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Review Article

Updated Diagnosis and Management of Osteoarticular Tuberculosis

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Abstract

Background

Tuberculosis (TB) of the osteoarticular system usually manifests as osteomyelitis and joint arthritis. The diagnosis of TB arthritis is often delayed due to the lack of awareness, insidious onset, lack of characteristic early radiographic findings and, often, lack of constitutional or pulmonary involvement. The purpose of this review is to provide an update on the diagnostic and therapeutic recommendations for TB arthritis.

Methods

The literature from a range of sources was reviewed and synthesized to provide an overview of contemporary approaches for the diagnosis and management of TB arthritis.

Results

This review summarizes the clinical, radiological, bacteriological, immunological, synovial fluid examination, and synovial biopsy approaches used in the diagnosis of TB arthritis. We also summarize the updated guideline for the treatment of TB arthritis.

Conclusion

Intense current and previous efforts into diagnostic, therapeutic, and preventive interventions have focused on pulmonary TB in adults, but TB arthritis has been relatively neglected. The development of better diagnostic and therapeutic methods for TB arthritis remains a significant challenge. As the strategies for the diagnosis and management of TB arthritis improve and the knowledge base increases, the implementation of these strategies will be crucial.

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Introduction

Tuberculosis (TB) remains a major health problem worldwide. In 2011, the World Health Organization (WHO) reported an estimated 8.7 million incident cases of TB, 12 million prevalent cases of TB, and 1.4 million deaths due to TB [1]. Most cases occurred in Asia (59%) and Africa (26%) [1,2]. As for active clinical TB, the most common form of tubercular disease is Pulmonary TB (PTB); nevertheless, in a widely variable proportion of cases, TB can also affect extra-pulmonary sites within the body, exclusive of or in combination with PTB [3].

Musculoskeletal tuberculosis is a relatively rare extra-pulmonary complication of *Mycobacterium tuberculosis*. Specific skeletal involvement is observed in 1% to 3% of patients with TB [4]. Among them, approximately one-half of cases show spinal involvement, and the remaining involve the extraspinal osteoarticular joint [5-7]. TB tenosynovitis and arthritis is usually monoarticular, and the organism can be isolated from the joint [8].

TB tenosynovitis and arthritis occurs primarily through hematogenous spread from a primary focus such as the lung, kidney, or lymph node or, infrequently, through contiguous spread from adjacent tissues by direct inoculation [8-12]. TB of the joint may be due direct invasion of the synovium, e.g., Poncet's arthritis [8,11]. It may also affect nonweight-bearing joints such as the wrist, elbow, and the small joints of the hands. Articular disease often starts as a synovitis progressing to periarticular demineralization, marginal erosions, and lastly, joint destruction [13]. The time period from synovitis to joint destruction can be rapid, particularly in weight-bearing joints. When tubercular tenosynovitis and arthritis are complicated by a secondary infection such as *Staphylococcus aureus* presents, they result in accelerated joint destruction associated with severe systemic features [14]. Joint tissue necrosis secondary to other diseases, as in the cases of osteonecrosis of the joints due to sickle cell disease and chondrocalcinosis may predispose an individual to tubercular infection [15,16].

Patients generally have mild local and constitutional symptoms, frequently leading to significant delays in diagnosis. The diagnosis of tubercular tenosynovitis and arthritis is also frequently delayed due to its varied clinical presentation and frequent lack of radiographic findings and constitutional features [7,17]. The delay in diagnosis and treatment, may result in additional bone or joint destruction, particularly in patients with TB tenosynovitis and arthritis due to infection caused by mycobacterial species [7,18]. Therefore, early diagnosis and treatment are essential. We therefore performed a review of these topics based on the recent literatures.

Data Collection

We initially collected all of the articles that were published from January 1990 through March 2014, which described subjects affected by TB tenosynovitis and arthritis. These articles were obtained by searching MEDLINE (National Library of Medicine, Bethesda,

Maryland, USA) using the key words "osteoarticular tuberculosis" [OR] "tuberculosis arthritis" [OR] "diagnosis of TB arthritis" [OR] "management of TB arthritis". All of the articles are included. Manuscripts without an abstract (which were assumed to not be original), and opinion articles were excluded from the review. After selecting the articles, the relevant information was extracted and classified according to TB arthritis diagnosis, TB arthritis management, the country of study, and the study design.

