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NOVEL ID CASES

A Canker Barking at the Wrong Knee: *Thyronectria austroamericana* Septic Arthritis

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The mold *Thyronectria austroamericana* is a plant pathogen that causes canker in honey locust trees. We describe the first case of this mold causing septic arthritis in humans.

Keywords. fungal septic arthritis; *Thyronectria austroamericana*.

CASE REPORT

A 78-year-old man from Missouri with a history of hypertension, coronary artery disease, and poorly controlled diabetes mellitus presented to the hospital with worsening left knee pain with warmth and swelling over the past 2 months. Notably, he had twisted his left knee 6 months previously, resulting in mild pain and swelling. The patient did not recall having any penetrating wound or skin tears, but noted he is an avid gardener who often kneels on mulch without any protection. Radiographs at the time showed a moderate joint effusion and his symptoms initially improved with analgesics. However, 2 months prior to presentation, his symptoms progressed. Physical examination revealed tenderness, decreased range of motion, and effusion of the left knee. This prompted an arthrocentesis that found straw-colored, cloudy fluid with 25 223 nucleated cells/μL (77% neutrophils), and no crystals or organisms on the Gram stain. Fluid culture showed no growth, and he was treated with an intra-articular steroid injection. However, symptoms persisted, and he developed a flexion contracture that led to the current visit. A new arthrocentesis was performed and showed 50 206 nucleated cells/μL (70% neutrophils). Within 48 hours the aerobic culture grew an unidentified mold, initially suspected to be a contaminant. A confirmatory arthrocentesis to exclude the existence of a true pathogen again grew mold. Magnetic resonance imaging of the knee showed medial and lateral meniscus tears with synovial hypertrophy compatible with synovitis, and a moderate to large effusion. The patient underwent arthroscopic debridement and intraoperative findings were significant for purulent synovial fluid, fibrin, and debris at the suprapatellar pouch and throughout the knee, plus a tear of medial and lateral meniscus. There were numerous small white spots lining the synovium (Figure 2A). Histopathology of the synovial tissue showed multinucleated giant cells mixed with a neutrophilic infiltrate. The Gomori methenamine silver stain revealed nonpigmented fragmented hyphal fungal forms that appeared to be septate and branched at 45 to 90 degrees (Figure 2B). Multiple intraoperative synovial fluid and tissue samples were sent for fungal cultures and all grew a mold, later identified as *Thyronectria austroamericana*, using Sanger sequencing (D2 rDNA target) with 100% match (National Center for Biotechnology Information, GenBank library). Susceptibility testing showed minimum inhibitory concentrations of 0.06 μg/mL for itraconazole and >8 μg/mL for micafungin. All blood cultures were negative, and a fourth-generation human immunodeficiency virus test was nonreactive.

The patient was initially treated with liposomal amphotericin B 3 mg/kg/day for 7 weeks and later transitioned to itraconazole oral solution without reported side effects. However, after 4 weeks of itraconazole, his symptoms worsened despite good adherence and therapeutic serum drug level (1.3 and 1.9 μg/mL). Because of poor response, itraconazole was changed to isavuconazole for preferable pharmacokinetics. Unfortunately, there was some delay initiating isavuconazole due to financial issues (clinical timeline as illustrated in Figure 1). After starting isavuconazole, the patient had progressive improvement without any side effects. After 12 months of treatment, he achieved complete resolution of the pain and swelling and regained normal function of his left knee. Thus, isavuconazole was discontinued. At the 6-month follow-up, the patient remains symptom free.

DISCUSSION

Fungal infection is an uncommon cause of chronic septic arthritis but is increasingly seen in immunocompromised or chronically ill patients, although it may sometimes occur in normal hosts [1]. The most common organisms causing septic fungal arthritis are *Candida* and *Aspergillus* species [2–4]. Despite being an extremely rare cause of septic arthritis, molds other than *Aspergillus* have been reported as potential emerging pathogens [4]. A prior systematic review of osteoarticular infections caused by

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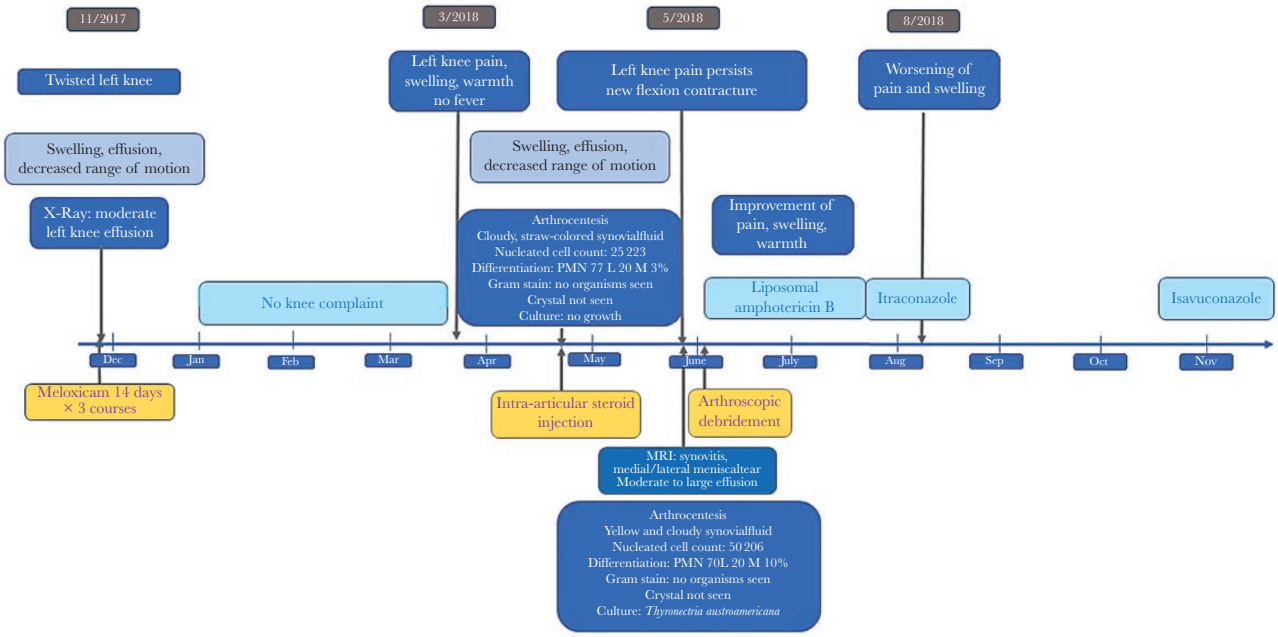

