Delayed Diagnosis of Tuberculous Arthritis of the Knee in an Air Force Service Member: Case Report and Review of the Literature

Drew Triplett, DO; Elizabeth Stewart, MD†; Stephanie Mathew, DO‡; Brandon R. Horne, MD§; Vidhya Prakash, MD‖*

ABSTRACT Tuberculosis (TB) is a common disease worldwide affecting more than 2 billion people, including latent, pulmonary, and extrapulmonary TB. The presentation of disseminated TB is variable and dependent on the organs affected. Therefore, making the diagnosis and providing appropriate treatment can be delayed. We present a case of disseminated TB in a patient with Sjögren's syndrome on hydroxychloroquine monotherapy without traditional risk factors.

INTRODUCTION

Tuberculosis (TB) is a common worldwide disease affecting more than 2 billion people.[1] The incidence of pulmonary and extrapulmonary TB in the U.S. military is less than that of the general U.S. population.[2] The lungs are the primary site for *Mycobacterium tuberculosis* infection, although extrapulmonary TB is reported in 20% of patients.[3] The most common extrapulmonary sites include the lymph nodes, pleura, genitourinary tract, bones and joints, meninges, peritoneum, and pericardium. We present a case of a patient with a history of untreated latent TB and Sjögren's syndrome with monoarticular arthritis.

CASE REPORT

A 53-year-old female with a history of Sjögren's syndrome on hydroxychloroquine monotherapy was referred to the Pulmonology Department for chronic cough, bronchiectasis, and pulmonary nodules. Before development of chronic cough, initial symptoms that led to a diagnosis of Sjogren's syndrome included gritty eyes, xerostomia, and generalized fatigue. Of note, she had a history of positive purified protein derivative in 2000 after returning from a trip to Panama. She did not have evidence of active TB and was not treated for latent TB. A computed tomography (CT) of the chest in June 2013 demonstrated multiple pulmonary nodules, which had increased in size since 2010. A bronchial alveolar lavage was negative for acid-fast bacilli. Laboratory evaluation included positive antinuclear antibody with titers of 1:160, positive Anti-Sjögren's-syndrome-related antigen A (SSA) with a level of >8 U, and rheumatoid factor level of 22.2 U/mL (normal <13.9 U/mL). The patient was subsequently referred back to the Rheumatology Department for evaluation of connective tissue–associated interstitial lung disease and monoarticular arthritis of her left knee. She reported a 7-year history of intermittent knee pain treated with hyaluronic injections to the left knee for presumed osteoarthritis. Plain knee radiographs showed mild tricompartmental osteoarthritis and a moderate effusion without erosive arthropathy. An arthrocentesis of the left knee showed 4,400 red blood cells and 9,600 white blood cells with 69% segmented neutrophils and 25% lymphocytes. Cultures from the arthrocentesis were positive for pan-susceptible *Mycobacterium tuberculosis*. A positron emission tomography scan was completed that showed increased uptake within the left external iliac lymph node chain. Biopsy of a left external iliac lymph node also confirmed the presence of *M. tuberculosis*. CT-guided fine-needle aspiration of a right middle lobe nodule confirmed granulomatous disease although cultures were negative. Left knee arthroscopy was performed with irrigation and debridement of multiple areas of abnormal appearing villous synovium. Synovial biopsy obtained during surgery showed noncaseating granulomas and intraoperative cultures were negative. The patient was referred to infectious disease and started on rifampin, isoniazid, pyrazinamide, and ethambutol therapy for tuberculous arthritis. The patient tolerated treatment well, completing 2 months of rifampin, isoniazid, pyrazinamide,

*Department of Internal Medicine, Boonshoft School of Medicine, Wright State University, 128 E. Apple Street, Weber CHE Building, 2nd Floor, Dayton, OH 45409.

†Department of Medicine, Dayton Veterans Affairs Medical Center, 4100 West 3rd Street, Dayton, OH 45428.

‡Rheumatology Clinic, Wright Patterson Medical Center, 4881 Sugar Maple Drive, Wright-Patterson Air Force Base, OH 45433.

§Orthopedics Clinic, Wright Patterson Medical Center, 4881 Sugar Maple Drive, Wright-Patterson Air Force Base, OH 45433.

‖Infectious Diseases Division, Department of Internal Medicine, Southern Illinois University School Of Medicine, 701 North First Street, #A482, Springfield, IL 62702.

Portions of this report have been presented as a poster presentation at the Dayton Area Graduate Medical Education Community Resident Research Forum, Dayton, OH, April 24, 2014 and the Ohio American College of Physicians Annual Meeting, Columbus, OH, October 17, 2014.