Literature searches were performed in July 2014 and August 2014. Using the search terms previously described, a total of 161 documents were retrieved from MEDLINE. After screening the articles, a total of 103 articles were considered to be relevant. The countries were primarily from India, the United States, Turkey, Korea, Taiwan, Germany and other countries. The setting that produced the most original information was India, with 35% of the articles. After analyzing the abstracts, we found that 83% of the studies were case reports, 10% were retrospective, and 7% referenced other designs.

Diagnosis of TB Infection

Tuberculin skin test

Table 1 shows the methods to diagnose tuberculosis arthritis. The Mantoux test is the recommended standard Tuberculin Skin Test (TST). Tuberculin is commercially available in 1, 2, and 5 Tuberculin Unit (TU) PPD (Purified Protein Derivative, RT23 equivalent) forms [19,20]. For the test, it is important to raise a wheal of approximately 6 mm after the intra-dermal injection. The test is read 48-72 hours after an injection. Ballpoint or palpatory methods are used to read the induration. The influence of a prior Bacillus Calmette-Guérin (BCG) vaccine on the PPD reaction depends on conditions such as the interval between the BCG vaccination and the TST and the age at vaccination [21]. If the prevalence of TB infection is high enough, the positive predictive value of the TST is also high [22]. If the patient returns for a reading beyond 72 hours but before the 7th post-injection day, a positive test can still be read [23]. A repeat test may be needed if there is no induration and the wheals present beyond the stipulated time for reading. A repeat tuberculin test, when required, should preferably be performed on the other arm. Although the TST is widely used for diagnosing TB infection, it has some limitations. It is reported that the sensitivity may be decreased due to some factors like malnutrition, severe tuberculosis disease and immunodeficiency. In addition, the biggest disadvantage of TST is the cross-reaction with nontuberculous mycobacteria or with *Mycobacterium bovis* vaccine strains [24].

Methods
Tuberculin Skin Test (TST)
Interferon Gamma Release Assays (IGRAs)
Enzyme-Linked Immunosorbent Assays (ELISA)
Bacteriology
Radiology
Computed Tomography (CT)
Magnetic Resonance Imaging (MRI)
Polymerase Chain Reaction (PCR)
Synovial fluid examination
Synovial biopsy

Table 1: Summarizing the methods to diagnose tuberculosis arthritis.

Interferon Gamma Release Assays (IGRAs)

In addition to the traditional TST, which is known to lack both sensitivity and specificity, blood-based assays have recently become available. These T-cell assays rely on the stimulation of host blood cells with M. tuberculosis-specific antigens and measure the production of Interferon (IFN)-γ. Several studies have compared the two available commercial assays, T-Spot TB (Oxford Immunotec, UK) and QuantiFERON-TB Gold (Cellestis, Australia), with the TST for both the detection of active disease and Latent Tuberculosis Infection (LTBI) [25]. The T-cell assays have proven to be more specific than the TST, but they are currently unable to distinguish between active disease and LTBI [25]. Therefore, interpretation of the results remains dependent on the clinical context. Two new IGRAs may offer improved specificity and sensitivity over the TST for the diagnosis of LTBI [26,27]. One of these, QuantiFERONTB Gold (QFT-Gold), showed encouraging results in low-risk BCG-vaccinated subjects [28] and patients with active TB [27]. QFT-Gold overcomes some of the shortcomings of the TST, such as the need for return visits, reader variability, variable specificity, and cross reactivity with BCG vaccination and nontuberculous mycobacterial infections [21,29,30]. Although these tests are valuable in screening for LTBI, the diagnostic accuracy varies according to the patient population. Overall, the results indicate that IGRAs have a modest predictive value similar to that of the TST. In settings with a low TB incidence, the IGRAs demonstrated a higher specificity (100% and 98% for the QuantiFERON-TB assay and the T-Spot assay, respectively) than the TST (58%) in patients with TB [31,32]. The results from a meta-analysis, the pooled sensitivity was 78% (95% CI, 73-82%) for QuantiFERON-TB Gold, 70% (CI, 63-78%) for QuantiFERON-TB Gold In-Tube, and 90% (CI, 86% to 93%) for T-SPOT.TB; the pooled specificity for QuantiFERON tests and T-SPOT.TB is 99% (CI, 98-100%) and 93% (CI, 86-100%), respectively, among non-BCG vaccinated subjects, but pooled specificity for TST in non-BCG vaccinated subjects is 97% (CI, 95-99%) [33]. The costs and technical demands of IGRAs will most likely limit their wider use in resource-poor settings, where better tests are the most needed.

