Periprosthetic hip joint infection with *Aspergillus terreus*: A clinical case and a review of the literature

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**ABSTRACT**

Fungal periprosthetic joint infections due to *Aspergillus* species are rare but are associated with significant cost and morbidity. We present a case of *Aspergillus terreus* prosthetic joint infection of the hip. The patient was successfully treated with a prolonged course of systemic antifungals along with surgical management.

1. **Introduction**

   While periprosthetic joint infections (PJI) complicate only 2% of all joint replacements, they are associated with significant cost and morbidity [1,2]. Fungal prosthetic joint infections are particularly rare, comprising approximately 1% of all PJIs [3] with the majority of cases attributed to *Candida* species, and only a few reported cases of PJI due to *Aspergillus* species. Here we present a rare case of *Aspergillus terreus* PJI of the hip joint managed at our institution.

2. **Case**

   This is a 54-year-old man with a history of obesity (BMI 38) despite prior gastric bypass surgery, controlled diabetes mellitus (HbA1c range 5.2–6.5%), cleared hepatitis C infection, and left total hip arthroplasty for osteoarthritis in October 2015 (day 0). Approximately 1 month later he developed purulent drainage from an ulcer proximal to the wound for which he received incision and drainage (I&D) and polyethylene liner exchange (day 36). All wound cultures were negative and frozen section was not consistent with infection. He quickly developed recurrence of drainage and underwent left hip I&D and explant of prosthesis and antibiotic spacer placement (day 161). Intraoperative cultures grew *Enterobacter cloacae* in only 1 specimen. He was briefly treated with piperacillin/tazobactam and IV vancomycin as an inpatient, then completed another 6 week course of IV vancomycin upon discharge. Thereafter, he was maintained on per os doxycycline 100 mg twice daily for an additional 6 weeks. His wound healed and inflammatory markers again normalized.

   In March 2016 (day 148), the patient underwent left hip revision arthroplasty, but quickly developed worsening pain and copious drainage from the surgical wound. He again required I&D, removal of prosthesis and antibiotic spacer placement (day 161). Intraoperative cultures again showed copious MRSA in addition to *Enterobacter cloacae* in only 1 specimen. He was briefly treated with piperacillin/tazobactam and IV vancomycin as an inpatient, then completed another 6 week course of IV vancomycin upon discharge. Thereafter, he was maintained on per os doxycycline 100 mg twice daily for an additional 6 weeks. His wound healed and inflammatory markers again normalized. Joint aspiration off antibiotics, showed no growth on cultures. The patient unfortunately developed another recurrence of PJI in August of 2016 in the setting of an elective dental extraction, which was treated with perioperative amoxicillin. Intraoperative cultures were again elevated. Fluid aspiration showed 39,000 WBC with 98% neutrophils. Fluid culture grew *Streptococcus mitis*. Patient then received repeat I&D and replacement of antibiotic impregnated spacer at that time (day 295). Postoperative course was complicated by dislocation of spacer and periprosthetic fracture requiring revision surgery. He was ultimately discharged to a skilled nursing facility to complete 8 weeks of high dose ceftriaxone followed by 4 weeks of amoxicillin, completed in November 2016.

   Despite prolonged antibiotic therapy, the patient continued to complain of left hip and groin pain associated with difficult ambulation. Exam of his left hip revealed no erythema or warmth and his previous surgical wounds were intact without drainage.

   He underwent CT guided hip joint aspiration for further work up which revealed 148 white blood cells with 59% neutrophils and 64,000...
red blood cells (day 401). Multiple cultures grew *Aspergillus terreus*, which was identified by macroscopic and microscopic morphology (see Image 1). Repeat aspiration revealed 1196 white blood cells with 60% neutrophils (day 408). Bacterial and fungal cultures again grew *Aspergillus terreus*. ESR and CRP increased to 56 mm/h and 2.4 mg/dL, respectively. Aspergillus galactomanan was normal at 0.1. Susceptibility testing results from the University of Texas reference laboratory are shown in Table 1. He was started on delayed-release oral posaconzole, which was gradually titrated up from 300 mg daily to 400 mg every morning and 300 mg every evening, based on posaconazole troughs of 0.7–1.2 micrograms per milliliter. Following 1 month of therapy, the patient reported a decrease in his hip pain and improvement in ambulation. In March 2017 (day 498), he underwent revision of the left hip implant using 2 g of vancomycin and 3 g of voriconazole impregnated into a cement spacer. Intraoperatively there was no evidence of active infection and multiple cultures were negative for bacterial or fungal species. Two months later (day 577) he underwent repeat aspiration while holding his posaconzole to ensure there was no inhibition of fungal growth. Cultures from this procedure were negative. Tentative plan for the patient is to continue posaconzole until ultimate revision arthroplasty in the coming weeks.

