musculoskeletal Infection Society [MSIS] criteria is <30 mm/h), C-reactive protein (CRP) was 67.50 mg/L (MSIS normal is <10 mg/L), and the peripheral white blood cell count (WBC) was 14,000 cells/cm^3. Furthermore, knee synovial fluid differential showed elevated total nucleated cell count of 1800 cells/uL, neutrophils at 31%, lymphocytes at 41%, and macrophages at 28%. The patient did not receive antibiotic or antifungal treatment before the laboratory workup.

Anteroposterior and lateral radiographs of the right knee taken in 2010 (approximately 8 years after implantation) demonstrated unicompartmental knee arthroplasty with radiolucency around the tibial component and varus collapse, in addition to a radiolucent area around the femoral component suggesting loosening of the components (Fig. 1).

Owing to the coexisting symptoms of rash and fever along with elevated inflammatory markers, it was suspected that the patient had disseminated histoplasmosis with associated periprosthetic loosening and deep fungal infection. He was started on a dual agent therapy with itraconazole and amphotericin B (for 2 weeks and 12 months, respectively) based on culture sensitivities. A formal irrigation and debridement of the knee with removal of the unicompartmental prosthesis and placement of an articulating cement spacer made up of four 40-g bags of cement each mixed with 200 mg of amphotericin B and 1 g of vancomycin was performed. Surgical fungal culture revealed one colony of *Histoplasma capsulatum* and surgical pathology showed reactive synovium with marked chronic inflammation and necrotic debris. This procedure was intended to be the first stage of a two-stage reconstruction, with the timing of the second stage relying on a positive response to the systemic treatment. However, 3 months after the first-stage process (resection), the patient developed increasing knee pain. Even though *Histoplasma capsulatum* antigen was not detected on blood

cultures, he still had elevated ESR (116 mm/h) and CRP (76.6 mg/L) levels. A knee aspiration was performed, but the amount of synovial fluid obtained was insufficient for analysis. With all available information, it was suspected that the periprosthetic knee infection persisted. Therefore, the patient underwent a second irrigation and debridement of the knee with antibiotic spacer exchange (composed of 4 bags of cement mix containing 200 mg of amphotericin B and 1 g of vancomycin per bag of cement) (Fig. 2).

After 11 months of systemic treatment, we proceeded with a total knee arthroplasty revision (Fig. 3) based on clinical evaluation and decreasing inflammatory markers (WBC [2300 cells/cm^3] and ESR [19 mm/h]) even though the high-sensitivity CRP level [6] was 16.34 mg/dL (of note, due to the systemic involvement, the CRP level was unreliable). The patient was kept on antifungal therapy for an additional 6 months (liposomal amphotericin B and posaconazole) after hospital discharge to reduce the risk of PJI recurrence because no standard duration of treatment for fungal PJI is generally accepted.

About 1.5 years after total knee revision, he presented with the clinical hallmarks of a SIRS with no signs of disseminated histoplasmosis (ie, fever, malaise, anorexia, weight loss) based on medical history and physical examination. A bronchoalveolar lavage performed showed no fungal presence, and tests for *Histoplasma capsulatum* antigen in urine and serum were also negative. Inflammatory markers were found elevated (CRP [111.8 mg/mL] and ESR [101.0 mm/h]), but no source of sepsis was identified on hematologic or radiological studies. The patient was admitted to a high-dependency-level care for supportive treatment. Ultimately, he improved on a treatment course including liposomal amphotericin B and prednisone.

Five months later, the patient was readmitted to the hospital due to the presence of episcleritis, epididymitis, diffuse arthralgias, and skin rash. His prosthetic knee remained asymptomatic, whereas his inflammatory markers were found elevated (CRP [85.5 mg/L] and ESR [121 mm/h]). Serum histoplasmosis antigen testing remained negative, and the diagnosis of an autoimmune reaction secondary to the previous histoplasmosis was made. The exclusion of persistent disseminated histoplasmosis was made based on the serum and urine antigen testing. The patient responded to a

Figure 2. Anteroposterior and lateral radiographs of the right knee showing the second antifungal cement spacer (composed of 4 bags of cement mix containing 200 mg of amphotericin B and 1 g of vancomycin per bag of cement) placed after explantation of the initial spacer. Molds were used.

Figure 3. Total knee arthroplasty revision with diaphyseal engaging press fit stems and metaphyseal press fit sleeve on the tibia. Simplex P with tobramycin bone cement (Stryker, Mahwah, NJ) was used on the implant surface.

continued course of liposomal amphotericin B and prednisone. His antifungal suppression was continued with posaconazole for 3 years after total knee arthroplasty revision. At the most recent follow-up visit, 3.8 years after knee reimplantation, the patient had completed the antifungal treatment and continued immunosuppression with corticosteroids for his inflammatory response. His knee remained clinically asymptomatic. The patient denies having any fever and the range of motion of the right knee is 0-120 degrees of flexion and non-painful. There is no clinical evidence of systemic or local infection.