In the general population, IGRAs appear to be more powerful than the TST for diagnosing active TB or LTBI [34]. T-SPOT, QuantiFERON-TB and the TST have good diagnostic value for chronic inflammatory arthritis, but indeterminate results may complicate their use [35].

Enzyme-Linked Immunosorbent Assays (ELISA)

Antibody detection tests (serological tests), used for the diagnosis of several infectious diseases, may potentially improve TB diagnosis. These tests measure the presence of specific antibodies directed against immunodominant antigens of the investigated pathogen. Compared to smear microscopy, antibody detection methods may enable rapid TB diagnosis, as these tests have the advantages of being quick (results can be available within hours) and technologically easy, requiring minimal training. In addition, these tests could be adapted to point-of-care formats that can be implemented at lower levels of health services in low- and middleincome countries [36,37]. The serology tests used for diagnosing TB have a long record in the TB literature, but have never been well-developed, due to their low diagnostic values with poor specificity and sensitivity [38]. Since the 1990s, newer approaches have been chosen using ELISA and highly purified

antigens or recombinant proteins [37]. Improvement of their performances has been obtained by using several different antigens simultaneously [39]. Serological tests based on ELISA using a panel of non-protein antigens such as glycolipids specific for *M. tuberculosis* have been developed and evaluated [40].

Diagnosis of tuberculosis tenosynovitis and arthritis

Clinical presentation: TB arthritis commonly presents with chronic joint pain and only minimal signs of inflammation. Tubercular arthritis is characteristically monoarticular and most commonly affects the spine and weight-bearing joints such as the knee, hip, and ankle; the synovial type of TB arthritis is more commonly involved in the knee, hip, and ankle joint [12].

The most common symptom is local pain and swelling followed by restriction of movement of affected area. There is wasting of the regional muscle, and deformity may occur. Less commonly, a painless cold abscess has been reported as the only clinical presentation. The involvement of multiple sites is observed in 5-30% cases of tubercular arthritis [41,42]. Reactivation of tubercular arthritis after treatment occurs in 17-34% of individuals and is most commonly observed in the hip joint [8,43].

Joint swelling and evidence of effusion, periarticular abscess and chronic sinus formation occur late. Systemic symptoms of fever, weight loss, and night sweats may or may not be present during active TB tenosynovitis and arthritis. Less than 50% of individuals with tubercular tenosynovitis and arthritis have active pulmonary TB at the time of diagnosis [44]. Patients with TB may have hypersensitivity phenomena such as erythema nodosum, episcleritis, uveitis and Poncet's arthritis.

Clinically, TB tenosynovitis and arthritis has been classified into 5 stages [45-47]. Stage I, or the synovitis stage, presents with soft tissue swelling, no bony lesions, and localized osteoporosis, and the outcome after treatment is excellent. Stage II is early arthritis with marginal erosions (one or more erosions or lytic lesions in the bone; discrete diminution of the joint space), and the outcome is good, with only mild stiffness [6]. Stage III is advanced arthritis with subperichondrial cyst formation and loss of joint space; the outcome is fair, with notable loss of motion [6]. Stage IV is more advanced arthritis with joint destruction and no motion at the joint after treatment. Stage V is ankylosis of the joint.

