CLINICAL FEATURES OF TUBERCULOUS SEPTIC ARTHRITIS IN KHON KAEN, THAILAND: A 10-YEAR RETROSPECTIVE STUDY

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Abstract. Tuberculous septic arthritis is difficult to diagnose. A retrospective analysis was done on patients over 15 years of age who attended Srinagarind Hospital, Khon Kaen, Thailand, between January 1, 1997 and December 31, 2006, whose synovial fluid culture was positive for *Mycobacterium tuberculosis*. The medical records of 77 patients were reviewed; one-third were in their sixth decade. Comorbid disease was found in 33 cases (42.9%), with systemic sclerosis being the most common (9 cases) followed by diabetes mellitus (5 cases) and chronic kidney disease (5 cases). Chronic monoarthritis was the most common presentation (34 cases) followed by acute monoarthritis (20 cases). More than half of the polyarticular involvements were disseminated tuberculosis. The knee was the most commonly affected joint (36.4%). Sixty percent had delayed diagnosis due to an incorrect diagnosis. Abnormal chest radiography and blood eosinophilia were found in 40 and 57.3% of cases, respectively. Synovial fluid and synovial tissue staining for acid-fast bacteria were positive in 30 and 40% of cases, respectively. A caseous granuloma was present in 57.5% of cases and non-specific synovitis in 12%. Sixty-three percent had bone erosions. Tuberculous septic arthritis should be considered in patients who present with acute or chronic monoarthritis, and who have an abnormal chest radiograph or eosinophilia. Polyarticular involvement was commonly related to having disseminated tuberculosis and may indicate systemic involvement of tuberculous infection.

Key words: *Mycobacterium tuberculosis*, tuberculous arthritis, tuberculosis, septic arthritis, disseminated tuberculosis

INTRODUCTION

Thailand is endemic for tuberculosis and there is a diversity of clinical manifestations (Desomchock and Tumrasvin, 1988). Tuberculous septic arthritis (TB arthritis) represents one-fifth (19.9%) of extrapulmonary tuberculosis cases reported (Huang *et al*, 2007). Despite the prevalence of TB arthritis in Thailand, there has been only one report in the last 20 years describing its clinical features (including spinal tuberculosis) and only the clinical data were presented (Desomchock and Tumrasvin, 1988). Although TB arthri-

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tis is a relatively rare manifestation of tuberculosis infection, it causes significant joint damage and disability, and may become a growing public health problem in an aging population.

TB arthritis is in the differential diagnosis of chronic monoarthritis, and is confirmed by positive acid-fast staining of the synovial fluid or a culture positive for *Mycobacterium tuberculosis*. Since TB arthritis is difficult to diagnose, particularly at an early stage, knowing the clinical characteristics of TB arthritis is crucial for early detection. Since *Mycobacterium tuberculosis* is an intracellular organism, we hypothesize there will be a difference in the clinical presentations of tuberculous septic arthritis between patients with underlying co-morbid rheumatic or non-rheumatic diseases and those having no underlying co-morbid disease; between patients with a monoarticular versus a polyarticular presentation. The objective of this study was to review the clinical presentation, laboratory data and treatment of patients positive for *Mycobacterium tuberculosis* by either synovial fluid or synovial tissue culture.

MATERIALS AND METHODS

We carried out a retrospective study of patients >15 years between January 1, 1997 and December 31, 2006 who were positive for *Mycobacterium tuberculosis* by synovial culture performed by the Microbiology Unit at Srinagarind Hospital, Khon Kaen University. Medical records were reviewed to obtain age, sex, co-morbidity, clinical presentation, medical treatment, complete blood count (CBC), synovial fluid analysis, radiographic data, pathological findings and treatment.

Chronic arthritis was defined as inflammatory arthritis that lasted for more than six weeks. Elderly was defined as being older than 60 years of age. Eosinophilia was defined as a total blood eosinophil count > 500 cells/mm^3. Steroid administration was classified as: (1) high dose, >30 mg prednisolone/day; (2) moderate dose, 15-30 mg prednisolone/d, and (3) low dose, <15 mg prednisolone/d.

Continuous data were presented as means±SD and categorical data as percentages. The chi-square or Fisher's exact test were used to analyze categorical outcomes. Statistical significance was defined as $p < 0.05$.