Figure 1. Clinical timeline. Abbreviations: MRI, magnetic resonance imaging; PMN, polymorphonuclear cells.

non-*Aspergillus* filamentous fungi found hyaline hyphomycetes to be the most common etiologic agent (67%), followed by dematiaceous mold (17%) and mucormycetes (16%) [4].

The mold *Thyronectria austroamericana* (homotypic synonym *Pleonectria austroamericana*, *Nectria austroamericana*) is in the family Nectriaceae, which includes about 20 genera and is a well-known plant pathogen that causes canker in honey locust (*Gleditsia triacanthos*; Figure 2C) [5–7].

In plants, the infection caused by this organism manifests as sunken, dead areas of bark (Figure 2D), die-back, reduced or yellow foliage, premature fall coloration, and early leaf drop [7]. It is noteworthy that the honey locust tree is native to central

Figure 2. *A*, Arthroscopic findings with numerous small white spots lining the synovium. *B*, Gomori methenamine silver stain of synovial tissue (photo courtesy of Dr Edward Bolesta, reproduced with permission). *C*, Honey locust tree (photo courtesy of Missouri Botanical Garden, reproduced with permission). *D*, Canker disease in honey locust (photo courtesy of Professor William Jacobi, reproduced with permission).

North America, and Missouri is in the natural range of distribution of this plant [8, 9]. Although this particular species has only been found in America, an asexual morph has also been described in Europe [6]. To the best of our knowledge, this is the first case report of this mold causing human infection.

The localization of the septic arthritis in this patient's knee is consistent with the most common joint involved in other cases of mold septic arthritis [1, 4, 10]. Further interview revealed that the patient had a honey locust tree in his backyard, where he often spent time kneeling while cultivating vegetables at his garden. Although the patient was not severely immunosuppressed, he had poorly controlled diabetes and had received an intra-articular steroid injection, which are known predisposing factors for fungal septic arthritis [1, 2, 11–13]. We hypothesize that he acquired the infection through direct inoculation, with an unrecognized minor penetrating injury serving as a portal of entry. Subsequent intra-articular steroid injection hindered the local immune response, creating the perfect milieu for worsening infection. Presumably, underlying poorly controlled diabetes leading to impaired cellular immunity is partly contributing.

Treatment of fungal arthritis often requires a combination of surgical debridement and prolonged antifungal therapy [1, 3, 4, 10, 13]. Amphotericin B has been the drug of choice of most fungal infections for several decades, but its toxic effects and lack of an equivalent oral form often limit its long-term use [3, 14]. Among triazoles, voriconazole combined with surgical intervention is the standard treatment for *Aspergillus* osteomyelitis and septic arthritis. Itraconazole and posaconazole have also been effectively used in a wide range of rare mold osteoarticular infections, as described in case reports [4, 14–17].

Isavuconazole (the active form of prodrug isavuconazonium sulfate) is a newer triazole, which is active against a broad spectrum of clinically important fungi, including in vitro activity against some hyaline and dematiaceous molds [18]. It was approved by the US Food and Drug Administration in March 2015 for the treatment of adults with invasive aspergillosis and mucormycosis. Compared to voriconazole, it has more predictable pharmacokinetics with low interpatient variability and less adverse skin, hepatobiliary, and visual side effects [19]. Unlike other triazoles, most studies have not shown an association with isavuconazole and QTc prolongation [20]. To date, there has not been a report of non-*Aspergillus*, non-Mucorales mold arthritis specifically treated by isavuconazole. Nevertheless, based on the mechanism of action, pharmacological properties, and previous clinical studies [19, 21, 22], we reasonably believed that *T austroamericana* was effectively treated by isavuconazole. The clinical response seen in our patient supports our hypothesis.

CONCLUSIONS

Molds are an extremely rare cause of septic arthritis, usually seen in immunosuppressed patients, but can be found in immunocompetent hosts with chronic comorbidities. *Thyronectria austroamericana* is first described here as an unusual cause of septic arthritis in humans. Successful treatment was achieved by surgical debridement in combination with prolonged antifungal therapy. Isavuconazole following induction with amphotericin B proved to be an effective and well-tolerated step-down for consolidation in this unusual mold infection.

Notes

Patient consent statement. Ethics approval or consent to participate was not applicable. Written consent for publication was obtained from the patient.

Potential conflicts of interest. A. S. has received grant support from Astellas and Mayne and has served as a consultant for Mayne, Scynexis, Viamet, Astellas, and Minnetronix. All other authors report no potential conflicts of interest.

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