CASE REPORT

First reported case of peroneal tenosynovitis caused by *Coccidioides immitis* successfully treated with fluconazole

Aneela Majeed,¹ Waqas Ullah,² Auon Abbas Hamadani,² Anca Georgescu¹

¹Infectious Disease Division, Department of Medicine, University of Arizona, Tucson, Arizona, USA

²Department of Medicine, University of Arizona, Tucson, Arizona, USA

Correspondence to

Dr Aneela Majeed, amajeed@deptofmed.arizona.edu

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SUMMARY

Coccidioidomycosis is an insidious infection caused by *Coccidioides* spp (*C. immitis* and *C. posadasii*). Disseminated disease occasionally involves tendon sheaths and synovium of the joints leading to tenosynovitis. Here, we describe the case of a 72-year-old woman from southern Arizona, who presented with right ankle pain, redness and swelling for 2 months. Her serum IgG was positive for *C. immitis* on complement fixation, and her MRI of the right ankle joint showed extensive tenosynovitis of the right peroneal tendons, and subtalar joint effusions with associated synovitis. The purpose of this case is to report an extremely rare manifestation of disseminated *C. immitis*, that is, peroneal tenosynovitis and challenges involved with diagnosis and treatment. We also document that azole therapy is an effective treatment option for peroneal tenosynovitis caused by *C. immitis*, and we had to double the dose for slow symptom resolution with 4-week trial with usual 400 mg oral dose of fluconazole.

BACKGROUND

Coccidioidomycosis is a fungal infection caused by *Coccidioides immitis* and *Coccidioides posadasii* first recognised by Posades and Wernicke in 1892.¹ Coccidioidomycosis usually causes a self-limiting pulmonary illness in immunocompetent individuals. However, immunologically compromised patients are at higher risk of disseminated disease, and it can manifest as osteomyelitis, septic arthritis or tenosynovitis. Occasionally, immunocompetent patients can present with disseminated disease.

Tenosynovitis presents with pain, swelling and erythema of the involved tendon sheaths and synovial. Patient can have constitutional symptoms like fatigue, myalgia, fever and night sweats. Diagnosis is usually made on findings based on clinical ground, by culturing the causative agent or by serological testing. Complement fixation testing (CFT) is considered diagnostic. Treatment involves the use of antifungal azoles and in severe cases high-potency antifungal agents along with surgical debridement. We present a rare case of *Coccidioides* induced right lower extremity peroneal tenosynovitis.

CASE PRESENTATION

A 72-year-old Caucasian woman presented with a 2-month history of right ankle pain and swelling. She described the pain as sharp and localised to the right ankle, with occasional radiation to the right

leg, aggravated by movement and relieved by rest. Her symptoms had been progressively getting worse and interfering with her activities of daily living. She also reported of fatigue and myalgias for the past 3 months. She had been living in Tucson, Arizona for the past 8 years. She reported having pneumonia in 2003 when she was living in Nevada from which she recovered completely after a course of intravenous antibiotics followed by an oral regimen. She reports no other respiratory symptoms, until she had an upper respiratory infection (URI) in 3 months ago with no residual pulmonary issues/symptoms. Chest x-ray was normal. She denied shortness of breath, productive cough, pleurisy, haemoptysis, dyspnoea on exertion, weight loss, fevers, but have night sweats for the past 3 years since she stopped her oestrogen replacement therapy. She had no previous history of diabetes, immunosuppressants/steroid use or HIV risk factors. She was evaluated by rheumatology in the past and received trial of colchicine for possible pseudogout. She was treated for pseudogout with colchicine and nonsteroidal anti-inflammatory drugs (NSAIDs) without significant improvement.

On admission to hospital for diagnosis and management of worsening symptoms of pain, she was afebrile and had a normal heart rate, respiratory rate and blood pressure. She was found to have right ankle joint swelling, erythema and tenderness. She had decreased range of movement at the right ankle joint. There was no cyanosis, clubbing or oedema. The pulses were 2/2 bilaterally. Rest of the systemic examination was unremarkable.

