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

Sasinuch Rutjanawech¹, Carlos Mejia-Chew¹, Chapelle Ayres¹, and Andrej Spec¹

¹Division of Infectious Diseases, Washington University School of Medicine in St. Louis, Missouri, USA

CONFLICT OF INTEREST

- AS: Grant support from Astellas and Mayne. Consulting for Mayne, Scynexis, Viamet, Astellas, Minnetronix.
- All other authors: none to declare

CORRESPONDING AUTHOR

Andrej Spec, MD
Instructor, Infectious Disease
Associate Director, Infectious Disease Clinical Research Unit
4523 Clayton Ave., Campus Box 8051
St Louis, MO, 63110-0193
T: 314.747.1725
F: 314.454.8294
E: andrejspec@wustl.edu

© The Author(s) 2021. Published by Oxford University Press on behalf of Infectious Diseases Society of America.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
ABSTRACT

The mold *Thyronectria austroamericana* is a plant pathogen that causes canker in honey locust tree. 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 male 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 two months. Notably, he twisted his left knee six months ago 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. X-Ray at the time showed a moderate joint effusion and his symptoms initially improved with analgesics. However, two 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 (GMS) stain revealed non-pigmented 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 (NCBI Genebank library). Susceptibility testing showed a minimum inhibitory concentration (MIC) of 0.06 µg/mL for itraconazole and >8 µg/mL for micafungin. All blood cultures were negative, and a fourth generation HIV test was non-reactive.

He was initially treated with liposomal amphotericin B 3mg/kg/day for seven weeks and later transitioned to itraconazole oral solution. However, after four weeks of itraconazole, his symptoms worsened despite therapeutic serum drug level (1.3 and 1.9 mcg/mL). Because of poor response, itraconazole was changed to isavuconazole. 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, swelling and normal function of his left knee. Thus, isavuconazole was discontinued. At the six-month follow up, the patient remains symptom free.

**DISCUSSION**

Fungal infection is an uncommon cause of chronic septic arthritis, but 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) In spite of 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 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 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 back yard, 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 intraarticular 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 and the intraarticular steroid injection hindering the local immune response, created the perfect milieu for worsening infection.

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 limits 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 (FDA) 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 Thyronectria austroamericana was effectively treated by isavuconazole. The clinical response seen in our patient supports our hypothesis.

CONCLUSION

Molds are an extremely rare cause of septic arthritis, usually seen in immunosuppressed patients but can be found in immunocompetent host 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.

PATIENT CONSENT STATEMENT

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

1. Ohl CA, Forster D. Infectious Arthritis of Native Joints. In: Bennett JE, Dolin R, and Blaser MJ, editor. Mandell, Douglas, and Bennett’s principles and practice of infectious diseases. 8th ed. Philadelphia: Elsevier Saunders; 2015. p. 1302-17.

2. Bariteau JT, Waryasz GR, McDonnell M, Fischer SA, Hayda RA, Born CT. Fungal osteomyelitis and septic arthritis. J Am Acad Orthop Surg. 2014;22(6):390-401.

3. Henry MW, Miller AO, Walsh TJ, Brause BD. Fungal Musculoskeletal Infections. Infectious disease clinics of North America. 2017;31(2):353-68.

4. Taj-Aldeen SJ, Rammaert B, Gamaletsou M, Sipsas NV, Zeller V, Roilides E, et al. Osteoarticular Infections Caused by Non-Aspergillus Filamentous Fungi in Adult and Pediatric Patients: A Systematic Review. Medicine (Baltimore). 2015;94(50):e2078.

5. NCBI. Taxonomy Browser [cited 2021 February 21]. NCBI Taxonomy Database. Available from: https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=1490972.

6. Jaklitsch WM, Voglmayr H. Persistent hamathecial threads in the Nectriaceae, Hypocreales: Thyronectria revisited and re-instated. Persoonia. 2014;33:182-211.

7. Jacobi WR. Honeylocust Diseases 2013 [cited 2021 February 21]. Available from: https://extension.colostate.edu/topic-areas/yard-garden/honeylocust-diseases-2-939/.

8. Missouri Botanical Garden. Gleditsia triacanthos [cited 2021 February 22]. Available from: http://www.missouribotanicalgarden.org/PlantFinder/PlantFinderDetails.aspx?kempercode=a871.

9. Wikipedia. Honey locust [updated February 21, 2021; cited 2021 February 21]. Available from: https://en.wikipedia.org/wiki/Honey_locust.

10. Kohli R, Hadley S. Fungal arthritis and osteomyelitis. Infectious disease clinics of North America. 2005;19(4):831-51.
11. Cuellar ML, Silveira LH, Citera G, Cabrera GE, Valle R. Other fungal arthritides. Rheum Dis Clin North Am. 1993;19(2):439-55.
12. Cuellar ML, Silveira LH, Espinoza LR. Fungal arthritis. Ann Rheum Dis. 1992;51(5):690-7.
13. Kumashi PR, Safdar A, Chamilos G, Chemaly RF, Raad, II, Kontoyiannis DP. Fungal osteoarticular infections in patients treated at a comprehensive cancer centre: a 10-year retrospective review. Clin Microbiol Infect. 2006;12(7):621-6.
14. Perez-Gomez A, Prieto A, Torresano M, Diez E, Mulero J, Labiano I, et al. Role of the new azoles in the treatment of fungal osteoarticular infections. Semin Arthritis Rheum. 1998;27(4):226-44.
15. Koehler P, Tacke D, Cornely OA. Bone and joint infections by Mucorales, Scedosporium, Fusarium and even rarer fungi. Crit Rev Microbiol. 2016;42(1):158-71.
16. Beaudreuil S, Buchler M, Al Najjar A, Bastides F, Francois M, Duong TH, et al. Acute septic arthritis after kidney transplantation due to Acremonium. Nephrol Dial Transplant. 2003;18(4):850-1.
17. Tirado-Miranda R, Solera-Santos J, Brasero JC, Haro-Estarriol M, Cascales-Sanchez P, Igualada JB. Septic arthritis due to Scedosporium apiospermum: case report and review. J Infect. 2001;43(3):210-2.
18. Miceli MH, Kauffman CA. Isavuconazole: A New Broad-Spectrum Triazole Antifungal Agent. Clin Infect Dis. 2015;61(10):1558-65.
19. Maertens JA, Raad, II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet. 2016;387(10020):760-9.
20. Wilson DT, Dimondi VP, Johnson SW, Jones TM, Drew RH. Role of isavuconazole in the treatment of invasive fungal infections. Ther Clin Risk Manag. 2016;12:1197-206.

21. Marty FM, Ostrosky-Zeichner L, Cornely OA, Mullane KM, Perfect JR, Thompson GR, 3rd, et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis. 2016;16(7):828-37.

22. Cornely OA, Mullane KM, Ostrosky-Zeichner L, Maher RM, Croos-Dabrera R, Lu Q, et al. Isavuconazole for treatment of rare invasive fungal diseases. Mycoses. 2018;61(8):518-33.
Figure 1: Clinical timeline
Figure 2 A: Arthroscopic findings with numerous small white spots lining the synovium, B: GMS stain of synovial tissue (Photo by courtesy of Dr. Edward Bolesta, reproduced with permission), C: Honey locust tree (Photo by courtesy of Missouri Botanical Garden, reproduced with permission), D: Canker disease in honey locust (Photo by courtesy of Professor William Jacobi, reproduced with permission)