

Case Report
Tuberculosis of the knee

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ABSTRACT

Tuberculosis is a worldwide problem that has persisted in developing countries and is re-emerging in developed ones. Infectious complications with *Mycobacterium tuberculosis* have also been reported with increasing frequency. Among these, skeletal and intra-articular infections continue to affect patients and pose a difficult diagnostic problem to physicians and orthopedic surgeons. This is so, as the non-specific clinical presentation which, overlaps with several infectious and non-infectious diseases, and the latency period of this bacteria that can persist up to several years after the initial infection, contribute to diagnosis and management delay. Thus due to the paucity of the disease, physicians should heighten their index of suspicion for diagnosing tuberculosis of the joints especially when faced with recurrent symptoms of what they think is a common problem. In this context, we present a case of a protracted recurrent illness of a knee joint, which was proved by culture to be due to *M.tuberculosis*. Moreover, the aspects of this disease entity that poses a diagnostic challenge to the treating physician are highlighted together with those that differentiate it from other overlapping diseases such as brucellosis, especially in endemic areas.

Keywords: Tuberculosis, arthritis, brucellosis.

Saudi Med J 2002; Vol. 23 (9): 1130-1135

Tuberculosis (TB) remains a highly tolling infectious disease with significant morbidity and mortality in both developing and developed countries around the world, including Lebanon.¹ Infections with *Mycobacterium tuberculosis* (*M.tuberculosis*) are diverse and can cause pulmonary as well as extrapulmonary complications. These can also overlap in their presentations with many infectious and non-infectious diseases, thus posing a diagnostic challenge. Skeletal complications of TB generally affect the spine and large weight-bearing joints such as the hip and knee. Tuberculosis of the joints is an important and serious local complication of a systemic disease, which may, if untreated lead to complete joint destruction. The frequency of the knee involvement is estimated to be around 14% of cases ranking after the spine (50%) and the hip (25%).² The clinical presentation of skeletal TB can mimic several infectious and non-infectious diseases, most notably brucellosis which is also co-endemic in many

countries including Lebanon.³ The non-specific signs and symptoms of these 2 diseases necessitate considering both in the differential diagnosis when either is suspected. Short of using specific tests such as culture and serology, the salient features in the clinical presentations between TB and brucellosis are difficult to delineate.

This study reports a patient who had a protracted recurrent illness of the knee joint. Both the orthopedist and the radiologist had low index of suspicion for TB. Consequently, the patient underwent several operations before a definite diagnosis of TB was reached. In this context, the focus is also directed at features that can help improve the index of suspicion of skeletal tuberculosis among physicians, especially in areas where brucellosis is also present and can share common features that are difficult to differentiate. Delineation between these entities can help physicians reach an early diagnosis, initiate specific

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Received 28th October 2001. Accepted for publication in final form 21st April 2002.

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therapy and subsequently avoid further investigations and deleterious sequelae. A review of the literature is also presented to address and highlight these aspects.

Case Report. A 39-year-old lady presented to the American University of Beirut Medical Center (AUB-MC) with right knee swelling and pain of one-year duration. Her symptoms started progressively and were mainly exacerbated upon walking and prolonged standing. Moreover, there was no response to non-steroidal anti-inflammatory drugs. The patient acknowledged a history of trauma to the right knee 3 years previously with no subsequent pain or sequelae. Otherwise, the patient had no history of any chronic or remote disease. The physical exam revealed swelling of the right knee and point tenderness medially and laterally, with limited flexion. There was no evidence of effusion or hotness but there was loss of lateral skin dimple. The varus test, Osmond Clark sign, drawer and Lachmans signs were all negative. The rest of the physical exam was unremarkable. Laboratory findings showed a white blood count (WBC) of 8900/mm³, neutrophils 79%, lymphocytes 14%, monocytes 6%, eosinophils 1%. There was 4-6 WBC/high power fields on urine analysis. The brucella standard agglutination test (SAT) was negative while the brucella indirect Coombs' showed a positive titer at 1:80.⁴ Magnetic resonance imaging (MRI) of the right knee carried out prior to presentation to our hospital was suggestive of chondromalacia patellas. Based on the clinical presentation and MRI findings, arthroscopy was decided. There was severe synovitis, with villae-like nodular changes over the parapatellar and parameniscal areas with grade 2-3 chondromalacia patellas and a small meniscal tear. Synovial debridement of the medial parapatellar and parameniscal area was carried out. Biopsy taken during operation revealed acute and chronic non-specific synovitis of moderate intensity. At this stage the sample was not sent for culture because an infectious process was thought to be unlikely. The patient was discharged home on non-steroidal drugs.