INVESTIGATIONS

Laboratory investigations revealed white cell count counts of 5.7 cells/ μ L with no eosinophilia, a haemoglobin of 11.3 mg/dL and thrombocytopenia with a platelet count of $29 \times 103/\mu$ L. Her serum sodium, potassium and calcium levels were 136 mEq/L, 3.9 mEq/L and 9.4 mg/dL, respectively. Her renal function tests, ESR (18 mm/hour) and CRP (0.39 mg/dL) were within normal limits. Her HIV by ELISA was negative, and her random blood sugar levels were 112 mg/dL. She had positive quantiferon gold test consistent with latent tuberculosis (TB). Axial fat-saturated T2-weighted MRI of right foot shows extensive bone marrow oedema involving all three cuneiforms bones and complex synovial fluid surrounding the peroneal sheaths (figure 1). Postcontrast T1 MRI images showed

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Figure 1 Axial fat-saturated T2-weighted image of right foot shows extensive bone marrow oedema involving the all three cuneiforms bones (arrows) and complex synovial fluid surrounding the peroneus longus and brevis tendon sheath.

abnormal heterogenous enhancing signal in distal peroneus brevis tendon in keeping with tendinopathy with abnormal enhancement of the complex synovial fluid representing tenosynovitis (figure 2). Similarly, postcontrast T2-weighted MRI images showed enhancement of peroneal tendons on postcontrast images representing with tenosynovitis (figure 3). Consequently, she underwent a direct sampling by synovial fluid aspiration and bone biopsy. The synovial fluid total leucocyte

Figure 2 On postcontrast T1 fat-saturated gradient echo sequences of right foot and ankle in sagittal planes show abnormal heterogenous enhancing signal in distal peroneus brevis tendon in keeping with tendinopathy with abnormal enhancement of the complex synovial fluid representing with tenosynovitis.

Figure 3 There is complex synovial fluid on fat-saturated T2-weighted images surrounding the peroneus longus and brevis tendon sheath, which shows enhancement on postcontrast images representing with tenosynovitis (arrow).

count was 89 with 68% neutrophils, 23% lymphocytes, 5% monocyte and 4% eosinophils. Fungal and bacterial cultures remained negative, histology was performed that showed minute fragment of viable cortical bone, with no evidence of osteomyelitis, and negative for malignancy. Her serum *C. immitis* antibody IgG by complement fixation was positive with titres 1:64 but negative for IgM antibodies. PCR testing was considered but was not performed due to significantly high cocci IgG titres.

DIFFERENTIAL DIAGNOSIS

On presentation, the differential diagnosis was broad and included cellulitis, osteomyelitis, TB and fungal infections. However, subsequently these possibilities were ruled out by negative laboratory investigations. The duration of symptoms prior to presentation made a typical bacterial infection less likely. Osteomyelitis was ruled out by MRI and pathology findings. The patient improved in the absence of anti-TB treatment, thus making this diagnosis less likely.

TREATMENT

Patient was started on oral fluconazole 400 mg daily with no clinical improvement after 4 weeks of therapy. Titres subsequently increased to 1:128 after a month on treatment, and fluconazole dose was increased to 800 mg daily with significant improvement in symptoms in ~3 weeks on higher dose. Patient declined therapy for latent TB and could not recall any particular history of exposure for TB.

OUTCOME AND FOLLOW-UP

She was subsequently discharged home on pain medications and fluconazole, and was evaluated 3 times in the next 7 months. She continued to improve clinically, with resolution of the ankle oedema and significant pain improvement on high fluconazole dose. *C. immitis* antibody IgG titres decreased from 1:128 to 1:32 after 7 months of therapy. The plan is to decrease dose to 400 mg po daily once further decrease in titres and continued clinical improvement. Duration of therapy should be at least 12 months.

DISCUSSION

Residents and travellers to the endemic areas like Arizona (Phoenix and Tucson), California as well as certain parts of Utah, New Mexico, Nevada and Texas are at great risk of coccidioidomycosis. There has been a tremendous increase in the incidence of coccidioidomycosis in the USA with an estimated rise of 804% in the last 15 years. This can mostly be attributed to the altered rainfall patterns and significantly warmer climates particularly in the states of Arizona and California.^{2 3}

Coccidioidomycosis primarily involves the pulmonary system, but dissemination of the disease is particularly common in patients having HIV, haematological malignancy, or those who are on steroid or immunosuppressant therapy. However, our patient has no risk factors for disseminated coccidioidomycosis other than the demographic conditions. Musculoskeletal system involvement has been reported in 20–50% of disseminated *Coccidioides* infection.⁴ Common manifestations include septic arthritis, and osteomyelitis of the spine, skull, mandible, hand and foot.^{5 6} Although many tenosynovitis cases of the wrist and knee joint has previously been described in the literature, there has been no reported case of peroneal tenosynovitis caused by *Coccidioides* spp.⁷