This study was approved by the Research Ethics Committee of the University of Khon Kaen (HE500329).

RESULTS

There were 77 cases in the study. The demographic data are presented in Table 1. The mean age was 51.1±14.2 years (range, 20-77). TB arthritis was principally found in persons in their fourth to sixth decades (57 cases; 74%); while 31.2% were over 60.

Co-morbid diseases were found in 42.9% of patients, of which 60% had either articular or connective tissue diseases, systemic sclerosis being the most common (Table 1). Sixty percent of elderly patients had co-morbid disease, while on 36% of the younger age groups had comorbid disease. Thirty-seven cases were referred to an orthopedist, 26 to a rheumatologist and 11 to both an orthopedist and a rheumatologist (*ie,* for co-treatment).

Ten cases (13%) received steroid treatment for two weeks before the onset of infection. High dose steroid treatment was given in one case (systemic sclerosis; SSC), moderate dose in two (systemic lupus erythematosus; SLE and nephrotic syndrome) and low dose in seven (1 with SSC,

Table 1
Demographic data.

Variable	Number of patients (%) $N = 77$
> 60 years old	24 (31.2)
Male to female ratio	47:30 (1.4:1)
Underlying disease	33 (42.9)
SSC	9
CKD	5
DM	5
Gout	5
SLE	4
MCTD	2
HIV	1
Chronic liver disease	1
Nephrotic syndrome	1
Clinical presentation	
Acute monoarthritis	20 (26)
Acute oligo-polyarthritis	8 (10.4)
Chronic monoarthritis	34 (44)
Chronic oligo-polyarthritis	15 (19.6)
Joint involvement	
Knee	28
Ankle	22
Wrist	16
Forefoot	8
Hip	7
Shoulder	6
Elbow	4

SSC, systemic sclerosis; CKD, chronic kidney disease; DM, diabetes mellitus; SLE, systemic lupus erythematosus; MCTD, mixed connective tissue disease; HIV, human immunodeficiency virus infection

Table 2
Findings of acid-fast staining and pathology.

Laboratory data	Number of patients (%)
Positive acid-fast staining of the synovial fluid	11 of 36 (30.5)
Positive acid-fast staining of the synovial tissue	16 of 35 (45.7)
Synovium biopsy	40
Granuloma	35 (87.5)
Caseous granuloma	23
Non-caseous granuloma	12
Nonspecific synovitis	5 (12.5)

1 with gout, 2 with mixed connective tissue disease; MCTD and 3 with SLE). None of the patients received other immunosuppressant therapy.

Chronic monoarthritis was the most common clinical manifestation (33 cases) followed by acute monoarthritis (20 cases), chronic polyarthritis (15 cases) and acute polyarthritis (8 cases) (Table 1). The knee was the most commonly affected joint (28 cases) followed by the ankle, wrist, forefoot, shoulder and elbow.

Adjacent soft tissue and bony involvement were found in 28 cases (18 with synovial cysts, 8 with osteomyelitis, 2 with tenosynovitis and 1 with a cutanous fistula. Twenty-five cases (32.5%) had disseminated tuberculosis; however, only one-third presented with constitutional symptoms. Twenty-one cases had pulmonary tuberculosis, 1 had tuberculous meningitis, 2 had both tuberculous meningitis and pulmonary tuberculosis, and 1 had tuberculous lymphadenitis and ileitis.

Forty-three patients (55.8%) had a delayed diagnosis because of an incorrect initial diagnosis (Table 2) and 19 of 43 had co-morbid disease. Nearly half the patients had underlying rheumatic disease. More than 65% of the underlying rheumatic disease cases were given a diagnosis of arthritis which correlated with their initial underlying disease. Diagnoses were delayed more frequently when the arthritis was acute than when it was chronic.

