Tuberculous arthritis: an overview

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ABSTRACT
Tuberculous arthritis is a part of tuberculosis infection. Although the number of this disease is very small compared to the other causes of musculoskeletal infection, it can cause joint damage and eventually disability to the patient. Tuberculous arthritis should always be considered as one of the differential diagnosis in cases with insidiously developed monoarticular arthritis of the large weight-bearing joints, especially in developing countries where there is a high prevalence of tuberculosis. Early recognition and treatment with antituberculosis drugs provide better outcome for the patient; however, surgery due to unresponsiveness to medical treatment or presence of large abscess, arthroplasty, and arthrodesis may be necessary.

Tuberculous (TB) arthritis is a chronic septic arthritis caused by *Mycobacterium tuberculosis*. This disease should always be taken into consideration as one of the causes of chronic arthritis, especially in the developing countries where there is a high prevalence of tuberculosis.

The diagnosis of osteoarticular TB is usually delayed because the possibility of tuberculosis is often overlooked in the differential diagnosis of joint disease. Early symptoms are often minimal, and the delay could sometimes stretch to months or even years, until disease progression and disability prompt more aggressive diagnostic investigation. The mean duration from the onset of initial symptoms to the confirmation of diagnosis is 19.5 months (ranging from 12 to 36 months). In one report it takes even longer, about 6.5–7 years.

EPIDEMIOLOGY
Tuberculosis continues to ravage the populations of developing countries, with 9.4 million new cases in 2009 and 1.7 million deaths. About one third of the world’s population is infected with tuberculosis, providing a reservoir that will continue to complicate its global control. Five to ten percent of people who are infected with TB bacilli will eventually become sick or infectious at some time during their life. Tuberculosis in Indonesia is ranked third globally after India and China, with the prevalence of 660,000 and incidence of 430,000 or 189 per 100,000 population in 2009.

Musculoskeletal TB accounts for about 5% of cases of tuberculosis, with estimated percentages ranging from about 2% of all TB cases in United States to more than 6% in developing countries. Tuberculous arthritis is the second most common form of musculoskeletal TB, following vertebral TB. Involvement of the osteoarticular system is most commonly found in the elderly in developed countries; however, in developing countries it could be found at any age, mostly in children and young adults. There has been reported an increased prevalence of tuberculous arthritis among HIV-infected individuals and those who received antitumor necrosis factor (anti-TNF) therapy.

PATHOPHYSIOLOGY
Arthritis is generally secondary to hematogenous seeding (at the time of initial infection or during reactivation), but it can also occur as a consequence of lymphatic dissemination or direct spread from a contiguous lesion, such as adjacent osteomyelitis. However, characteristic pulmonary or extrapulmonary findings are not always present.

In long bones, hematogenous spread commonly affects the synovium, causing erosive deforming arthritis. Initially the synovium develops an inflammatory reaction followed by formation of granulation tissue, which lead to development of pannus. The margins and surface of the joints can be eroded by the pannus. As the effusion develops, fibrin may precipitate, forming “rice bodies” in synovial fluid, bursae and tendon sheath. However, the “rice bodies” are not typical for tuberculosis; they can also be found in patients with rheumatoid arthritis (RA). The granulation tissue erodes and eventually destroys the cartilage, leading to demineralization of the bone and caseating necrosis. Because *M. tuberculosis* does not produce collagenases, and because this proteolytic enzymes are absent from the tuberous exudates, joint destruction is more insidious than in septic arthritis due to pyogenic organisms. The infection then spreads to the upper metaphysis and epiphysis on either side of the joint through the periarticular vasculature. In advanced and later stage of disease, para-osseous cold abscesses develop around the joints. Spontaneous drainage of the cold abscesses results in sinus tract formation and may develop into cutaneous fistulae. *M. tuberculosis* is rarely isolated from these sinus tracts because of frequent pyogenic contamination.