Bacteriology: A confirmation of Acid Fast Bacillus (AFB) from any body fluid or tissue is the gold standard for the diagnosis of tuberculosis. Several studies have reported bacteriological positivity rates as high as 33% even for primary disease states, such as hilar adenopathy [48]. Therefore, every attempt must be made to bacteriologically prove the diagnosis in every case of suspected tuberculosis. Whatever method a clinician uses, he/she needs to collect at least two, preferably three, samples. A Ziehl-Neelsen (ZN) stain can reveal AFB only if the sample contains greater than 10,000 bacilli per mL. Different culture methods, such as Lowenstein-Jensen medium and radiometric (Bactec 12B liquid medium) and non-radiometric (Bactec MGIT 960 system) culture, can be used to confirm the diagnosis in the paucibacillary state [49]. The newer methods are capable of providing faster results and may be used if available. Mycobacterial culture assumes special significance in cases of suspected drug resistance [49].

There is a push to switch from (ZN to auramine microscopy. Despite World Health Organization guidelines that one staining

method is sufficient, in some countries national guidelines prescribe that auramine-positive samples should be confirmed by ZN [50]. A positive auramine result followed by a negative ZN result could not be used to exclude TB or to indicate the presence of NTM species. Confirming auramine-positive samples using ZN provided no clinically informative information and was a waste of resources.

Based on the results of bacteriological methods, Multidrug Resistant (MDR) tuberculosis is defined as tuberculosis resistant to at least both isonizid and rifampicin [51]. Extensively Drug-Resistant (XDR) tuberculosis is defined as tuberculosis resistant to isoniazid and refampicin; and any fluoroquinolone; and at least one of the three second-line injectable drug (capreomycin, kanamycin, and amikacin) [51]. Recently, WHO has revised the case definitions of TB and drug-resistant TB so that also the results of WHO-endorsed new molecular and nonmolecular methods can be used to define a case. Case definitions were further revised to avoid judgmental language, so the terms "defaulter" and "TB suspect" have been replaced by "lost to follow-up" and "presumptive TB", respectively [51].

The main Drug Susceptibility Testing (DST) methods are the absolute-concentration method and the Proportion Method (PM) on Lowenstein-Jenson (L-J) medium, but both methods take some weeks for the results. Automation of culture using BACTEC MGIT 960 (M960) system is being widely implemented [52].

Accurate and rapid detection of Tuberculosis (TB) and drug resistance are critical for improving patient care and decreasing the spread of TB. The Xpert MTB/RIF assay, which enables simultaneous detection of Mycobacterium Tuberculosis (MTB) and Rifampicin (RIF) resistance, was endorsed by WHO in 2010 [53]. Xpert may also be valuable as an add-on test following microscopy for patients who have previously been found to be smear-negative. An Xpert result that is positive for rifampicin resistance should be carefully interpreted and take into consideration the risk of MDR-TB in a given patient and the expected prevalence of MDR-TB in a given setting.

Radiology: Radiographic features are usually noted 2 to 5 months after disease onset [7]. The classical triad of radiologic characteristics of TB tenosynovitis and arthritis is juxta-articular osteoporosis, peripheral osseous erosion and gradual narrowing of the intra-articular space (Figure 1) [6,54,55]. In contrast to rheumatoid arthritis, the joint space is relatively preserved in early TB arthritis. In children, an enlargement of the epiphysis may be observed. A bone scan shows increased uptake, but bone scan findings are non-pathognomonic.

Imaging: Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are helpful in further defining the disease (Figure 2) [6,56]. MRI defines soft tissues better, while CT is good for bony lesions. The MRI features of tubercular tenosynovitis and arthritis include synovitis, effusion, central and peripheral erosions, active and chronic pannus, abscess, bone chips, and hypo-intense synovium. MRI is the investigation of choice to reveal both the extent and severity of damage [16]. MRI is also nonspecific but better depicts the extent of the lesion when compared with X-rays. These imaging features in an appropriate clinical setting may aid the diagnosis of tubercular tenosynovitis and arthritis [55]. Positron Emission Tomography (PET) using 2-[18F]-Fluoro-2-Deoxy-D-Glucose (FDG) has been used to diagnose in breast, colorectal, head and neck, lung, lymphoma, melanoma, oesophageal and thyroid cancers [57]. However, other management decisions require further research to

Figure 1: Radiograph of tuberculosis tenosynovitis and arthritis at tibial tuberosity. Swelling was present with or without a draining sinus. Radiographs showed erosion or lucent lesion at the site of the tendon attachment to bone [6].

show the impact of FDG-PET on patient management or added value in the diagnostic pathway for tuberculosis arthritis.