Almost one year later, the patient presented again with recurrence of symptoms, namely swelling of the knee joint with pain not responding to non-steroidal anti-inflammatory drugs. Magnetic resonance imaging of the knee showed a moderate amount of fluid in the intra-articular cavity with thickened synovium and nodules projecting into the joint cavity, suggestive of villonodular synovitis (**Figure 1**). Arthroscopy showed typical appearance of involvement of the suprapatellar, medial and lateral gutters as well as the intercondylar notch. The patient underwent arthroscopic right knee synovectomy and excision of a loose body. Synovial biopsy obtained again revealed non-specific chronic synovitis. Three months later, the patient presented with pain and

tenderness of the right knee and MRI showed a moderate amount of fluid in the intra-articular cavity. There was a bone bruise in the lateral femoral condyle, and evidence of synovial hypertrophy along the posterior body of both femoral condyles, more so on the lateral side. There were no meniscal or ligament tears seen, but a small 2cm popliteal cyst was noted. No surgical intervention was entertained at this stage and she was prescribed non-steroidal anti-inflammatory drugs that partially relieved the symptoms. Five months later another synovectomy was performed upon the recurrence of symptoms (right knee swelling, pain, and evidence of effusion) and the pathology of synovial biopsy revealed non-caseating granuloma (**Figure 2**). No polarizable particles were seen within the granuloma. Gram-stain, acid fast stain and periodic acid-Schiff stain were negative for microorganisms, however culture of the joint obtained intraoperatively grew



Figure 1 - Thickened synovium and nodules projecting to the joint cavity.

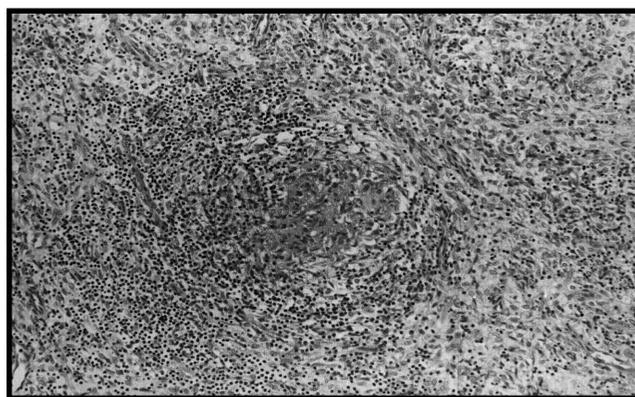


Figure 2 - Non-caseating granulomatous inflammation with evidence of acute and chronic inflammation.

M.tuberculosis in the BACTEC broth media (Becton Dickinson Microbiology Systems, Cockesville, MD). This strain was susceptible to isoniazid, rifampicin, streptomycin and ethambutol, as determined using the BACTEC system.¹ A purified protein derivation skin test showed 13mm induration but the chest x-ray was negative. The patient was started on a combination of antituberculous medication consisting of isoniazid, rifampicin, ethambutol, and pyrazinamide on which there was marked improvement. A 3-year follow-up proved that the patient remained free of symptoms and cured of her illness.

Discussion. Osteoarticular TB is usually a chronic infection that can entail a perplexing diagnosis. Moreover, reports have indicated that it is not unusual to take several months after the onset of symptoms to reach a diagnosis, especially when there is a low index of suspicion and absence of other criteria to aid the diagnosis.² This can explain the delay in diagnosis of our patient. The clues to the clinical diagnosis of TB of the knee joint are non-pathognomonic, as summarized in **Table 1**. Since the presentation of TB arthritis is non-specific and the index of suspicion for TB infection can be low, it is not unusual to entertain diagnoses other than TB. In our case and in the absence of current or previous signs and symptoms suggestive of TB, and in the presence of non-specific pathology results on biopsy specimens, the diagnosis of villonodular synovitis was the first to be considered prior to the final diagnosis of TB arthritis. In retrospect, the nonpathognomonic symptoms of ongoing TB infection in the knee may have mimicked villonodular synovitis leading to a delayed diagnosis. Several diseases have been reported to mimic TB knee arthritis including rheumatoid arthritis,⁵ gout,⁶ osteoarthritis,⁷ pyogenic infection⁸ and brucella monoarthritis.⁵ In our case villonodular synovitis was thought to be the diagnosis. Whether tuberculous knee diseases could coexist with this knee disease has not to our knowledge been reported before. Moreover, whether TB was the presenting illness or a complication of an already existing diseased joint remains open for speculation. Such an usual presentation should make the physician consider TB in the differential diagnosis of common knee problems, especially when they recur or progress in an atypical manner in an endemic region. Also it is interesting to note that local trauma to the knee, as noted in our case, was reported to precede the manifestation of TB of the knee joint.⁹ In our patient we do not know if the meniscal tear is the result of trauma or TB.