Discussion

Periprosthetic knee infection due to *Histoplasma capsulatum* is rare (ranking 10th in the order of frequency among all fungal PJIs) [4]. Plain radiographs can help identify chronic infections where implant loosening becomes obvious [7]. Serology, joint aspiration, and culture are necessary to make the diagnosis according to the MSIS criteria [4,7]. Two-stage reconstruction for chronic PJI has shown good success [5,7,8]. Nevertheless, the success rate of fungal PJI treatment is lower than that observed when treating bacterial PJIs [8]. To the best of our knowledge, there are no reports concerning the success rates of two-stage revisions in patients with *Histoplasma capsulatum* PJI [5].

Previous investigations have reported the use of amphotericin-loaded cement spacers coupled with chronic systemic oral azole or amphotericin for the treatment of fungal PJIs [8-10]. The recommended antifungal treatment in a cement spacer includes 200 mg of amphotericin B or 800 mg of voriconazole or fluconazole per 40 g of cement [8].

In relation to the use of amphotericin B–loaded cement spacers, it is important to recognize its chemical pharmacokinetics. Its heat stability characteristics (up to 170°C) and availability in sterile powder form make amphotericin B an ideal candidate for use in cement spacers [11]. However, its elution profile has been shown to be lacking in previous studies. Goss et al. [12] found no elution of amphotericin B from Simplex bone cement (Stryker, Mahwah, NJ) after 1 week in vitro. Marra et al. [11] showed undetectable serum concentrations of amphotericin at 50 hours in vivo when mixed with

PALACOS bone cement (Biomet, Warsaw, IN). In contrast, the wound drainage fluid had a maximal concentration of 3.2 mg/L. As such, the elution profile of this antibiotic has yet to be determined [13].

Systemic treatment includes either oral fluconazole (400-800 mg/d) or intravenous amphotericin B (15-35 mg/d). Their use ranges from 3 weeks to lifelong antifungal suppression [8]. After the antifungal course, the timeline for prosthesis reimplantation might vary, but it is common practice to keep an antifungal impregnated spacer for a period of 4-6 weeks alongside systemic antifungals [1,5,14]. This period is followed by another 2-6 weeks free of systemic antibiotics during which time, the patient is re-evaluated for any signs of ongoing infection [1,5].

Immunocompromised patients (those affected by chronic steroid use, acquired immune deficiency syndrome, hematologic malignancies, and transplant recipients and infants with immune system immaturity) are disproportionately affected as they are unable to develop an effective cell-mediated immunity against the *Histoplasma capsulatum* organism; the importance of the cell-mediated response has been previously highlighted [15].

Symptoms associated with disseminated histoplasmosis include fever, malaise, anorexia, and weight loss. Laboratory studies usually show nonspecific increases in ESR and CRP levels [15]. The definitive diagnosis is based on bone marrow, pulmonary, and skin biopsy cultures or positive stains using methenamine silver or periodic acid schiff [15]. In patients with disseminated histoplasmosis, aggressive treatment is required with removal of the source infection (when possible) and long-term antifungal treatment. Antifungal treatment recommendations and duration vary. Liposomal amphotericin B (for 1-2 weeks) followed by 1 year of itraconazole is most commonly used, and this treatment is recommended until the absence of *Histoplasma capsulatum* antigen in urine and serum [2].

SIRS is a clinical diagnosis that describes a host's response to an infectious or noninfectious cause [16]. Although autoimmune reactions may manifest in multiple ways, SIRS is characterized by systemic inflammation and widespread tissue injury and may present in a similar fashion to disseminated histoplasmosis. For a SIRS diagnosis, a patient must be positive for at least 2 of the following clinical variables: (1) temperature >38°C or <35°C, (2) heart rate >90 beats/min, (3) respiratory rate >20 breaths/min or PCO_2 <32 mmHg, and (4) WBC >12,000 cells/mm^3 or <4000 cells/mm^3 [17]. Treatment guidelines for SIRS include early lung-protective ventilation and antibiotics with goal-directed therapy, with a thorough search for source of infection and rapid identification of causative organism for focused antibiotic treatment [18].

To the best of our knowledge, the current report is the first to describe a *Histoplasma capsulatum* PJI complicated with an autoimmune-induced SIRS. Failure of self-tolerance is a fundamental part of the pathology of autoimmunity, and environmental and/or infectious factors have long been postulated to trigger autoimmune reactions [19]. There have been many mechanisms by which host infection by a pathogen can cause autoimmunity, with 2 of the main mechanisms including molecular mimicry and bystander activation [19]. Molecular mimicry relates to the fact that a pathogen may carry antigens similar to the self-antigen, which causes activation of T and B cells thereby leading to direct damage to self-tissue. Bystander activation causes autoimmunity via epitome spreading whereby an immune response directed to a pathogen causes damage to self-tissue; antigen released by host tissue are uptaken by antigen presenting cells, which initiates a self-specific immune response. As such, disruption of the immune responses, checks, and balances can lead to an autoimmune reaction [20].