Figure 2: Comparison of imaging of radiography and Computed Tomography (CT). (**a**) The sequestrum is not apparent on the plain radiograph. (**b**) A tubercular sequestrum in the left iliac crest are noted on CT imaging [6].

PCR testing: Nucleic acid amplification tests using Polymerase Chain Reaction (PCR) cannot differentiate living bacilli from dead bacilli. Thus, these tests continue to give positive results even after successful treatment. PCR is positive in 95% to 100% of culture-positive cases and in 50% to 60% of culture-negative cases [58]. In one study, a multiplex real-time PCR with species-specific primers based on senX3-regX3+IS711 sequences proved to be sensitive and specific and useful for the highly efficient detection of *M. tuberculosis* and *Brucella* spp. in different clinical samples [59]. Over the past several decades, the diagnostic methods for *M. tuberculosis* have improved, and nucleic acid amplification techniques now allow rapid and sensitive detection in clinical settings [60].

Synovial fluid examination: Synovial fluid is usually nonhemorrhagic and turbid, with moderate elevation of the white blood cell count, ranging between 10,000 and 20,000 cells/mL with a predominance of polymorphonuclear leukocytes. Culture for *M. tuberculosis* should also be planned. Joint fluid aspiration from the affected joint for standard/routine investigation and TB culture is recommended, when possible, for at-risk patients, even if previous cultures have been negative. Synovial fluid culture is positive in approximately 20-40% of cases [61,62]. PCR analysis in synovial fluid, tissue samples, bone marrow aspirate, and peripheral blood is faster and more specific but less sensitive and less widely available [62,63].

Synovial biopsy: The gold standard for the diagnosis of tubercular arthritis is synovial biopsy, with positive results in 80% of cases [64]. It shows caseating granulomas, lymphocyte infiltration, and giant cells with caseation, which are very characteristic of tubercular arthritis.

Management of TB arthritis

Splints may be used for a short time to relieve acute symptoms and for a long time in specific cases of tuberculosis of the joints to prevent deformities of the infected extremities [65,66]. Operative treatment is usually limited and includes obtaining a biopsy and performing open or arthroscopic debridement, incision and drainage of abscesses, and synovectomy [65,67]. A randomized trial performed primarily among ambulatory patients by the Medical Research Council Working Party on Tuberculosis of the Spine [68] demonstrated no additional benefit of surgical debridement or radical operation (resection of the spinal focus and bone grafting) in combination with chemotherapy when compared with chemotherapy alone. In some circumstances, however, surgery appears to be beneficial and may be indicated. Such situations include failure to respond to chemotherapy with evidence of ongoing infection, the relief of cord compression in patients with persistent of recurrence of neurological deficits, or instability of the spine. Surgical procedures should be restricted to joints with severe cartilage destruction, joint deformity, large abscesses, multiple drug resistance [66,68,69].

The mainstay treatment of TB arthritis is appropriate anti-TB drug therapy (Table 2). Early antimicrobial therapy can result in near-complete resolution and preservation of function. In TB arthritis without pulmonary involvement, the risk of transmission to contacts is minimal and thus constitutes little threat to public health. Antimicrobial therapy in general should be of at least 6-9 months duration but should be continued longer in children and immunocompromised hosts [9,12,13]. The basic principles that underlie the treatment of pulmonary tuberculosis also apply to extra-pulmonary forms of the disease (Table 2) [54]. Although many fewer studies have examined the treatment of extra-pulmonary tuberculosis compared with pulmonary disease, increasing evidence, including some randomized controlled trials, suggests that the 6- to 9-month regimens (2 months of Isoniazid (INH) and Rifampicin (RIF), Pyrazinamide (PZA), and Ethambutol (EMB) followed by 4-7 months of INH and RIF) are recommended as initial therapy unless