The approach to diagnosing TB of the knee joint is suggested to include history, clinical presentation, bone and joint imaging, but the definitive diagnosis

relies on detecting granuloma formation in synovial biopsies or a positive culture. Although plain radiography is essential to the diagnosis and remains the cornerstone for imaging, newer cross-sectional modalities are becoming increasingly valuable in early and accurate diagnosis.¹⁰ Computerized tomography (CT) is useful in the evaluation of these cases, frequently revealing bone destruction, soft-tissue masses and calcifications, which are characteristic but not specific for TB. Magnetic resonance imaging, on the other hand, is more sensitive than CT in delineating the extent of disease and evaluating response to therapy.¹¹ The definitive diagnosis of osteoarticular TB requires isolation of *M.tuberculosis* from the involved skeletal site; thus, the diagnosis almost always requires biopsy of bone, synovial tissue or both.¹² In our case, and in spite of several MRIs performed and biopsies taken, the TB diagnosis was delayed due to the presence of a previous knee problem and low index of suspicion of the treating doctor. Hence, the caring physician should suspect the diagnosis of TB, especially in refractory cases in TB endemic areas. In such a case he should also alert the pathologist and microbiologist to this possibility, which can be overlooked in an unfocused search of a cause, as was the case with our patient. Moreover, as our region is considered endemic for brucella which is known for its skeletal complications, the brucella indirect Coombs titer of 1:80 makes the physician think of brucellosis in this patient. Because both TB and brucella coexist in endemic areas, such as ours, and could clinically overlap in many aspects especially osteoarticular complications, these entities are discussed to alert the physicians and help delineate clues to their diagnoses. This is important as reaching early and specific diagnoses are essential to initiate adequate therapy and avoid extensive damage. Although brucellosis was considered early in the investigation, this was not the case with TB, a drawback resulting in delayed diagnosis. Thus, in endemic areas to these diseases, we suggest that both disease entities should be considered when either is entertained in the differential diagnosis of osteoarticular diseases. **Tables 2 & 3** summarize the general characteristics and diagnostic aspects, pertaining to patients with TB versus brucella as reported in the literature. Since both infections can show overlapping clinical and radiological features, the use of reliable diagnostic tools is of great importance. In contrast to TB, which relies on culture for isolating *M.tuberculosis* from synovial fluid or tissues,¹³ serological tests, such as enzyme-linked immunosorbent assay, have been relied upon and are considered less invasive and more sensitive than culture in the diagnosis of brucellosis.¹⁴ However, caution should be exercised when interpreting serologic tests, especially in endemic areas. In our patient the positive brucella Coombs titer of 1:80 in

Table 1 - Clues to clinical diagnosis of tuberculosis of knee joint.

<p>Monoarticular involvement of insidious onset, or subacute course¹⁵ Recurrence of what is thought a frequently diagnosed knee problem or atypical presentation or progression out of proportion to the assumed diagnosis Old age or chronically swollen knees in the elderly^{8,10} Cruciate ligament deterioration, torn menisci or ruptured tendons without history of trauma¹⁶ Remote or recent history of tuberculosis with or without reactive purified protein derivative^{5,7} Recent history of trauma¹⁰ Presence of medical conditions or medication precipitating immunosuppression¹⁷ No other identified disease to account for the condition (namely tumors, brucellosis, fungal, and so forth)⁵ Tuberculous knee infection can coexist with other knee conditions (namely pyogenic infections, gout, rheumatoid arthritis)^{5,6} Presence of pus cells in the absence of pyogenic bacteria on direct smear, or culture¹⁸</p>
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the absence of brucella SAT titers suggest a previous exposure to this infection.⁴ In brucella endemic areas this could be confusing since many brucella exposed individuals may show positive results in the brucella serologic tests in the absence of active disease.¹⁴ New advances in molecular amplification technology can hopefully help in the diagnosis of these diseases.

In conclusion, extrapulmonary TB, including osteoarticular complications, can have a wide spectrum of clinical presentations that mimic many infectious and non-infectious diseases. Villonodular synovitis mimicked TB in our case. A protracted illness of the knee joint as presented should call the attention of treating physicians to consider TB in the differential diagnosis, especially in countries where this disease remains endemic. In addition, we suggest that physicians considering either TB or brucella in osteoarticular diseases should include the other in countries where these co-exist.