Tuberculosis related to anti-TNF inhibitors may be due to the inhibition of a TNF-dependent
chemokine gradient disrupting the cellular migration necessary to maintain the integrity of granulomas. The pro-inflammatory cytokines, such as interleukin (IL)-1, IL-2, IL-6, IL-12, interferon γ (IFNγ), and TNFα, play a key role in protection against tuberculosis and also in granuloma formation. TNFα recruit macrophages, leading to granuloma maintenance and formation (Ghon’s lesion), which is very important to contain and kill Mycobacterium microorganisms and are indicators of an effective immune response.10

CLINICAL MANIFESTATIONS
Constitutional symptoms such as fever, night sweats, and weight loss are typically subtle or absent in patients with TB arthritis. The classic presentation is that of monoarthritis with pain (with or without movement), stiffness, and gradual loss of function over weeks to months.8

The peripheral joints most frequently affected are the large weight-bearing joints such as the hip and knee. Other joints commonly involved include the sacroiliac, shoulder, elbow, ankle, carpal, and tarsal joints.8,15 Monoarticular involvement is much more frequent than polyarticular disease.16–19 Oligoarticular involvement of both knees was reported more commonly than other joints.20

On physical examination, the joint is swollen with or without warmth. Limited motion due to pain and boggy swelling due to synovial hyperthrophy and effusion could also be found. Periarticular abscesses and draining sinus tracts are late findings. Prolonged immobility due to pain may eventually lead to deformity.8

Clinical features of tuberculous arthritis can mimic other processes such as juvenile RA21 and gout,25 which may obscure and delay the diagnosis. However, septic arthritis including tuberculosis must also be considered among the possible causes of infectious arthritis occurring in patients with pre-existing RA.23 On the other hand, rheumatoid factor (RF) may be present in tuberculosis, leading to diagnostic confusion in the presence of monoarthritis.24

There is a type of reactive arthritis called Poncet’s arthritis in patients with active TB infection. It is associated with extrapulmonary TB, usually lymphadenitis TB. This is a separate entity from TB directly affecting joint spaces. The joint fluid analysis does not reveal the presence of M. tuberculosis. It usually manifests itself as polyarticular inflammation of the large joints associated with fever and malaise.8,10,25 Tuberculin test is frequently positive, and the clinical symptoms of Poncet’s resolve with antituberculosis therapy.8,10,13

DIAGNOSIS
The definitive diagnosis should be made by culture and histopathological analysis of biopsy specimen.8,16 However, several diagnostic tools can help in making the diagnosis of tuberculous arthritis, such as radiograph (including chest X-ray), magnetic resonance imaging (MRI), radionuclide, tuberculin skin test (TST), and synovial aspiration and analysis.

Imaging
Radiographic abnormalities may only appear later in the course of disease, although newer imaging techniques have resulted in earlier detection of abnormalities and the distinction of tuberculosis from other infections as well as neoplasm.26,27

Initially, the infection may be primarily synovial, with radiographic evidence of joint swelling resulting from a combination of synovial hyperthrophy and effusion. The chronic synovitis leads to hyperemia and periarticular osteoporosis. The normally sharp, subarticular cortical outline becomes blurred, smudged, or even invisible. Eventually destruction of articular cartilage leads to narrowing of the joint space.13 Additional radiographic findings that may be present include soft tissue swelling, subchondral cysts, periostitis, and calcifications.12 Another typical feature is lack of sclerosis or periostitis in the early stage, except for children, in whom a layered periostial reaction is seen. The end stage of tuberculous arthritis is characterized by severe joint destruction and eventually sclerosis and fibrous ankylosis when the active infectious stage has slowly extinguished. Bony ankylosis is only occasionally seen, but this sequel is more frequent in pyogenic arthritis.28

The Phemister’s triad is the characteristic radiographic findings of tuberculous arthritis, consisting of juxta-articular osteoporosis, marginal erosions, and gradual joint space narrowing. Similar changes can occur in other forms of infection or RA.8,12

