Medical Mycology Case Reports 18 (2017) 24–27

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

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

Rachel Bartash[a,*], Yi Guo[b], John B. Pope[c], Michael H. Levi[d], Wendy Szymczak[d], Nidhi Saraiya[b], Priya Nori[a]

[a] Division of Infectious Diseases, Department of Medicine, Montefiore Medical Center, 111 E. 210th Street, Bronx, NY 10467, USA
[b] Department of Pharmacy, Montefiore Medical Center, 111 E. 210th Street, Bronx, NY 10467, USA
[c] Department of Orthopedic Surgery, Montefiore Medical Center, 111 E. 210th Street, Bronx, NY 10467, USA
[d] Microbiology Laboratory, Montefiore Medical Center, 111 E. 210th Street, Bronx, NY 10467, USA

ARTICLE INFO

Keywords:
Fungal prosthetic joint infection
Aspergillus terreus

ABSTRACT

Fungal periprosthetic joint infections due to Aspergillus species are rare but are associated with significant cost and morbidity. We present a case of Asperigillus 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 *Asperigillus 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 with placement of an antibiotic impregnated spacer in December 2015 (day 46). Multiple intraoperative cultures grew methicillin-resistant *Staphylococcus aureus* (MRSA). He developed ongoing serous drainage for which he required repeat I & D approximately 2 weeks later (day 56). He was discharged to a skilled nursing facility (SNF) to complete 8 weeks of IV vancomycin. His wound healed and inflammatory markers normalized (see Fig. 1).

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 periprocedural amoxicillin. Inflammatory markers 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 skill 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

* Corresponding author.
E-mail address: rbartash@montefiore.org (R. Bartash).

http://dx.doi.org/10.1016/j.mmcr.2017.07.006
Received 20 April 2017; Received in revised form 19 July 2017; Accepted 24 July 2017
Available online 25 July 2017

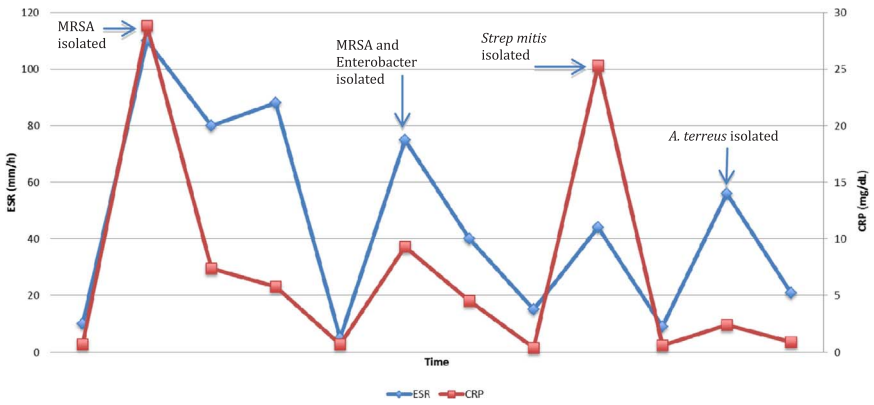

Fig. 1. ESR and CRP Trend.

Image 1. A. terreus growth on plates and culture of joint fluid.

Table 1
Susceptibilities of *A. terreus* by broth microdilution.

Antifungal agent	Minimum inhibitory concentration
Amphotericin B	2 mcg/ml[a]
Capsofungin	0.125 mcg/ml[a,b]
Micafungin	< 0.015 mcg/ml[a,b]
Fluconazole	> 64.0 mcg/ml[a]
Voriconazole	0.25 mcg/ml[a]

[a] breakpoint not defined.
[b] reported value for echinocandins is minimum effective concentration.

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 (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 posaconazole to ensure there was no inhibition of fungal growth. Cultures from this procedure were negative. Tentative plan for the patient is to continue posaconazole 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 Gamaletsou 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

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 these 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 amphotericin B deoxycholate and its lipid formulations are appropriate alternatives for initial or salvage therapy. Echinocandins are generally recommended for salvage therapy only [10]. However, these guidelines address all invasive *Aspergillus* infections and are not specific for native or prosthetic joint infections. In case reviews of *Aspergillus* joint infections, triazoles, amphotericin B, and 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 *Apergillus species* [12]. *Aspergillus terreus* is unique due to in vitro 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 we 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 biodgradable 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/mmcr.

Conflict of interest

There are none.

Acknowledgements

Josh Nosanchuk MD
Marne Garretson MPH
Hitesh Patel
Anthony Braffi

References

[1] W. Zimmerli, A. Trampuz, P.E. Ochsner, Prosthetic-joint infections, N. Engl. J. Med. 351 (16) (2004) 1645–1654.

[2] R.O. Darouiche, Treatment of infections associated with surgical implants, N. Engl. J. Med. 350 (14) (2004) 1422–1429.

