

## Features of Extra-spinal Musculoskeletal Tuberculosis: A Retrospective Study from an North Indian Tertiary Care Institute

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### Abstract

**Background:** The aim is to study the clinical features and diagnosis of primary extra-spinal musculoskeletal manifestations of tuberculosis (TB) in otherwise healthy individuals.

**Methods:** In this retrospective study of 10 years duration electronic database and case records of patients with musculoskeletal TB were analyzed. Patient's positive for HIV and rheumatic diseases with or without immunosuppressive drugs or biological agents were excluded from the study.

**Results:** Fifty-one patients were identified with the mean age at presentation of 33.35 years (range 4–72), male: female ratio of 1.1:1 and mean duration of disease was 14.65 months (range, 0.25–120). The most frequent manifestation was articular (arthritis/arthralgia  $n = 40$ , monoarthritis  $n = 28$ , oligoarthritis  $n = 10$ , polyarthralgia  $n = 2$ ) followed by tenosynovitis ( $n = 6$ ), tuberculous osteomyelitis ( $n = 5$ ), isolated bursitis ( $n = 1$ ), and pyomyositis ( $n = 1$ ). Poncet's disease was diagnosed in five patients. Disseminated TB was detected in four patients. Pain ( $n = 50$ ) followed by swelling of the involved site ( $n = 37$ ) were the most common presenting symptoms. Fever was present in 15 (29.4%) patients. Nine patients had a previous history of TB. Concurrent pulmonary TB was present in two patients. Lymph node enlargement was present in 12 (23.5%) patients. A definite diagnosis of musculoskeletal TB was made in 31 (61%) patients and probable TB in 20 (39%) patients.

**Conclusion:** Musculoskeletal manifestations of TB can occur at any age. Chronic monoarthritis is the most common presentation; however, oligoarthritis and/or tenosynovitis may be a presenting manifestation. The absence of fever should not discourage the diagnosis of musculoskeletal TB.

**Key Words:** Arthritis, extra-spinal, musculoskeletal, Poncet's disease, tuberculosis

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### Introduction

Tuberculosis (TB) in India accounts for the one-fourth of the global cases, adding almost 2.8 million cases annually.<sup>[1]</sup> TB primarily involves the lungs, but 10% of cases manifest as extra-pulmonary TB (EPTB). According to a report from Revised National TB Control Program (RNTCP), EPTB accounts for 20% of total TB cases in India.<sup>[1]</sup> Osteoarticular TB accounts for 1%–5% of total TB cases and 10%–18% of EPTB cases.<sup>[2]</sup> Spinal TB is the most common site of skeletal TB accounting for 50% of cases followed by septic arthritis (28.3%), osteomyelitis (10.1%), tenosynovitis (4.0%), bursitis (2%), and pyomyositis (2%).<sup>[3-5]</sup>

TB arthritis usually presents as slowly progressive chronic monoarthritis affecting weight-bearing joints, particularly knee and hip in association with nonspecific constitutional symptoms.<sup>[6-13]</sup> The radiological manifestations are characterized by juxta-articular osteoporosis, gradual narrowing joint space, and peripherally located osseous erosion (Phemister's triad).<sup>[14]</sup>

The association between TB and rheumatologic diseases has been widely recognized and is bidirectional.<sup>[10,14]</sup> TB can directly infect the musculoskeletal system, and on the other hand, patients with rheumatic diseases are predisposed to TB infection due to a variety of reasons.

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The manifestations of musculoskeletal TB can be classified into four groups:

1. Direct musculoskeletal tubercular infection – such as spondylitis, septic arthritis, osteomyelitis, pyomyositis, bursitis, subcutaneous abscesses, and tenosynovitis
2. TB infections in patients with rheumatic diseases
3. Drug-induced syndromes – antitubercular treatment (ATT)-induced lupus, tenosynovitis, hyperuricemia, gout, etc.
4. Reactive phenomenon such as Poncet's disease, erythema nodosum, erythema induratum, and amyloidosis.<sup>[15]</sup>