Table 2 - General characteristics reported on patients with tuberculosis versus brucella arthritis.

Characteristic	Tuberculosis	Brucella	References
Mean age (year)	40	All age groups	5,17,19
Sex (male/female)	0.4/1-1.6/1	1.16/1-1.4/1	5,17,19,20
Tuberculosis status			
% Positive PPD	50%		21
Active TB	50%		6
Old TB	30%		7
Mean duration of symptoms before diagnosis (months)	8-18	< 1 month - 9 month	22,23
Presence of coexisting disease	Rheumatoid arthritis, gout, osteoarthritis, pneumococcal arthritis, brucellosis	Can coexist with TB in endemic area, chondrocalcinosis and osteoarthritis	5,6,7,8,24
Predisposing factors and associated conditions	Steroid, HIV, IV abusers, trauma, diabetes, alcoholism	Occupation: Dairymen and farmers, intake of unpasteurized milk	5,19
Onset	Late	Early in disease course	5,19
Pathogenesis	Reactivation from a latent focus seeded during primary illness, or through lymphatic drainage, rarely by direct inoculation	Seeding from blood	18,19
Progression	More chronic, slowly progressive and destructive, leads to joint instability	More acute, less destructive, leads to osteophytes and ankylosis. Destructive arthropathy is rare	17,25
Presence of constitutional symptoms	52-80%	More common, 65-100%	7,20,26
Bacteremia %	Not reported	<20% but can reach 70% in abattoir workers	19,23
Relapse rate	5.1%, depends more on compliance, stage of disease, and duration of treatment	5-39%, occurs in treatment regimens <6 weeks, or re-infection	23,27
Preceding trauma	37%	Few cases	28
Knee symptoms and % of overall osteoarticular involvement	Swelling and pain, limitation of motion, doughy consistency and no erythema,14-40%	Hotness, tenderness, and redness, 0% -38%	2,7,19,29,30
TB - tuberculosis, PPD - purified protein derivation, HIV - human immunodeficiency virus, IV - intravenous			

Table 3 - General diagnostic characteristics in patients with tuberculosis versus brucella arthritis.

Characteristic	Tuberculosis	Brucellosis	References
Radiographic joint changes %	54-100, non-specific.	Normal in early disease. Sensitivity 21% in one study.	21,25,27,31
MRI	Highly sensitive in early disease. Intra-articular lesions with low or intermediate intensity found on T2-weighted MRI images should suggest TB	More sensitive than radiography, CT, and bone scan. Gadolinium enhancement may help distinguish active disease	32-34
Bone scintigraphy	Sensitivity 63-100%, not specific	Sensitivity 69% but not specific. Better screening tool than radiography	25,35
Synovial fluid analysis	Elevated proteins, low fluid sugar, fair to poor mucin clot formation, WBC* ranges 10,000 – 20,000 cell/mm ³ (varies widely), mainly leukocytes	Protein ranges 3.3-5.2g/dl, sugar content ranges 60-100mg/dl, WBC ranges 6,000-18,600/mm ³ , predominance of lymphocytes	17,19
Positive acid fast stain of synovial fluid (%)	20 - 30		7
Positive culture in synovial fluid (%)	60 - 80	Extremely low, depends on culture medium used	17,28,36
Positive culture in synovial tissue (%)	50 - 90	Better yield than synovial fluid culture but unnecessary procedure	17,28,36
Presence of granuloma on synovial tissue(%)	95.6	Low yield, invasive and mostly non-specific inflammation	7,17,28,29,36
Sinus tract culture findings	<i>M.tuberculosis</i> , negative aerobic and anerobic culture, or <i>S. epidermidis</i> alone	Tendency to fistulate is rare	31
PCR on synovial fluid	Can be an additional diagnostic tool for early and specific testing	Still experimental, potentially can be helpful	37
LISA	Serology not useful	Provides a reliable diagnostic test especially in chronic and complicated cases	4,19,38
Response to therapy	Good and favorable in approximately 80%	Very good with appropriate therapy	19,38
Need for surgery	More encountered, for severely damaged and unstable joints	Minimal	27,29

MRI - magnetic resonance imaging, PCR - polymerase chain reaction, LISA - linked immunosorbent assay, TB - tuberculosis, WBC - white blood cell count, *M.Tuberculosis* - *Mycobacterium tuberculosis*, *S. epidermidis* - staphylococcus epidermidis, CT - computerized tomography

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