Compared with pyogenic joint infections, minimal sclerosis and relative preservation of joint space favor the diagnosis of tuberculous arthritis.29 By using MRI to evaluate tuberculous arthritis, Sung et al reported that bone erosion was more common in patients with tuberculous arthritis than in those with pyogenic arthritis, while subchondral marrow signal intensity abnormality was seen more frequently in patients with pyogenic arthritis than in those with tuberculous arthritis.30 Furthermore, tuberculous abscesses have thin and smooth rim enhancement, while most pyogenic abscesses have thick and irregular rims.30 M. tuberculosis forms tubercles with central caseating necrosis that shows intermediate signal intensity on T2-weighted images of MRI.31

In 1988, Martini and Ouahes32 classified the radiographic findings in tuberculosis of the bone and joint as:

- Stage I : no bony lesions, localized osteoporosis
- Stage II : one or more erosions (or cavities) in the bone, discrete diminution of the joint space
- Stage III : involvement and destruction of the whole joint without gross anatomic disorganization
- Stage IV : gross anatomic disorganization

Radionuclide bone scan is useful in the initial stages to detect the tuberculous arthritis when radiograph do not yet demonstrate characteristic abnormalities, as well as computed tomography (CT) scan.13 CT scan may demonstrate bony destruction, bony sequestration, and extension of disease to the surrounding soft tissue.31

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Laboratory
Getting a correct diagnosis requires vigorous pursuit and usually includes synovial biopsy and culture. Initial studies are often misleading and may contribute to delayed diagnosis or misdiagnosis. Synovial effusion is often minimal, and the fluid, even if it is obtainable, shows variable, usually turbid and cloudy, and do not distinguish this arthropathy from other inflammatory or septic arthritides. Cell counts more often suggest inflammatory rather than septic arthritis and contain a preponderance of neutrophils (approximately 60%), but occasionally of lymphocytes. Synovial fluid protein is usually elevated but glucose tends to be low and more than 10 mg/dL below fasting serum levels, but nonfasting determinations are often misleading.

The diagnosis may be facilitated if the organism is observed on an acid-fast smear of synovial fluid, but only 20% of cases are positive. In contrast, 80% of synovial fluid cultures are positive. Synovial biopsy specimens can reveal the histologic finding of TB in approximately 80% to 90% of patients, although proper selection of tissue is paramount because the histologic picture can vary depending on the site of biopsy. The histologic examination alone may be confusing because granulomatous synovitis may also be found in atypical mycobacterial infection, sarcoidosis, erythema nodosum, brucellosis, Crohn’s disease, and foreign body reaction. With the open-biopsy technique, granulomatous histologic features and positive cultures are present in 94% of cases. No data are available for direct amplification tests in mycobacterial arthritis, but their use should be considered in suspected cases to provide earlier diagnosis. One report has suggested that a synovial fluid lymphocyte proliferation assay using tuberculin protein may have diagnostic value. Correct diagnosis is highly dependent, in most cases, on demonstration of the infectious agent by microscopic examination and culture of affected tissue. The role of nucleic acid amplification tests in diagnosing these infections is still being defined, and they must be interpreted with caution in extrapulmonary tissue specimens and when the clinical suspicion of infection is low.

Other laboratory test such as elevated erythrocyte sedimentation rate and C-reactive protein level, are nonspecific.

Tuberculin skin test (TST)
Tuberculin and other skin tests may provide useful clues to etiology, but results are not invariably positive, especially in debilitated or immunosuppressed patients. This test is unable to distinguish latent infection from active disease and may be negative in the face of severe active TB. False negative results may occur in patients using corticosteroid 15 mg/day or more, elderly and malnourished patients. Likewise, false positive results may be found in the case of infection with nontuberculous mycobacteria or previous Bacille Calmette-Guérin (BCG) vaccine. This test is an important but imperfect screening tool for M. tuberculosis infection.

Interferon γ release assays
This test has been developed due to the limitations of traditional TST. These assays measure the production of IFNγ by whole blood mononuclear cells stimulated by specific M. tuberculosis antigens. It has good sensitivity and specificity for latent TB infection.