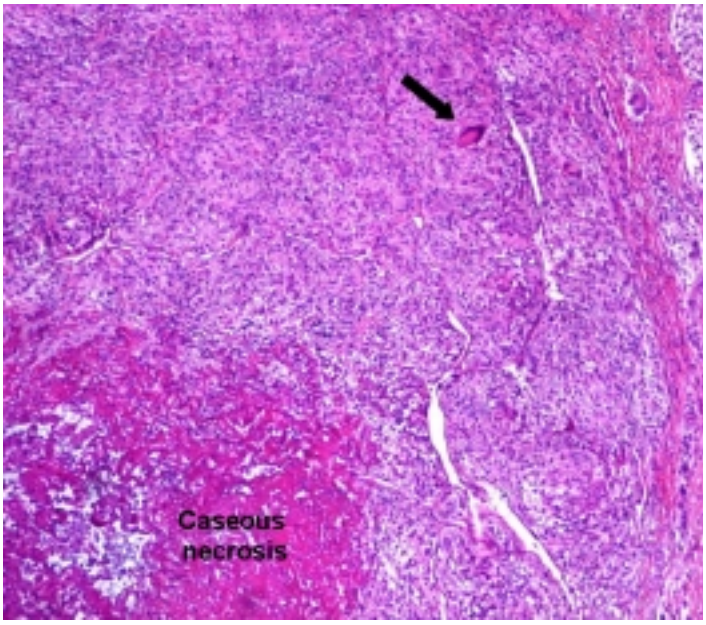

Fig 1–Caseous granuloma of tuberculous septic arthritis. In the lower left of the figure is an area of caseous necrosis surrounded by epithelioid macrophages and Langhans giant cells (black arrow).

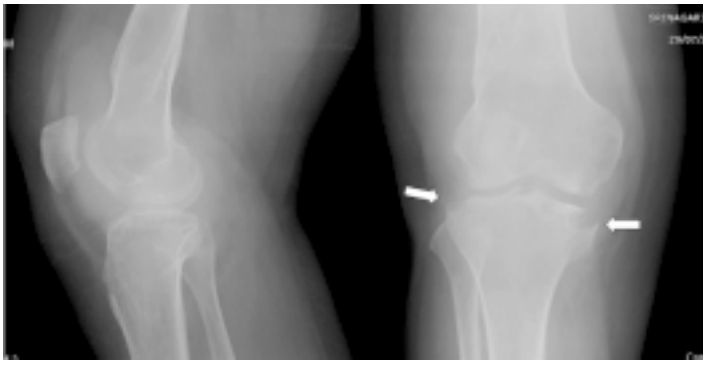

Fig 2–Radiographic changes typical of early tuberculous septic arthritis in the knee joint (left: lateral view; right: anteroposterior view). The findings reveal a normal joint space with soft tissue swelling and marginal boney erosion of the tibia (arrow).

Non-tuberculous bacterial septic arthritis was the most common initial diagnosis for the cases of acute onset (12 cases). Other initial diagnoses were synovial tumor (6 cases), scleroderma arthritis (5 cases), gouty arthritis (5 cases), soft tissue tumor (4 cases), osteoarthritis (4 cases), rheumatoid arthritis (3 cases), undifferentiated arthritis (3 cases) and SLE arthritis (1 case). In almost 40% of the delayed-diagnosis cases, the diagnosis of TB arthritis was not made before 6 months after onset. On average a diagnosis of TB arthritis was made at 17.7±31.4 (1-71.7) months.

Chest radiography was performed on 53 of the patients and in 21 an abnormality was detected (39.6%): 18 had upper lobe infiltration and 3 had miliary infiltration. A complete blood count was done in 68 patients, of whom 39 had eosinophilia (57.3%).

Arthrocentesis was performed on 62 of the patients and most of the synovial fluid results (79.2%) showed inflammation with neutrophilia predominated. A non-inflammatory fluid result and septic profile were found in 12.5 and 8.3%, respectively. Purulence was found in 44% of cases; straw and bloody color were found in 40 and 17%, respectively. The synovial sugar was 20% lower than the serum sugar in 83% of cases. The synovial fluid and synovial tissue were positive on acid-fast staining in 30 and 40%, respectively (Table 2). Three-quarters of those with purulent fluid were positive on acid-fast staining, compared to

Table 3
Comparison of clinical symptoms between patients with underlying co-morbid rheumatic or non-rheumatic diseases and no underlying co-morbid disease.

