CASE REPORT

Coccidioides immitis septic knee arthritis

Scott A Weisenberg

Department of Medicine, New York University School of Medicine, New York, USA

Correspondence to
Dr Scott A Weisenberg, scott.weisenberg@nyumc.org

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SUMMARY

A 78-year-old man developed right knee pain and swelling without other systemic symptoms. He had travelled frequently to the Central Valley of California. He was diagnosed with coccidioidomycosis based on joint fluid culture. Coccidioidal complement fixation antibody titres were extremely elevated. Arthroscopic debridement and fluconazole therapy did not lead to satisfactory improvement. Subsequent open debridement and change to itraconazole was followed by resolution of clinical signs of infection.

BACKGROUND

Coccidioidomycosis is caused by the dimorphic fungi *Coccidioides immitis*, and *C. posadasii*. Over half of infections are asymptomatic. Among symptomatic patients, the most common presentation is an acute pneumonia often with headache and fatigue.[1] A minority of symptomatic patients require antifungal treatment. Bone and joint infection with *Coccidioides* can occur and represents disseminated disease.[2 3] Optimal treatment of *Coccidioides* septic arthritis is not defined in recent guidelines.[4] Surgical treatment is often recommended,[5] though some experts find that infection limited to the synovium can be treated medically.[6] We present a case where aggressive surgical and medical therapy were necessary to obtain a good long-term outcome.

CASE PRESENTATION

A 78-year-old man presented with right knee pain that began in May 2013. The pain improved with treatment which included pain medications, physical therapy and arthroscopy in 2013. Imaging did not suggest an erosive process and there was no suspicion of infection by the treating clinicians. His pain returned and he presented with several months of worsening right knee pain and swelling around March 2014. He did not have fever, chills, night sweats, weight loss or other systemic symptoms. Of note, he had cough and evidence of pneumonia with a lower lobe infiltrate on chest imaging in March 2013, and was treated for community-acquired pneumonia. Cough subsequently resolved. The chest imaging findings were resolved by his 2014 presentation.

His medical history included hypertension and a remote history of splenectomy after trauma. He is a former smoker. He smoked about a pack a week to a pack a month since he was a teenager, and had smoked even less in recent years.

He lived in the San Francisco Bay area and travelled frequently to the Central Valley of California.

INVESTIGATIONS

Findings from MRI in April 2014 included a large joint effusion, severe synovitis, large cortical erosions and loss of cartilage. Oedema was described in the posterior compartment muscles, and a 2.2 cm soft tissue mass was seen in the anterior-medial soft tissues.

Right knee joint arthrocentesis in April 2014 revealed 2475 white blood cells/µL, with 90% lymphocytes. Joint culture from the arthrocentesis grew a mould identified as *Coccidioides* species. Subsequent molecular identification identified it as *C. immitis*. Cultures from subsequent debridements in April 2014 and September 2014 also grew *C. immitis*.

Coccidioidal complement fixation titre was positive at 1:1024 (Focus Diagnostics Inc., Cypress, CA).

Erythrocyte sedimentation rate was 113 in April 2014. Absolute eosinophil count (AEC) was 600 cells/µL (0–500) in July 2013 (before diagnosis). AEC ranged from 500 to 700 cells/µL when he represented in March and April 2014.

DIFFERENTIAL DIAGNOSIS

His initial differential diagnosis included non-infectious causes of knee pain, including mechanical causes and inflammatory arthritis. Among infectious aetiologies, the indolent course suggested a fungal or mycobacterial cause, though other pathogens were not excluded.

TREATMENT

His initial surgery in the April 2014 included debridement, extensive synovectomy and a partial lateral meniscectomy. He was treated with fluconazole 800 mg/day.

He continued to experience right knee pain, swelling and warmth. His infection was not considered to be under adequate control.

In September 2014, he underwent open surgery with additional debridement. Culture again grew *C. immitis*. The antifungal was changed to itraconazole 200 mg two times per day due to the possible superiority in skeletal disease over fluconazole.[7 8] Liposomal amphotericin was considered, but was not chosen due to toxicity risk after discussion of risk benefit with the patient. Antifungal susceptibility testing was not performed.

OUTCOME AND FOLLOW-UP

He continued to have severe pain and local swelling after the first surgery in April 2014. After the second surgery in September 2014 and change to

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itraconazole, he exhibited progressive improvement with eventual resolution of all prior signs of infection. He has no right knee pain, swelling or disability, though he does have some stiffness. Itraconazole levels have been therapeutic, and he has exhibited no medication toxicities aside from mild indigestion.

Coccidioidal complement fixation (CF) titre was 1:1024 at diagnosis (Focus Diagnostics) in April 2014. Six months into treatment, CF titre was 1:256 at the University of California (UC) Davis (Coccidioidomycosis Serology Laboratory, Davis, California, USA). Fourteen months after his initial diagnosis, CF titre was 1:64 at UC Davis, which decreased to 1:8, 2.5 years into treatment. Three years after diagnosis, CF Ab titre was down to 1:4 at UC Davis (where samples are compared with retested prior samples).

Baseline erythrocyte sedimentation rate (ESR) was 113. It was down to 55 by the time of the second surgery, and subsequently improved to 4 on therapy. Absolute eosinophil count reduced into the normal range after the second surgery.

He remained on long-term itraconazole therapy. He was changed back to fluconazole in June 2017 due to intestinal side effects, and his knee continued to do well with plans for lifelong suppression.