doi: 10.7205/MILMED-D-15-00232

TABLE I. Reported Cases of Tuberculous Arthritis of the Knee

Reference	Age (Sex)	Time to Diagnosis	Underlying Condition(s) and Immunosuppressive Therapy	Duration of Anti-TB Therapy	Extent of Joint(s) Destruction	Clinical Outcome as Described in the Case Report
Present Case	53 (F)	7 Years	Sjogren's Syndrome on Hydroxychloroquine	9 Months	Synovial Inflammation	Improved Range of Motion and Reduced Swelling
8	56 (F)	17 Months	Sjogren's Syndrome	Unknown	Synovial Hyperplasia, Bone Erosions, Crippled Ligaments, Edema	Unknown
9	42 (F)	Unknown	Rheumatoid Arthritis on Rituximab	3 Months	Synovial Effusion with Capsular Rupture	Symptomatic Improvement
10	72 (F)	2 Months	Rheumatoid Arthritis on Etanercept/Adalimumab	Unknown	Marked Osteodegenerative Changes and Osteophyte Formations, Marked Cartilage Loss	Decreased Bilateral Joint Circumference and Declining Inflammatory Markers
11	22 (F)	7 Years	Seronegative Arthropathy with Intra-articular Steroid Injection; Sulfasalazine	9 Months	Extensive Erosions	Functionally Independent
12	75 (F)	3 Months	Prior History of TB Arthritis of Affected Knee, Prosthetic Knee	9 Months	Severe Knee Joint Destruction after a Resection Arthroplasty	Improved Range of Motion
13	36 (F)	10 Years	Prosthetic Joint	12 Months	Extensive Destruction Requiring Total Knee Arthroplasty and Revision	Cure
14	65 (M)	Unknown	None	6 Months	Synovial Inflammation	Cure
15	20 (M)	4 Years	None	6 Months	Articular Destruction and Abscess	Cure
16	50 (F)	6 Months	None	1 Year	Bony Erosions	Cure
17	22 (M)	14 Months	None	12 Months	Diffuse Synovitis with Synovial Proliferation	Cure
18	23 (M)	4 Months	None	12 Months	Destruction of the Articular Surface	Persistent Destructive Changes
19	13 Months	2 Months	None	12 Months	Marked Thickening of Synovium, Effusion	Cure
20	62 (M)	4 Months	None	12 Months	Complete Destruction of the Articular Surfaces	TB-Free and Knee With Functional Mobility

and ethambutol therapy followed by a continuation phase of rifampin and isoniazid for 7 months. Her CT chest findings also showed improvement. At the completion of therapy, her left knee swelling was improved and her range of motion was near-normal.

DISCUSSION

In 2013, a total of 9,582 TB cases (a rate of 3.0 cases per 100,000 persons) were reported in the United States.[4] The incidence of active TB in the military population is less than that of the general population with a rate of 0.7 cases per 100,000 persons.[2] The strongest risk factor for acquiring active infection actually existed before accession into military service.[2] There was no consistent association between active TB and deployment, although there was an association with military members permanently stationed in TB-endemic countries.[2] Globally, bone and joint infection account for about 9% of extrapulmonary TB cases and for 2% of all TB cases.[5]

Tuberculous arthritis most commonly arises from hematogenous spread from a primary focus (lungs, renal, or lymphatic). Over time, patients develop joint erosions and ultimately joint destruction.[6] Monoarticular disease is most frequently encountered although patients may occasionally present with oligoarticular or polyarticular findings. Weight-bearing joints such as hips and knees are the most commonly affected.[7] Our patient developed nondestructive tuberculous arthritis of the knee with preserved range of motion. The lack of more extensive joint damage despite the duration of her TB infection, likely played a role in her delayed diagnosis. This is in contrast to four other case reports of tuberculous arthritis in patients with rheumatologic disease (see Table 1).[8–11] The patients in these cases had significant knee joint destruction. These additional cases of tuberculous arthritis were found in patients with Sjögren's syndrome, rheumatoid arthritis, and seronegative arthropathies who were on disease-modifying drugs. Of note, there were two patients with prosthetic infections who also suffered significant joint damage.[12,13]

Interestingly, patients without underlying immunosuppressive conditions or prosthetic joints had profound articular destruction.[14–20] These findings raise the question of whether there is any correlation between underlying comorbidities and degree of joint destruction in tuberculous arthritis. *M. tuberculosis* stimulates the release of interferon γ leading to the production of catabolites, which result in increased polarization toward a Th-17 profile. Th-17, in turn, attracts neutrophils and activates phagocytes, which lead to tissue destruction.[21] One hypothesis regarding the lack of overt joint destruction in our patient is the suppression of Th-17 cells and reduction of pro-inflammatory cytokines IL-6, IL-17, and IL-22 by hydroxychloroquine.[22]

The diagnosis of tuberculous arthritis requires a high index of suspicion as its clinical sequence can imitate other types of inflammatory arthritis, have an indolent course or occur in the background of a primary connective tissue disease. Plain film findings of the affected joint may include effusions early on, whereas peripheral osseous erosions, articular destruction with joint space narrowing, and juxta-articular osteoporosis (Phemister's triad) are later radiographic findings.[23] Magnetic resonance imaging may display nonspecific findings such as bone marrow edema, cortical erosions, synovitis, joint effusions, tenosynovitis, soft tissue collections, and myositis that can help aid in the diagnosis of tuberculous arthritis in the correct clinical setting.[24,25] Definitive diagnosis requires synovial biopsy and aspirate culture.[26]

Treatment of tuberculous arthritis entails 6 to 9 months or more of antimicrobial therapy.[27] Of the case reports reviewed that listed the duration of therapy, all patients were treated for 3 to 12 months, with a mean of 9.75 months of treatment. Patients require careful monitoring for signs of disease regression and medication side effects.[1] Eleven out of 12 cases reporting outcomes reported clinical improvement or cure after anti-TB therapy.[8–20] Although optimal antimicrobial therapy is greater than 90% effective,[28] surgery can be necessary for treatment of unresponsive cases, uncertain diagnosis, or where large abscesses are present. Typically, surgical treatment is directed toward the sequelae of advanced tuberculous arthritis such as bony sequestrum threatening the joint, deformity correction, or joint fusion.[29]

The diagnosis of tuberculous arthritis requires a thorough history with emphasis on relevant travel, careful physical examination, and appropriate diagnostic testing. Early diagnosis and timely initiation of appropriate anti-TB therapy are of paramount importance in limiting joint damage and achieving clinical cure. It appears as though regardless of degree of underlying immunosuppression, damage to the affected joint is typical, which is what makes our case fairly unique given overall preservation of the joint. Our case highlights the importance of entertaining a diagnosis of tuberculous arthritis in service members deployed to endemic areas who present with new onset joint pain and swelling that is not responsive to traditional arthritis therapy.

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