Most studies describing rheumatological manifestations of TB have been described from orthopedic units, which predominantly report spinal involvement, whereas involvement of joints, tendons, and other manifestations are underreported, a possible referral bias. Small numbers of studies from rheumatology centers have reported musculoskeletal TB as a complication of immunosuppressive therapy, use of disease modifying drugs or anti-tumor necrosis factor alpha therapy, where TB is high on the list of differential diagnosis. However, there is a paucity of data on rheumatological manifestations of TB occurring in immunocompetent and otherwise healthy individuals without any predisposing factors. Herein, we present our 10-year experience with cases referred to our unit as suspected rheumatological diseases in immunocompetent individuals and were later diagnosed to have musculoskeletal TB. The clinical manifestations and diagnosis of such cases are discussed to sensitize the clinicians about varied manifestations so as to minimize delay in diagnosis and treatment.

### Methods

In this retrospective study, case records or electronic database of patients diagnosed with musculoskeletal TB between January 2001 and June 2010 at our unit were retrieved. Data were analyzed for demographic, clinical features, and diagnostic methodology. Definite diagnosis of musculoskeletal TB was made when either (1) joint aspiration or tissue biopsy/fine-needle aspiration cytology (FNAC) revealed acid-fast bacilli (AFB), (2) culture of the synovial fluid (or tissue/pus aspirated) grew *Mycobacterium tuberculosis*, or (3) histopathology/FNAC revealed granulomatous lesions with or without caseation with AFB positivity [Figure 1]. Probable TB was considered if there was no direct evidence of AFB or granuloma, but clinical, radiological, and serological evidence suggested TB and the patient responded to empirical antitubercular therapy. Other tests include tuberculin skin sensitivity (Mantoux) test and TB interferon  $\gamma$ -assays. Radiology included X-ray of the chest, X-ray of the involved site, computed tomography (CT), or magnetic resonance imaging (MRI) of the joint/organ involved. CT-guided biopsy or fine-needle aspiration and arthroscopic biopsies

were also performed as required. Polymerase chain reaction (PCR) for TB was not performed. The patient had disseminated TB if three or more noncontiguous sites were involved.

HIV positive or AIDS patients, those suffering from primary rheumatological diseases with or without disease-modifying drugs or those on biological therapy were excluded. Patients on chemotherapy for malignancies were also excluded. Patients presenting with the spine as the only osteoarticular involvement were also excluded from the study.

### Ethical approval

The study was approved by the ethics committee of the institute.

### Results

Fifty-one patients were diagnosed with extraspinal musculoskeletal TB, with male:female ratio of 1.1:1. Mean age at presentation was 33.35 (range 4–72) years. The mean duration of illness at presentation was 14.65 months (range, 1 week to 120 months). Pain ( $n = 50$ ) and swelling ( $n = 37$ ) were the chief

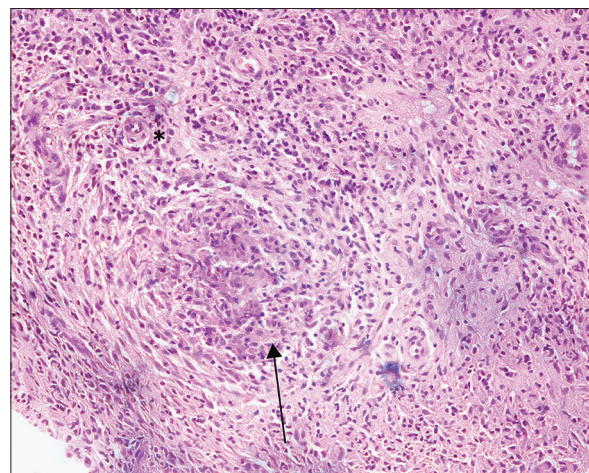


Figure 1: Hematoxylin and eosin staining with 100X magnification of synovial biopsy showing granuloma (arrow mark) with reactive vascular proliferation (asterix)

