Prosthetic finger joint infection due to *Aspergillus terreus*

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Abstract

Fungal periprosthetic joint infections (PJI) are rare but associated with significant mortality. We report a case of a finger PJI secondary to *Aspergillus terreus* in an immunocompetent patient with soil exposure, successfully treated with surgical debridement and voriconazole. Identification of *A. terreus* is important because of intrinsic amphotericin B resistance.
Case:

A 74-year-old female with a history of severe osteoarthritis of her bilateral hands underwent left ring finger proximal interphalangeal (PIP) joint arthroplasty with a silicone implant to improve functional use of the finger. At her 2-week post-operative follow up, her surgical wound was healing well. She presented one month after her initial surgery with complaints of acute redness, swelling and pain at the surgical site. She also complained of a small blister at the surgical site that drained purulent fluid. She denied fever, chills, or weight loss. Patient did not have any other medical problems other than dry eyes for which she used artificial tears eye drops. She had not been on any antibiotics recently. She had no recent travel or any pets at home. She enjoyed gardening and liked creating miniature fairy gardens. She stated that she used soil and moss in her gardening. She also maintained several bird feeders at home which were noted to be moldy. Initial vitals were unremarkable, without fever. Physical examination revealed erythema and edema at the PIP joint of the left ring finger (figure 1). A blister was noted which when unroofed, revealed a small sinus tract with purulent drainage. Laboratory work up revealed a normal white blood cell count, liver function and kidney function tests. C-reactive protein was less than 0.5 mg/DL and erythrocyte sedimentation rate was 12 mm/Hr. Human immunodeficiency virus testing was negative. X-ray of the left finger showed periprosthetic lucency and mild periosteal reaction at the middle phalanx suggesting osteolysis versus infection (figure 2). Given concern for infection, the patient underwent irrigation and debridement of the left ring PIP joint. During the surgery, purulent material was seen, and the old implant was removed with placement of a new silicone implant. Joint fluid and tissue samples were sent for culture, which subsequently grew *Aspergillus terreus* in all three sets of cultures that were sent. Unfortunately, tissue was not sent for histopathology during the procedure. She was seen by an infectious diseases physician and was started on voriconazole. Given that she had a fungal PJI, the decision was made to remove the implant two months later to ensure
eradication of infection. Tissue cultures sent during the explantation of the implant remained negative. She was continued on voriconazole for 3 additional months after the second surgery for a total of 5 months from initial surgery. At follow up patient had a well healed incision with no motion at the PIP joint but good range of motion at the distal interphalangeal joint and metacarpophalangeal joint at which time voriconazole was stopped. Plans were made to consider reimplantation arthroplasty or fusion of the joint at 3 to 6 months after stopping antifungals. At one year follow up, the incision was well healed (figure 3) and the patient did not have any pain or swelling. She was able to do all her daily activities including lifting weights, knitting and sewing. Therefore, the decision was made to not reimplant or fuse the joint. At two-year telephone follow up, the patient continued to do well with no concerns for infection.

Discussion:

Aspergillus species are ubiquitous in nature, and infection may occur after inhalation of conidia or through direct inoculation. Infection is uncommon in immunocompetent patients and occurs most frequently in the setting of immunosuppression associated with therapy for hematologic malignancies, hematopoietic cell transplantation, and solid organ transplantation. Most invasive infections are caused by members of the A. fumigatus species complex, followed by A. flavus, A. niger and A. terreus [1] [2].

A. terreus is a thermotolerant fungus found worldwide in soil, compost, dust, and decaying plant matter [3]. It is an industrially relevant fungus since its metabolites lovastatin and itaconic acid have been used as a cholesterol lowering drug and in the polymer industry respectively [4]. A. terreus is cinnamon brown in color in slide culture, unique among common Aspergillus species, and gets darker as it ages while maintaining a non-pigmented reverse (Figure 4). A. terreus conidia are small (2.0 to 2.5 um), smooth walled and can be
light yellow in color. Unique to this species is the production of aleurioconidia (Figure 5) [3].

A. terreus has been recognized as an emerging opportunistic fungus which constitutes 4% of all invasive aspergillus infections [5]. A. terreus can cause a spectrum of disease including invasive pulmonary infections, allergic bronchopulmonary aspergillosis, bronchitis and/or tracheobronchitis, and disseminated aspergillosis including at extrapulmonary sites such as the skin, brain, heart, etc [3] [6] [7]. Identification of this species has become increasingly important because of its intrinsic resistance to amphotericin B [8]. A. terreus infections are associated with higher mortality and treatment failure than infections due to other Aspergillus species. Although there are not antimicrobial susceptibility breakpoints, voriconazole is considered first-line treatment because of superior outcomes [9].