Coccidioides spp can be diagnosed by clinical history, examination findings, serological testing, synovial fluid culture and histopathological studies. Serum IgM and IgG testing by ELISAs are preferred for diagnosis of primary infection and for initial testing as they are regarded as the most sensitive tests but false-positive results can occur particularly for IgM detection.⁸ Quantitative immunodiffusion assays and complement fixation assays are needed afterwards, and the presence of coccidioidomycosis is confirmed if either of these two tests is positive. Generally, complement fixation titres >1:32 signify disseminated coccidioidomycosis.⁹ Primary disease is diagnosed by an early IgM response, however, IgG usually outlasting the IgM indicates chronic coccidioidomycosis. Rising and falling trends of IgG titre indicate progression and regression of the disease, respectively. (R) Synovial fluid culture is also diagnostic, but it may take several weeks to become positive and also poses risk to laboratory personnel of acquiring the infection.¹⁰ It is also important to note that even though direct visualisation in tissue or detection by culture remains the gold standard for diagnosis, a negative culture does not exclude the possibility of *Coccidioides* infection. *Coccidioides* antigen testing has been proved useful particularly in diagnosing meningitic dissemination with a specificity of 100% in different reports,^{11 12} but more data are needed to support its use in other forms of dissemination. RT-PCR detection may represent a faster diagnostic tool to replace the labour-intensive current methodology.¹³

Therapy selection for individual patients with disseminated coccidioidomycosis varies according to risk for complications, the location of lesions and the rate of disease progression. Amphotericin B was previously considered to be the most effective treatment for *Coccidioides* tenosynovitis.¹⁴ But due to its nephrotoxicity, it is no more considered as a drug of choice.¹⁴ Iverson *et al*'s¹⁵ study recommended synovectomy as the standard treatment to avoid tendon rupture, while Szabo *et al*'s¹⁶ report suggested amphotericin B and synovectomy in such patients.

Researchers now believe that fluconazole and itraconazole are the first-line treatment for coccidioidomycosis. Many open trials have documented its efficacy in coccidioidomycosis management.¹⁴ Galgiani *et al*'s¹⁷ study indicated a trend towards superiority of itraconazole, especially in patients with skeletal lesions.

Itraconazole therapy may be associated with potential difficulties with oral absorption and drug–drug interaction (ie, Warfarin, antiretroviral therapy, etc) which may limit its use. Intravenous form of itraconazole may be difficult to administer but has the potential to overcome issue of poor oral absorption.¹⁷ Bercovitch¹⁴ preferred fluconazole as it is less toxic at high doses and easily available in parenteral formulations.

Our case is unique in which our patient did not have a good response to the standard dose of fluconazole (400 mg/day) initially, but her symptoms resolved quickly as the dose was increased to 800 mg/day. Whether or not this was a delayed response to therapy or an effect of a higher dose is not clear. We would like to mention that we found it clinically reasonable to increase the dose of fluconazole rather than changing therapy to amphotericin due to the safety profile of fluconazole and its well-established efficacy at high doses. Such patients require prolonged therapy for many months and can potentially relapse even after several years. Therefore, regular follow-up should be scheduled, and patients should be treated for at least 6–12 months.¹⁸

Learning points

- ▶ Residents of and travellers to coccidioidomycosis endemic areas are at high risk of acquiring the disease. There is no known difference in the racial susceptibility to coccidioidomycosis.
- ▶ Patients from *Coccidioides immitis/posadasii* endemic areas presenting with joints pain, swelling or redness should be investigated for possible disseminated coccidioidomycosis and may have tenosynovitis.
- ▶ In high-risk patients, it is important to consider the possibility of *Coccidioides* tenosynovitis even if synovial fluid culture and tissue biopsy are negative. High serological antibodies titres are helpful and diagnostic.
- ▶ Fluconazole can safely be considered as a first-line treatment for *Coccidioides* tenosynovitis, and amphotericin B should be reserved for recalcitrant infections. Only resistant or relapsed cases should undergo synovectomy. Higher dose of fluconazole can be considered in slow responders, but utility of this approach is not supported by the evidence-based literature.

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