Table 1: Clinical features of patients with musculoskeletal tuberculous

Parameter	number (%)
Pain (%)	50 (98.03)
Swelling (%)	37 (72.54)
Fever (%)	15 (29.41)
Previous TB (%)	9 (17.64)
Arthritis (%)	40 (78.43)
Tenosynovitis (%)	6 (11.76)
Osteomyelitis (%)	5 (9.80)
Poncet's (%)	5 (9.80)
Associated lymphadenopathy (%)	12 (23.52)
TB: Tuberculosis	

presenting complaints [Table 1]. Fever was present in 15 patients. Continuous fever was observed in patients with Poncet's disease and intermittent fever in patients with osteomyelitis and disseminated TB. Nine patients had TB in the past. Arthritis/arthralgia was the most common manifestation ( $n = 40$ ), of which 28 had monoarthritis, 10 had oligoarthritis, and two had polyarthralgia [Table 1]. Total numbers of joints involved were 54; knee was the most common ( $n = 18$ ), followed by ankle ( $n = 15$ ), hip ( $n = 7$ ), sacroiliac ( $n = 5$ ), wrist ( $n = 5$ ), shoulder ( $n = 3$ ), and sternoclavicular joint ( $n = 1$ ) [Table 2]. Arthritis was followed by tenosynovitis ( $n = 6$ ); two had isolated tenosynovitis, two were associated with oligoarthritis, and one each was associated with monoarthritis and disseminated TB. Osteomyelitis was diagnosed in five patients. The bones involved were metatarsal, metacarpal, calcaneum, humerus, and rib. Poncet's disease was diagnosed in five patients. Two patients had polyarthralgia, two had oligoarthritis, and one had erythema nodosum with oligoarthritis. All the patients with Poncet's disease had lymph node as foci of TB. The synovial fluid examination was negative for TB in all the five patients with Poncet's disease. Other manifestations were bursitis ( $n = 1$ ), dactylitis ( $n = 1$ ), and pyomyositis ( $n = 1$ ). Disseminated TB was diagnosed in four patients. Twelve patients had associated lymphadenopathy, two had active pulmonary TB, and one had a pleural effusion.

Thirty-one patients were diagnosed as definite musculoskeletal TB, 18 had AFB positivity, 21 had histopathology revealing either AFB or granulomas, and 10 were culture positive for *M. tuberculosis*. Twenty patients were diagnosed as probable musculoskeletal TB. Empirical ATT was successful in relieving the symptoms. Mantoux was positive in 15 patients (available in 16). Quantiferon  $\gamma$  assay was positive in eight patients (available in eight). MRI was carried out in 24 patients. MRI revealed synovitis ( $n = 18$ ), bone marrow edema ( $n = 10$ ), bone erosions ( $n = 4$ ), osteomyelitis ( $n = 4$ ), tenosynovitis ( $n = 10$ ), para-articular abscess ( $n = 6$ ), and soft tissue involvement ( $n = 5$ ).

**Table 2: Pattern and number of articular involvement in musculoskeletal tuberculosis**

Joints involved	Total	Monoarthritis	Oligoarthritis
Knee	18	10	8
Ankle	15	4	11
Hip	7	6	1
Sacroiliac	5	4	1
Wrist	5	1	4
Shoulder	3	1	2
Sternoclavicular	1	1	-

## Outcome

All the patients received ATT for 12–18 months; four drugs, rifampicin (R), isoniazid (H), ethambutol (E), and pyrazinamide (Z) for 3 months followed by two drugs (RH) with pyridoxine for the rest of the duration. Thirty-five patients completed the treatment and recovered completely from the symptoms. Sixteen patients were referred to the local RNTCP clinic. There was no mortality. Patients of Poncet's disease have responded within 2–4 weeks of treatment with ATT. None of the patients had a relapse of the disease.

## Discussion

In an endemic country like India, musculoskeletal TB is not uncommon in a Rheumatology clinic and may mimic other inflammatory arthritis. It affected patients of all ages (children to elderly). Although chronic cold monoarthritis remains the most common clinical presentation, oligoarthritis was observed in almost a quarter of cases followed by tenosynovitis and Poncet's disease. Constitutional symptom like a fever was observed in less than one-third of the cases, and active pulmonary TB was uncommon.