the organisms are known to be or strongly suspected of being resistant to the first-line drugs. If PZA cannot be used in the initial phase, the continuation phase must be increased to 7 months, as described for pulmonary tuberculosis. Several studies have examined the treatment of bone and joint tuberculosis and have shown that the 6-9-month regimens containing RIF are at least as effective as the 18-month regimens that do not contain RIF [68,70,71]. Myelopathy with or without functional impairment most often responds to chemotherapy. In two Medical Research Council studies conducted in Korea, 24 of 30 patients in one study [70] and 74 of 85 patients in an earlier study [72] had complete resolution of myelopathy or complete functional recovery when treated medically. The recommended dosages are listed in table 3 [23,54].

Category of treatment	Category of TB cases	Anti-TB drug regimens	
		Intensive phase	Continuation phase
I	New Patient Regimen New smear-positive PTB Smear-negative PTB with extensive Parenchymal involvement Severe forms of EPTB other than TB meningitis	2HRZE	4HR
II	New Patient Regimen Smear-negative PTB without extensive P Parenchymal involvement Less severe forms of EPTB (e.g., TB cervical adenitis)	2HRZ	4HR
III	New Patient Regimen TB meningitis	2HRZS[a]	4HR
IV	Retreatment regimen Previously treated smear-positive PTB (relapse, treatment after interruption or treatment failure) If low risk for MDR-TB or risk unknown, continue with retreatment regimen If high risk for MDR-TB, use MDR-TB regimen below	2HRZ-ES/1HRZE	5HRE
V	MDR Regimen MDR-TB	Individualized regimens	

Table 2: Treatment regimens for tuberculosis recommended by the WHO [42].

[a] Other regimens are recommended for the treatment of TB meningitis, including replacing streptomycin with ethionamide and treating for 9-12 months.

E: Ethambutol; EPTB: Extra-Pulmonary Tuberculosis; H: Isoniazid; HIV: Human Immunodeficiency Virus; MDR-TB: Multi-Drug Resistant Tuberculosis; PTB: Pulmonary Tuberculosis; R: Rifampicin; S: Streptomycin; Z: Pyrazinamide; 2HRZ 4HR: Denotes a Two-month Intensive Phase of Daily Isoniazid, Rifampicin, and Pyrazinamide followed by a Four-month Continuation Phase of Daily Isoniazid and Rifampicin

Conclusions

TB is still an important public health problem throughout the world. TB arthritis accounts for approximately 1-3% of all cases of tuberculosis and for approximately 10-11% of extra-pulmonary cases. Nonspinal skeletal TB is rare and insidious in onset and is often difficult to diagnose. Early diagnosis and specific and adequate treatment can improve the possibility of maintaining good joint function.

	Recommended	Dose per day
	Adults	Children
Drug	Dose and range (mg/kg body weight)	Dose and range (mg/kg body weight)
Isoniazid	5 (4-6)	12 (10-15)
Rifampicin	10 (8-12)	15 (10-20)
Pyrazinamide	25 (20-30)	35 (30-40)
Ethambutol	15 (15-20)	20 (15-25)
Streptomycin	15 (12-18)	15 (12-18)

Table 3: Recommended doses of first-line anti-tuberculosis drugs for adults [42,60].

There is usually a long delay in diagnosis, due partly to its tendency to mimic other diseases as a result of its varied clinical presentation and radiographic appearance [3,67,73]. TB arthritis should be considered in patients who present with indolent symptoms of chronic tenosynovitis [18]. Early diagnosis of arthritis due to TB is essential to preserve the articular cartilage and joint space. The mainstay of treatment is multidrug anti-TB therapy (for 12-18 months) and active-assisted nonweight-bearing exercises of the involved joint throughout the period of healing. Operative intervention (synovectomy and debridement) is required when the patient is not responding after 4-5 months of anti-TB therapy.

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