### 3. Discussion

#### 3.1. Discussion

*Aspergillus* species joint infections are exceedingly rare. A review of the literature from 1967 to 2015 identified only 31 reported cases [4]. The majority of these were caused by *Aspergillus fumigatus* (77%), followed by *Aspergillus flavus* (13%) [4]. To our knowledge, ours is only the 2nd PJI due to *A. terreus* described in the literature [5]. While other reviews have reported on cases of *A. terreus* osteoarticular infections, these were not specifically attributed to a PJI [6].

*Aspergillus* species are found worldwide in soil and decaying matter. Invasive *Aspergillus* infections and *Aspergillus* joint infections are typically seen in patients with significant underlying immunosuppression. In a review of 31 cases by Gamaletou et al., 26% had an underlying hematologic malignancy while 19% and 6% had undergone solid organ and bone marrow transplantation, respectively [4]. Neutropenia and treatment with corticosteroids were also commonly reported risk factors. Twenty-six percent of patients had a history of orthopedic surgery [4], though it is uncertain if the involved joints were surgically manipulated. A series of fungal PJIs described by Kuiper et al. reported that 16% of patients were classified as “immunocompromised” while 26% of patients had underlying diabetes [7]. Of note, the majority of fungal PJIs they reviewed were due to *Candida* species, which may be associated with different risk factors, such as prolonged hospitalization.

Few cases of *Aspergillus* PJI have been reported in patients without

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**Table 1**

Susceptibilities of *A. terreus* by broth microdilution.

| Antifungal agent | Minimum inhibitory concentration |
|------------------|----------------------------------|
| Amphotericin B   | 2 mcg/ml                          |
| Caspofungin      | 0.125 mcg/ml                      |
| Micafungin       | < 0.015 mcg/ml                    |
| Fluconazole      | > 64.0 mcg/ml                     |
| Voriconazole     | 0.25 mcg/ml                       |

*a* breakpoint not defined.

*b* reported value for echinocandins is minimum effective concentration.

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**Image 1.** *A. terreus* growth on plates and culture of joint fluid.
obvious immunosuppression, as in the case we described herein [3,8]. Though the source of infection in our patient remains unclear, we hypothesize that the patient’s primary risk for infection was recurrent operations on the same unstable hip joint and multiple prior courses of antibiotics, which likely selected for growth of a mold species. As there have been no other cases of _A. terreus_ at our institution, we believe it is unlikely that there is an ongoing environmental issue with this organism and therefore, suspect that contamination during surgery was less likely.

While 87% of patients present with pain and 26% of patients present with swelling, erythema and draining fluid are less common clinical presentations (10% and 6% respectively) [4]. In patients with septic arthritis due to _Aspergillus species the knee_ remains the most common site (35%), followed by intervertebral joint (26%) and hip (16%) [4]. Gamaletsou et al. reported that 10% of the 31 reported cases of _Aspergillus_ septic arthritis occurred in prosthetic joints [4]. The other reported _Aspergillus terreus_ PJI occurred in a total elbow arthroplasty [5]. Therefore, ours is perhaps one of the first cases of _Aspergillus terreus_ involving a total hip arthroplasty.

Given the non-specific clinical presentation, the diagnosis of these infections can be challenging. Studies suggest that inflammatory markers are often elevated, as in our patient, but these too are non-specific [4,7]. _A. terreus_ infections may produce high levels of galactomannan [9], though this was not seen with our patient. It should be noted that high levels of galactomannan have been seen in invasive pulmonary aspergillosis [9] and it is unclear if these levels should be expected in joint infections caused by _A. terreus_. Therefore, while serum fungal markers may be helpful, a definite diagnosis can only be made on microbiologic culture, either from synovial fluid culture or direct tissue culture. If _Aspergillus species_ is isolated from a joint, it should be considered a true pathogen and managed with systemic antifungals and a 2-step surgical approach according to a review by Kuiper et al., which assessed 164 fungal PJIs (94 knee arthroplasties and 70 hip arthroplasties) [7].