Musculoskeletal TB is classically described in elderly population involving single joint, especially weight-bearing joints, especially knee and hip.<sup>[10,11,16-18]</sup> We have observed musculoskeletal involvement in quite a young population with a knee as the most common joint involved followed by ankle and hips. Similar to the previous reports, pain and swelling of the affected joints were the predominant presenting complaints.<sup>[12,13,17]</sup> Oligoarticular involvement has been reported in <10% of the cases in the previous studies and hip as the second common joint to be involved.<sup>[10,11]</sup> The reason for this discrepancy may be either due to endemicity, referral bias or different ethnic, and local environmental factors that predispose to musculoskeletal TB. The mean delay in the diagnosis in this study was 14 months which was similar to earlier studies.<sup>[2,19]</sup> The mean age at presentation in this study was 33 years, but osteoarticular TB is classically described in the elderly patients.<sup>[5]</sup> Although, all the patients in this study were HIV negative and had no co-morbid conditions, mean age at presentation was younger. A study in Nigeria also had osteoarticular TB prevalent during the second and third decades (mean age: 27.3 years); a similar study from Iran reported the first and second decades to be most commonly affected, but Houshian *et al.* found that the most common age was over 60 years.<sup>[20-22]</sup> A study at Bradford highlights the high proportion of musculoskeletal TB in the immigrant population, the majority of whom were originally from the Indian subcontinent.<sup>[23]</sup> This indicates that even in western countries, the prevalence of musculoskeletal TB is higher in persons who are initially natives of



endemic regions and patients are affected at a younger age without any predisposing conditions. A study from Thailand found that in the extra spinal osteoarticular TB group, most of the patients had preexisting conditions which predisposed them to infection, such as localized fracture, internal fixation/prosthesis, surgery, intra-articular or intra-regional corticosteroid injection, systemic corticosteroids/immunosuppressive drugs, chronic arthritis/osteoarthritis, avascular necrosis, and diabetes.<sup>[5]</sup> Different studies have described varying male to female ratios, from 0.8:1 to 2:1 ratio.<sup>[24-26]</sup> In this study, male and female were almost equally affected. This may be referral bias to the tertiary care center.

Interestingly, one-fourth of the patients had regional peripheral lymphadenopathy. Lymphadenopathy with TB arthritis has not been described previously. This provided a clue to consider infective etiology rather than inflammatory causes, especially in a setting of mono or oligoarthritis. Biopsy/FNAC of these lymph nodes was diagnostic of TB (granulomatous lesion and AFB positivity). In contrast to earlier reports, where concurrent pulmonary TB incidence varied from 19% to 42.6% in patients with spinal TB, we observed an incidence of only 4% of patients.<sup>[6,9,24]</sup> This may be explained by the fact that spinal involvement is likely to spread from the lymph nodes draining the affected lungs.

Osteomyelitis has been reported in up to 25% of the cases with musculoskeletal TB.<sup>[4]</sup> The most commonly involved bones are femur, tibia, and small bones of hands and feet.<sup>[4]</sup> Different studies have shown the variable involvement of the bones. In a study from Iran, long bones (femur and tibia) and short bones (calcaneus and toes) were equally affected (4.4% each) in TB osteomyelitis.<sup>[19]</sup> In our study, osteomyelitis involved the small bones of the hands and feet. These patients were referred as rheumatoid arthritis and on evaluation were diagnosed as TB. Disseminated TB was diagnosed in four patients, of which two patients had multidrug-resistant TB. Other rare involvements such as bursitis, dactylitis, and pyomyositis were also seen in a similar proportion to previous studies.<sup>[5]</sup>

Various presentations of Poncet's have been mentioned both with arthritis and also arthralgias.<sup>[27]</sup> In our series, we observed symmetric polyarthralgia and constitutional symptoms in two patients. Two patients had oligoarticular involvement, and one had erythema nodosum. In Poncet's polyarthralgia, one salient observation was a disproportionately severe pain when compared to joint inflammation and flexed position of the involved joints. This was the characteristic feature we observed in two of our patients. The synovial fluid examination did not reveal AFB. All these patients had tubercular lymphadenitis. Erythema nodosum has been traditionally considered to be frequently due to TB but was seen in only 6% of cases.<sup>[27]</sup>