Variable	Underlying disease			*p*-value
	No underlying disease $N = 43$	Rheumatic disease $N = 20$	Non-rheumatic disease $N = 14$	
> 60 years old	23.3%	35%	50%	0.143
Females	27.9%	55%	50%	0.078
Constitutional symptoms	35.7%	77.8%	61.1%	0.029[a]
Acute arthritis	37.2%	70%	64.3%	0.067
Oligo-polyarthritis	20.9%	50%	28.6%	0.078
Disseminated tuberculosis	32.6%	35%	28.6%	0.925
Abnormal chest radiography	39.3%	37.5%	44.4%	0.942
Bony erosions	88.2%	70.6%	50%	0.064
Eosinophilia	66%	44.4%	50%	0.563
Synovial fluid AFB positive	15.8%	57.1%	0%	0.024[a]
Synovial tissue AFB positive	35%	70%	40%	0.200

[a]significant difference

17 and 8% of those with bloody colored and yellow colored fluid.

A synovial biopsy was done in 40 patients (Table 2), revealing that 40% and 44% of patients with positive acid-fast staining of synovial fluid and synovial tissue, respectively, had granulomatous lesions (Fig 1). One patient had non-specific synovitis (20%) positive for acid-fast staining of the synovial tissue.

A bone radiography was performed in 61 patients; boney erosions were found in 47 cases (63.9%) (Fig 2). Fourteen patients with acute arthritis had early bone erosion at onset; the erosions trended to increase the longer the case went untreated.

Eighteen patients underwent acid-fast staining of their synovial fluid, and had chest and bone radiography. Only two had abnormal results on all three tests, while seven had two abnormal results and six had one abnormal result. Three cases had a normal result on all three tests.

The majority of TB arthritis case presenting as acute onset arthritis were confirmed by: (1) positive acid-fast staining; (2) early onset bony erosions; or, (3) finding a granuloma on pathology. Positive acid-fast staining of the synovial fluid occurred in both acute and chronic onset cases of TB arthritis (37.5 and 25%; p=0.483) whereas caseous granulomas were found in 70% of acute and 53.3% of chronic onset arthritis cases (p=0.148).

Tuberculosis treatment was started before culture results were back in 21 cases. Eleven cases had acid-fast positive synovial fluid and 10 had boney erosions at onset. Most of the cases were treated with a standard regimen of isoniazid (I), rifampicin (R), pyrazinamide (Z) and ethambutol (E) (IRZE). Eight cases were switched to other regimens due to adverse

Table 4
Comparison of the clinical features with joint involvement.

Variable	Number of joint involvement		*p*-value
	Monoarticular ($N = 54$)	Polyarticular ($N = 23$)	
> 60 years of age	29.6%	34.8%	0.655
Females	33.3%	52.2%	0.121
Constitutional symptoms	41.7%	68.4%	0.049[a]
Acute arthritis	50%	52%	0.851
Disseminated tuberculosis	22.2%	56.5%	0.003[a]
Abnormal chest radiography	29.4%	57.9%	0.042[a]
Bony erosion	76.7%	77.8%	0.708
Eosinophilia	59.1%	54.5%	0.803
Synovial fluid AFB positive	26.1%	38.5%	0.439
Synovial tissue AFB positive	38.5%	66.7%	0.143

[a]significant

drug reactions (hepatitis in 5 cases and rash in 3 cases). Thirty-three cases received tuberculosis treatment for more than 6 months: these included disseminated tuberculosis (3 cases), disseminated tuberculosis with extensive bony erosions (22 cases), and a regimen change due to adverse drug reactions (8 cases). Arthrotomy and drainage were done in 20 cases; 12 were given an initial diagnosis of non-tuberculous bacterial septic arthritis.

A clinical comparison of TB arthritis between the patients who had an underlying co-morbid disease (rheumatic *vs* non-rheumatic) and no underlying co-morbid disease is shown in Table 3. Constitutional symptoms and positive acid-fast staining of the synovial fluid were more frequently found in patients with underlying rheumatic disease than other groups (p=0.029 and 0.024, respectively).

Acute onset polyarthritis was found more frequently in those with underlying rheumatic disease. Elderly onset arthritis was found slightly more frequently in patients with co-morbid disease, but this was not significant. There were no significant differences in numbers of patients with disseminated tuberculosis, abnormal chest radiography, bony erosions and eosinophilia.

A comparison between those with monoarticular and polyarticular arthritis is shown in Table 4. Polyarticular presentations at onset were more likely to be found in patients with constitutional symptoms, abnormal chest radiography and disseminated tuberculosis, than in those with a monoarticular presentation. Positive acid-fast staining of synovial fluid or tissue was slightly more common in cases with polyarticular involvement than in cases with monoarticular involvement, but this was not significant.