Successful treatment of _Aspergillus species_ and fungal PJIs described in the literature often requires both a surgical and medical approach [3,4,7]. Systemic antifungals, such as triazoles, amphotericin B, and echinocandins have all been used to treat invasive aspergillosis [10,11]. According to the Infectious Diseases Society of America Practice Guidelines for the Diagnosis and Management of Aspergillosis 2016, triazoles are the preferred agents for treatment in most patients, while echinocandins have all been used in conjunction with surgical management [4,5,7]. _A. terreus_ infections are associated with higher mortality and treatment failure than infections with other _Aspergillus species_ [12]. _Aspergillus terreus_ is unique due to its anti and in vivo resistance to the fungicidal effect of amphotericin B [13]. Therefore, our patient was treated with delayed-release posaconazole oral tablets. Though voriconazole is recommended by guidelines for _Aspergillus species_ infections [10], there are no recommendations specifically for _A. terreus_ infections or PJIs. We selected posaconazole rather than voriconazole given its better tolerability and its lack of reliance on the cytochrome P450 system for metabolism. Furthermore, prolonged voriconazole is associated with periostosis, which may have a negative impact on bone healing following joint surgery, as in our patient. Since our patient improved on posaconazole without the development of side effects, we decided to continue treatment rather than switch to voriconazole after the susceptibilities were available (Table 1).

We treated our patient with the delayed-release formulation of posaconazole as it has improved bioavailability and is not significantly affected by food or gastric acid suppression therapy compared to the oral suspension [14]. Delayed-release tablets also demonstrate higher serum concentrations than the oral suspension in patients with hematologic malignancies and solid organ transplants, without affecting the side effect profile [15,16]. To ensure therapeutic efficacy, drug level monitoring once steady state is achieved, and corresponding dose adjustment based on drug levels is recommended.

While there are no established guidelines, the majority of available literature recommends systemic antifungal therapy along with surgical management for maximal chance of cure of fungal PJIs, thus this was the management strategy employed [5,7]. A study by Deelstra et al. describes successful use of an antifungal cement spacer as adjunctive treatment to augment activity of systemic antifungals [17]. The goal of installation of antifungal and antibacterial agents into the bone cement spacer is to provide localized drug delivery, which may achieve higher drug levels at the site of infection [18]. However, the elution characteristics of antifungal agents may vary in vitro and in vivo depending on the use of a nonbiodegradable or biodegradable material and the porosity of the substance, which can impact the duration, rate, and the amount of antifungal released from the cement [19,20]. Grimsrud et al. examined the in vitro elution characteristic of voriconazole from non-absorbable polymethyl-methacrylate beads and from absorbable calcium sulfate beads, and found the rate of elution decreased before 48 h, then voriconazole concentrations remained relatively constant with enough antifungal activity to inhibit growth of the control yeasts for 2 weeks [19]. Although case reports of amphotericin B, voriconazole, fluconazole, and itraconazole spacers have been reported with favorable outcomes, the sustained bone durability was not thoroughly assessed and the duration of follow up was limited [20]. Based on the limited data, it is difficult to make general recommendations on the use of antifungal agents in cement spacers, though available data also does not demonstrate excess harm.

4. Conclusion

Fungal PJIs are extremely rare, with _Aspergillus species_ comprising a small number of these infections. Here we present a case of _Aspergillus terreus_ PJI of the hip managed at our institution, which we believe is one of very few reported cases [5]. Consistent with the management strategy recommended in available literature, our patient was treated with a combined surgical and medical approach involving joint I & D, voriconazole impregnated cement, and many weeks of oral delayed-release posaconazole. Close monitoring of clinical status, inflammatory markers, and posaconazole levels is planned to ensure maximal chance of cure.

Ethical form.

Please note that this journal requires full disclosure of all sources of funding and potential conflicts of interest. The journal also requires a declaration that the author(s) have obtained written and signed consent to publish the case report from the patient or legal guardian(s).

The statements on funding, conflict of interest and consent need to be submitted via our Ethical Form that can be downloaded from the submission site http://www.ees.elsevier.com/mmc.

Conflict of interest

There are none.

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