[3] M. Yilmaz, B. Mete, R. Ozaras, G. Kaynak, F. Tabak, Y. Tenekecioglu, et al., Aspergillus fumigatus infection as a delayed manifestation of prosthetic knee arthroplasty and a review of the literature, Scand. J. Infect. Dis. 43 (8) (2011) 573–578.

[4] M.N. Gamaletsou, B. Rammaert, M.A. Bueno, N.V. Sipsas, B. Moriyama, D.P. Kontoyiannis, et al., Aspergillus arthritis: analysis of clinical manifestations, diagnosis, and treatment of 31 reported cases, Med. Mycol. 55 (3) (2017) 246–254.

[5] C.A. Kwong, S.K. Puloski, K.A. Hildebrand, Fungal periprosthetic joint infection following total elbow arthroplasty: a case report and review of the literature, J. Med. Case Rep. 11 (1) (2017) 20.

[6] P.R. Kumashi, A. Safdar, G. Chamilos, R.F. Chemaly, I.I. Raad, D.P. Kontoyiannis, Fungal osteoarticular infections in patients treated at a comprehensive cancer centre: a 10-year retrospective review, Clin. Microbiol. Infect. 12 (7) (2006) 621–626.

[7] J.W. Kuiper, M.P. van den Bekerom, J. van der Stappen, P.A. Nolte, S. Colen, 2-stage revision recommended for treatment of fungal hip and knee prosthetic joint infections, Acta Orthop. 84 (6) (2013) 517–523.

[8] K.S. Austin, N.N. Testa, R.K. Luntz, J.B. Greene, S. Smiles, Aspergillus infection of total knee arthroplasty presenting as a popliteal cyst, Case Report. Rev. Lit. J. Arthroplast. 7 (3) (1992) 311–314.

[9] E. Mokaddas, M.H. Burhamah, S. Ahmad, Z.U. Khan, Invasive pulmonary aspergillosis due to Aspergillus terreus: value of DNA, galactomannan and (1- > 3)-beta-D-glucan detection in serum samples as an adjunct to diagnosis, J. Med. Microbiol. 59 (Pt 12) (2010) 1519–1523.

[10] T.F. Patterson, G.R. Thompson 3rd, D.W. Denning, J.A. Fishman, S. Hadley, R. Herbrecht, et al., Practice guidelines for the diagnosis and management of Aspergillosis: 2016 update by the Infectious Diseases Society of America, Clin. Infect. Dis. 63 (4) (2016) e1–e60.

[11] H.R. Ashbee, R.A. Barnes, E.M. Johnson, M.D. Richardson, R. Gorton, W.W. Hope, Therapeutic Drug Monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology, J. Antimicrob. Chemother. 69 (5) (2014) 1162–1176.

[12] W.J. Steinbach, D.K. Benjamin Jr., D.P. Kontoyiannis, J.R. Perfect, I. Lutsar, K.A. Marr, et al., Infections due to Aspergillus terreus: a multicenter retrospective analysis of 83 cases, Clin. Infect. Dis. 39 (2) (2004) 192–198.

[13] D.A. Sutton, S.E. Sanche, S.G. Revankar, A.W. Fothergill, M.G. Rinaldi, In vitro amphotericin B resistance in clinical isolates of Aspergillus terreus, with a head-to-head comparison to voriconazole, J. Clin. Microbiol. 37 (7) (1999) 2343–2345.

[14] N.P. Wiederhold, Pharmacokinetics and safety of posaconazole delayed-release tablets for invasive fungal infections, Clin. Pharmacol. 8 (2016) 1–8.

[15] U. Durani, P.K. Tosh, J.N. Barreto, L.L. Estes, P.J. Jannetto, A.J. Tande, Retrospective comparison of posaconazole levels in patients taking the delayed-release tablet versus the oral suspension, Antimicrob. Agents Chemother. 59 (8) (2015) 4914–4918.

[16] D.S. Jung, F.P. Tverdek, D.P. Kontoyiannis, Switching from posaconazole suspension to tablets increases serum drug levels in leukemia patients without clinically relevant hepatotoxicity, Antimicrob. Agents Chemother. 58 (11) (2014) 6993–6995.

[17] J.J. Deelstra, D. Neut, P.C. Jutte, Successful treatment of Candida albicans-infected total hip prosthesis with staged procedure using an antifungal-loaded cement spacer, J. Arthroplast. 28 (2) (2013) 374 (e5-8).

[18] S.L. Henry, K.P. Galloway, Local antibacterial therapy for the management of orthopaedic infections, Pharmacokinet. Consid. Clin. Pharmacokinet. 29 (1) (1995) 36–45.

[19] C. Grimsrud, R. Raven, A.W. Fothergill, H.T. Kim, The in vitro elution characteristics of antifungal-loaded PMMA bone cement and calcium sulfate bone substitute, Orthopedics 34 (8) (2011) e378–e381.

[20] K.M. Percival, J.T. Brock, N.D. Peterson, Delivery of antifungal agents from bone cement, Curr. Fungal Infect. Rep. 10 (1) (2016) 30–36.