DIFFERENTIAL DIAGNOSES
- Gouty arthritis typically presents as intermittent episodes of (rather than persistent) monoarthritis in a patient with risk factors for hyperuricemia. The radiographic findings of erosions in chronic recurrent gouty arthritis usually overhangs the edge
- Pyogenic arthritis is also monoarticular but has a more rapid progression
- Rheumatoid arthritis is usually polyarticular, and involves mainly the small bones of the hands and feet. Occasionally, it may be monoarticular at the onset or affects only a few medium-size joints, and can simulate other causes of mono- or oligoarthritis including TB arthritis. In some cases, TB can superimpose on an RA joint.
- Osteoarthritis is much less inflammatory affecting weight bearing joints. Radiographic findings include subchondral bony sclerosis and osteophyte formation.

MANAGEMENT
Education
During the acute phase, immobilization and rest are reserved for relief of pain, and followed by early, active mobilization without weight bearing for 4 to 6 weeks.

Multidrug therapy
Various regimens have been proposed, from the conventional duration of 18 to 24 months to shorter but more intensive multidrug therapy for 6 months (table 1). However most recommended regimens for extrapulmonary tuberculosis should last at least 9 to 12 months. The longer courses for musculoskeletal disease were based on poor tissue penetration into osseous tissues and high rates of relapse.

The daily doses of antituberculosis drugs are isoniazid 5 mg/kg or 300 mg, rifampicin 10 mg/kg or 450 to 600 mg, pyrazinamide 15 to 30 mg/kg, and ethambutol 5 to 15 mg/kg or streptomycin 15 mg/kg or 1 g intramuscularly. Pyridoxine 25 to 50 mg daily, may be added to daily regimens that include isoniazid.

The overall clinical response to anti-mycobacterial therapy is good. However, allergic reaction can occur to any drug; thus careful attention must be paid to toxicity. Streptomycin can affect the vestibulocochlear nerve, resulting in deafness or vestibular functional derangement. Rifampicin can produce hepatotoxicity; hence the level of aspartate and alanine aminotransferase must be monitored. Ethambutol can produce depressed thyroid function.

Radiographic features of mycobacterial disease may not change much after 6 months of treatment, and response to treatment is based mainly on clinical features, including reduction in pain, resolution of constitutional symptoms, and improvement in mobility.
**Table 1** Antituberculosis therapy

<table>
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<tr>
<th>Regimen (month)</th>
<th>Initial phase</th>
<th>Continuation phase</th>
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<tbody>
<tr>
<td></td>
<td>Drugs</td>
<td>Duration (month)</td>
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<tr>
<td>18–24</td>
<td>INH, RIF ± ETB or STM q.d.</td>
<td>2</td>
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<tr>
<td>9</td>
<td>INH, RIF q.d.</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>INH, RIF, PZA ± ETB or STM q.d.</td>
<td>2</td>
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INH, isoniazid; RIF, rifampicin; PZA, pyrazinamide; ETB, ethambutol; STM, streptomycin; q.d., daily; b.i.w, twice weekly.

**Surgery**

Surgical intervention is indicated as a diagnostic tool and when necessary to drain abscesses unresponsive to medical treatment. Articular procedures for tuberculous infection include excisional arthroplasty (hip and elbow) and arthrodesis (knee, shoulder, ankle, and wrist). Individuals requiring total hip or knee replacement for quiescent TB should receive perioperative antituberculosis therapy (isoniazid and rifampicin) 1 to 4 weeks before and 6 to 9 months after surgery to minimize risk of reactivation.

**REFERENCES**


**SUMMARY**

The diagnosis of tuberculous arthritis is often delayed because the failure to consider the diagnosis. Condition which should alert physicians to the presence of tuberculous arthritis is an insidious onset of a monoarthritis, especially in the country with high burden of tuberculosis disease. The gold standards of diagnosis are culture and histopathology. Early diagnosis of this disease as well as adherence to chemotherapy are important in order to minimize the risk of deformity and enhance the outcome.