DISCUSSION

Coccidioidomycosis is an increasingly prevalent fungal infection caused by *C. immitis* and *C. posadasii*. *Coccidioides* species are dimorphic fungi whose mould phase grows in desert soil in endemic regions. Arthroconidia arise from branching septate hyphae, detach and may remain stable in the environment for years. Human infection occurs via inhalation of aerosolized arthrocondia.[9] Inside the lung, large endospore-containing spherules are formed.[10] Coccidioidomycosis occurs in desert areas of California, Arizona and other Western States, as well as areas of Mexico, Central and South America.[9]

Coccidioides species most commonly cause asymptomatic infection or acute pneumonia,[1] and recovery from symptomatic disease often takes several months.[11] A small percentage of patients develop extrapulmonary or disseminated disease.[10] Many patients with disseminated coccidioidomycosis experience a preceding illness consistent with primary coccidioidomycosis within the previous 2 months but others present months or even years after primary infection.[2 12] In the case patient, the cough and pulmonary infiltrate in the March 2013 may well have been a primary infection that preceded his knee infection, though a coincidental bacterial community-acquired pneumonia cannot be excluded.

Identifying patients at risk for disseminated coccidioidomycosis can be challenging. Patients with known immunosuppression and pregnancy have increased risk for disseminated disease, as do diabetics and those with cardiopulmonary disease.[3] Discrete primary immune deficiencies involving the transcription 3 (STAT3) and interleukin-12/interferon-γ have been discovered in some patients with disseminated disease.[13] Racial and ethnic differences in risk of disseminated disease have been noted, including increased risk for disseminated disease among blacks and Filipinos.[3]

Among patients with disseminated coccidioidomycosis, some have bone and joint disease in either the vertebrae or peripheral bones and joints. In most cases of peripheral joint coccidioidal septic arthritis, the involved joint is the only site of clinical disease, though in a minority of patients other organs are involved in active infection.[14] Contiguous bone involvement is common and represents a potential site of relapse.[2] The clinical course of infected patients is variable, and some patients may exhibit a chronic fluctuating course.[14]

Diagnosis of coccidioidal septic arthritis can be confirmed by fungal culture, pathology specimens and serology.[1] For any cultured material, laboratory personal must be notified due to infectious risk.[15] Pathology specimens should always be sent with suspected infection and show granulomatous inflammation with diagnostic spherules. Serology for immunoglobulin (Ig)M and IgG antibodies should be sent in suspected cases using immunodiffusion and complement fixation.[16] Complement fixation titres of $\geq$1:16 are associated with disseminated disease,[10] and CF titres of $\geq$1:256 are associated with increased relapse risk after therapy.[17] MRI can define the extent of infection in and around an involved joint.[18] Looking forward, molecular testing may expedite diagnosis.[19]

Treatment for coccidioidomycosis is typically with azoles. In a subgroup analysis from a randomised, double-blind trial, itraconazole was superior to fluconazole for coccidioidal bone infection.[7] Itraconazole requires monitoring of drug levels. Amphotericin B is used for limb-threatening infection,[4] though side effects remain problematic. We did not use amphotericin in this case after careful consideration of risks and benefit. Azole treatment for bone and joint infection is often for several years or lifelong.[5] Elevations in fluconazole mean inhibitory (MIC) are common compared with mold-active azoles, though the clinical significance of fluconazole MIC elevations and role of resistance testing remains to be determined.[8 20] Some experts feel that antifungal susceptibility testing should be performed based on existing data,[8] though others disagree (personal communications). Susceptibility was not performed in this case. Studies on the effect of in vitro antifungal resistance on clinical outcomes are urgently needed.

Surgical or arthrocentesis drainage is necessary for optimal cure of most pathogens causing bacterial septic arthritis.[21] Surgery is often, but not always used to treat dimorphic fungal septic arthritis.[22] Surgery has been felt necessary to cure coccidioidal septic arthritis in pre-azole eras,[14] though others noted success in select patients treated medically.[12 23] Current guidelines make no recommendations on non-vertebral bone and joint coccidioidal infection.[4] Experts have commented that surgical debridement may not be necessary for cases limited to the synovium,[6] though others recommend synovectomy in addition to antifungal therapy.[5] The soft tissue and bone involvement in the case patient were likely factors that required debridement as well as prolonged medical therapy for clinical control in the case patient, as opposed to other patients who have responded to medical therapy.[12] Systematic analysis of treatments and outcomes of published and non-published cases, as well as ongoing coordination and discussion of experts through collaborative working groups,[20] may better define optimal treatment for individual patients.

This case report illustrates the challenges of caring for patients with coccidioidal septic arthritis. The largest barrier to successful treatment is probably consideration of the diagnosis. Surgical pathology specimens and cultures, as well as serologic testing, should be performed early in suspected cases. Potential weaknesses of this case report include lack of pathology and, in the eyes of some experts, lack of antifungal susceptibility testing.[8] Furthermore, lack of consideration of *C. immitis* as a potential cause for the pneumonia the year previous makes the relationship of that respiratory infection to his subsequent course unclear.

C. immitis is an unusual cause of septic arthritis, but should be considered and sought in patients with epidemiological risk factors. As shown the case patient, accurate diagnosis followed

by appropriate therapy can lead to a long-term satisfactory outcome.

Learning points

- Coccidioidomycosis should be included in the differential diagnosis of patients with septic arthritis after travel to endemic areas.
- Septic arthritis caused by *Coccidioides* species in some cases requires aggressive surgical as well as prolonged medical therapy.
- Long-term control can be achieved in patients with coccidioidal septic arthritis with a good functional outcome.

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