This entity has not been widely described in the literature [21]. The clinical symptoms of disseminated histoplasmosis and the ones of an autoimmune-induced SIRS reaction are similar; therefore, it is important to consider an inclusive differential diagnosis when

assessing a patient and consider autoimmune conditions as a cause of SIRS [20,22]. To obtain a definitive diagnosis of disseminated histoplasmosis, the organism must be isolated [15], and in the absence of this, other etiologies must be explored. Our case was unique because it was accompanied by a persistent systemic inflammation, which made the serology unreliable while keeping plausible the presence of a disseminated histoplasmosis infection or an autoimmune-induced SIRS reaction. The management protocol used in this case was successful and included a staged arthroplasty reconstruction combined with chronic antifungal and steroid pharmacotherapies.

Summary

The current report describes the case of a *Histoplasma capsulatum* PJI complicated with an autoimmune-induced SIRS. The treatment performed involved a staged arthroplasty reconstruction combined with chronic antifungal and steroid pharmacotherapies. Nearly 4 years after total knee reimplantation, the patient has shown no clinical evidence of systemic or local infection.

References

[1] Tande AJ, Patel R. Prosthetic joint infection. Clin Microbiol Rev 2014;27(2):302.
[2] Wheat LJ, Azar MM, Bahr NC, et al. Histoplasmosis. Infect Dis Clin North Am 2016;30(1):207.
[3] Agarwal P, Capoor MR, Singh M, et al. An unusual presentation of disseminated histoplasmosis: case report and review of pediatric immunocompetent patients from India. Mycopathologia 2015;180(5-6):359.
[4] Falster L, Marin MB, Gomes JL. Histoplasmosis diagnosed after arthroscopy of the knee: case report. Braz J Infect Dis 2015;19(5):546.
[5] Nowbakht C, Garrity K, Webber N, Eraso J, Ostrosky-Zeichner L. Prosthetic joint infection due to Histoplasma capsulatum complicating a total knee arthroplasty. Open Forum Infect Dis 2017;4(3):ofx118.
[6] Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003;111(12):1805.
[7] Kapadia BH, Berg RA, Daley JA, et al. Periprosthetic joint infection. Lancet 2016;387(10016):386.
[8] Jakobs O, Schoof B, Klatte TO, et al. Fungal periprosthetic joint infection in total knee arthroplasty: a systematic review. Orthop Rev (Pavia) 2015;7(1):5623.
[9] Wu MH, Hsu KY. Candidal arthritis in revision knee arthroplasty successfully treated with sequential parenteral-oral fluconazole and amphotericin B-loaded cement spacer. Knee Surg Sports Traumatol Arthrosc 2011;19(2):273.
[10] Wyman J, McGough R, Limbird R. Fungal infection of a total knee prosthesis: successful treatment using articulating cement spacers and staged reimplantation. Orthopedics 2002;25(12):1391. discussion 4.
[11] Marra F, Robbins GM, Masri BA, et al. Amphotericin B-loaded bone cement to treat osteomyelitis caused by Candida albicans. Can J Surg 2001;44(5):383.
[12] Goss B, Lutton C, Weinrauch P, et al. Elution and mechanical properties of antifungal bone cement. J Arthroplasty 2007;22(6):902.
[13] Azzam K, Parvizi J, Jungkind D, et al. Microbiological, clinical, and surgical features of fungal prosthetic joint infections: a multi-institutional experience. J Bone Joint Surg Am 2009;91(Suppl 6):142.
[14] Reddy KJ, Shah JD, Kale RV, Reddy TJ. Fungal prosthetic joint infection after total knee arthroplasty. Indian J Orthop 2013;47(5):526.
[15] Kauffman CA. Histoplasmosis: a clinical and laboratory update. Clin Microbiol Rev 2007;20(1):115.
[16] Balk RA. Systemic inflammatory response syndrome (SIRS): where did it come from and is it still relevant today? Virulence 2014;5(1):20.
[17] Angele MK, Pratschke S, Hubbard WJ, Chaudry IH. Gender differences in sepsis: cardiovascular and immunological aspects. Virulence 2014;5(1):12.
[18] Russell JA. Management of sepsis. N Engl J Med 2006;355(16):1699.
[19] Rosenblum MD, Remedios KA, Abbas AK. Mechanisms of human autoimmunity. J Clin Invest 2015;125(6):2228.
[20] Ercolini AM, Miller SD. The role of infections in autoimmune disease. Clin Exp Immunol 2009;155(1):1.
[21] Thornberry DK, Wheat LJ, Brandt KD, Rosenthal J. Histoplasmosis presenting with joint pain and hilar adenopathy. "Pseudosarcoidosis". Arthritis Rheum 1982;25(12):1396.
[22] Sherbet G. Bacterial infections and the pathogenesis of autoimmune conditions. Br J Med Pract 2009;2:6.