Recently, Sharma *et al.* presented one of the largest series on Poncet's disease till date and proposed a new set of diagnostic criteria for it.<sup>[28]</sup> Although they have proposed arthritis as one of the essential criteria for diagnosing Poncet's disease, we have observed polyarthralgia with "out of proportion pain" in two of our patients. All the patients with Poncet's responded well to anti-tubercular therapy in our series as well. In three patients of Poncet's disease with oligoarthritis, we could not demonstrate mycobacterial infection in the synovial fluid either on staining or culture. Here lies the importance of the newer diagnostic techniques in diagnosing TB. Sharma *et al.* demonstrated the utility of multiplex PCR utilizing two target genes specific for *M. tuberculosis*, that is, IS6110 and MPB 64.<sup>[29]</sup> They could show a sensitivity of 100% in confirmed cases and 81.8% in clinically suspected cases. Routine availability of these kinds of newer diagnostic tests will help the clinicians in diagnosing TB quickly and confidently.

The treatment duration of TB arthritis has varied widely.<sup>[30]</sup> Except for disseminated TB and TB meningitis, the recommended treatment duration of extrapulmonary TB is 6–9 months according to the American Thoracic Society and Centers for Disease Control and Prevention (CDC; Atlanta, GA, USA) recommendations.<sup>[31]</sup> The duration of ATT could be extended to 18 or 24 months for multifocal osteoarticular TB because of the high rate of resistance of pathogens to chemotherapeutic agents and the typically impaired host immunity.<sup>[32]</sup> However, as conventional practice in our region, patients were treated for 12–18 months.

This study highlights few peculiar features of primary musculoskeletal TB; it can occur in immunocompetent individuals, generally does not present with constitutional symptoms and or pulmonary lesions, and may involve more than one joint and/or present with polyarthralgias. The classical textbook teaching that "TB arthritis is always monoarticular" needs to be changed to "TB arthritis is commonly monoarticular but it may present as oligoarthritis or polyarthralgias." History of previously suffering from TB or history of contact with a patient of TB and presence of peripheral lymphadenopathy should lower the threshold for considering the diagnosis of musculoskeletal TB even in HIV-negative individual.

A study of this nature is not without some limitations. Being a retrospective study, all the parameters were not available in all the patients. Mantoux test, Quantiferon assays, and TB culture were not done in all patients. Comparing with the previous studies is difficult because our study describes purely extra-spinal and in HIV-negative individuals [Table 3].

In conclusion, we would like to emphasize that musculoskeletal manifestations of TB can occur at any

**Table 3: Comparison of demographic and clinical features of musculoskeletal tuberculosis (case series)**

	Present study	Muangchan <sup>[5]</sup>	Yagi <sup>[30]</sup>	Talbot <sup>[23]</sup>	Huang <sup>[18]</sup>
Total number of patients (musculoskeletal TB)	51	99	24	61	51
Mean age (years)	33.4	50.9	50.5	42	58.9
Male:female	1.1:1	0.8:1	2.3:1	1.3:1	2.18:1
Delay in diagnosis (months)	14.7	3	8.9	-	25.4
Spinal involvement (%)	None	66.7	75	47.6	None
Associated pulmonary lesion (%)	3.9	30.3	79.16	13	51
Associated lymph node involvement (%)	23.5	-	-	-	-
Constitutional symptoms (fever, weight loss) (%)	17.6	38.4	-	-	8
Comorbidities	No	Yes	-	-	Yes

TB: Tuberculosis

age. Although chronic monoarthritis is the most common presentation, oligoarticular involvement with or without tenosynovitis is not uncommon. Primary musculoskeletal involvement in the absence of systemic symptoms may delay the diagnosis. Careful search for lymphadenopathy and/or positive past, family or history of contact may provide clues to the diagnosis.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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