Fungal PJIs are rare and account for about 1% of all PJIs, with the majority of cases attributed to Candida species [10]. Prior bacterial PJI, preceding antimicrobial use, immunosuppressive therapy, and diabetes have been suggested as risk factors [11] [12]. PJIs due to Aspergillus spp. are extremely rare with several of the reported cases occurring in immunocompetent individuals [10] [13]. A review of the literature from 1967 to 2015 identified only 31 reported cases of Aspergillus arthritis [14]. In the article 55% of the patients were immunocompromised with conditions such as neutropenia, chronic steroid use, diabetes mellitus, etc. and likely had hematogenous seeding of their joints. Our patient who was immunocompetent likely acquired the infection through direct inoculation as suggested in this article. We postulate that our patient acquired her infection through direct inoculation of her incision with the organism while gardening. Soil in potted plants has been postulated as a source of nosocomial Aspergillus infections [15]. Clinical manifestations include pain (87%), edema (26%), and limited function (23%), with knees (35%), intervertebral discs (26%), and hips (16%) being most commonly affected. Aspergillus fumigatus constituted 77% of cases followed by Aspergillus flavus in 13%, Aspergillus niger in 3%, and species not
specified in 7% [14]. A review article on Aspergillus osteomyelitis (excluding septic arthritis and PJI) by Gameletsou et al. demonstrated *A. terreus* as the etiology of infection in only 3% (5/180) of the cases [16]. There are only a handful of PJs secondary to *Aspergillus terreus* reported to date [14] [17] [18]. To the best of our knowledge, our case is the first case of a finger PJI secondary to *A. terreus*.

Diagnosis of fungal PJI is made by histopathological examination and culture in concert with clinical and radiological findings. Though tissue was not sent for histopathology in our case, it is an important tool to define the diagnostic significance of positive culture results when contamination is suspected. *A. terreus* infections may produce high levels of serum galactomannan, however serum galactomannan was negative in our case and the other PJI case reported in the literature due to *Aspergillus terreus* [18]. This is likely because these infections are limited to the joint and are not disseminated. Therefore, PJI should still be suspected in the presence of negative serum fungal markers. If Aspergillus species is isolated from a joint, it should be considered a true pathogen and treated appropriately [14].

Fungal PJs are not only difficult to diagnose but are challenging to treat. Guidelines for the treatment of PJI published by the Infectious Diseases Society of America (IDSA) do not address the treatment of fungal PJs [19]. However, IDSA guidelines on management of Aspergillus infections do recommend voriconazole as first-line treatment for all invasive aspergillus infections with liposomal amphotericin B and isavuconazole as alternative options [20]. Successful treatment of fungal PJs including infections caused by *Aspergillus spp.* require both a surgical and medical approach [17] [21]. According to a review of 31 reported *Aspergillus* cases, nineteen patients (61%) were managed with combined medical and surgical therapy, 10 (32%) with medical therapy only, and 2 (6%) surgery only [14]. Amphoterin B and itraconazole were the most frequently used agents with median duration
of therapy of 219 days (range 30–545). Complete response of Aspergillus arthritis was achieved in 22 cases (71%), partial response in 5 (16%), relapse in 5 (16%), and death in 11 (35%). Voriconazole is the drug of choice for first-line treatment of infections due to A. terreus since this organism is inherently resistant to amphotericin B [3] [22]. Limited data is available for itraconazole, posaconazole, isavuconazole or caspofungin. There are reports of cases successfully treated with posaconazole, while the resistance rate of A. terreus to posaconazole in European countries was reported to be around 5% [18] [23]. In our case, the patient was treated with voriconazole for 5 months with removal of the infected prosthesis and resolution of infection. A patient with Aspergillus terreus PJI in a total elbow arthroplasty was successfully treated with 2 debridements followed by definitive resection arthroplasty and eight weeks of caspofungin, followed by a short course of voriconazole [12]. Another case of PJI due to A. terreus in a total hip arthroplasty was treated with resection of hardware and posaconazole though the duration of treatment was not mentioned [18]. Given the association with higher mortality and treatment failure, prospective studies are needed to investigate the optimal agent and the treatment duration for PJI due to A. terreus.

In conclusion, fungal periprosthetic joint infection due to Aspergillus species is rare but is associated with significant cost and morbidity. Aspergillus spp. need to be considered as an etiology of joint infection even in immunocompetent patients. Identification of A. terreus has become increasingly important because of its intrinsic resistance to amphotericin B and treatment with voriconazole is associated with better outcomes.

**Funding:** none

**Patient consent:** The patient’s written consent was obtained.

**Ethical approval:** The local ethical committee approval dose not apply in this case.

**Conflict of interest:** no disclosures
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**Figure 1:** Swelling and erythema demonstrated at the left ring finger PIP joint. Slight wound dehiscence with purulent drainage noted from this area. Exam noted minimal motion at the PIP joint.
Figure 2:

X-ray of left ring finger showed periprosthetic lucency and mild periosteal reaction at middle phalanx concerning for infection.
Figure 3: no swelling or erythema seen at 1 year follow up.
Figure 4: *Aspergillus terreus* complex grow moderately rapidly on potato flake media to form a cinnamon-brown velvety colony.
**Figure 5:** *Aspergillus terreus* complex produce vesicle with biseriate phialides over the top half. Aleurioconidia (asexually reproduced conidia) are indicated (lactophenol aniline blue, x1000)