DISCUSSION

TB arthritis is usually discovered in persons of an advanced age (*ie*, over 50 years of age) (Berney *et al*, 1972; Desomchok

and Tumvasvin, 1988; Reider *et al*, 1990; Huang *et al*, 2007). The majority of TB arthritis patients in our study were in their fourth to sixth decade; one-third were over 60. Males slightly outnumbered females. In some countries females are more often affected than males (Jutte *et al*, 2004). Nearly half of patients had a previous underlying disease. Rheumatic diseases (SSC, gout, SLE, MCTD and RA) and immunocompromised conditions (*eg*, DM, CKD, HIV and chronic liver disease) constituted the majority of comorbidities in our study.

SSC was the most common comorbidity in our study. Although one patient had a history of moderate steroid use, the majority of SSC patients had no history of immunosuppressant or steroid treatment. TB arthritis has been reported to occur with SLE and DM (Berney *et al*, 1972; Decsomchok and Tumrasvin, 1988), but to our knowledge, not with SSC; although there is one case report of tuberculous fasciitis in SSC (Lee *et al*, 2004).

An association between SSC and tuberculosis has not been proven. T-lymphocyte reduction in SSC (Whiteside *et al*, 1983) may be the predisposing factor to TB infection and TB reactivation. The 65 kDa *Mycobacterium tuberculosis* heat shock protein (HSP) has been found in various autoimmune diseases, including SSC (Danieli *et al*, 1992; Karopoulos *et al*, 1995). Molecular mimicry between bacterial HSP and human HSP may explain antibody production with autoimmune disease, particularly with SSC (Smiley and Hoffman, 1991). The level of tumor necrosis factor alpha (TNF-alpha), which plays an important role in granulomatous formation, especially in response to TB infection (Fenhalls *et al*, 2002), was elevated in patients with: 1) localized SSC (Hasegawa *et al*, 2003); 2) limited cutaneous SSC; and, 3) diffuse cutaneous SSC (Hasegawa *et al*, 1997). It may be a key cytokine explaining the correlation between SSC and tuberculosis. A possible mechanism for this correlation is unclear; further investigation is warranted.

The typical presentation of TB arthritis is chronic monoarthritis in a weight-bearing joint (Huang *et al*, 2007). TB arthritis may present as acute monoarthritis, particularly in patients with baseline rheumatic disease or advanced age. Polyarticular involvement was seen in 30% of our cases, and more than half had disseminated tuberculosis, versus one-fifth of cases with monoarticular involvement. A polyarticular presentation may indicate systemic involvement with tuberculosis infection.

Diagnosis of TB arthritis remains problematic in Thailand (Deesomchok and Tumrasvin, 1988) because of the low rate of positives with acid-fast staining (Muangchan and Milganuwong, 2009). Only 30% and 45% of our patients had positive acid-fast staining of the synovial fluid and synovial tissue, respectively. Therefore, a delayed diagnosis and an incorrect initial diagnosis were common in more than half the patients in our study.

Underlying rheumatic disease, acute onset arthritis and nearby soft tissue masses can also affect the initial diagnosis. Infiltrative lesion(s) seen on the chest radiograph and constitutional symptoms may provide clinical clues to facilitate the early diagnosis of TB arthritis, although such evidence is present in a minority of cases (Jutte *et al*, 2004; Gardam and Lim, 2005).

In our study, a large number of caseous granulomas and eosinophilia were found in those with acute onset TB arthritis. Eosinophilia and synovial biop-

sies may help to increase the likelihood of early diagnosis. Although caseous granulomas are a pathopneumonic finding for the diagnosis of TB arthritis, nonspecific synovitis can also be seen as a strong indicator of TB arthritis. Our study revealed positive acid-fast staining in cases with nonspecific synovitis. Acid-fast staining should be done when the pathological finding of nonspecific synovitis is present, especially if TB arthritis is being considered.

Eosinophilia was found in more than half of our cases. A previous study found an association between blood eosinophilia and tuberculosis (Ellioff *et al*, 2003). Eosinophilia, eosinophilic pleural effusions and eosinophils on bronchoalveolar lavage have been reported in pulmonary tuberculosis (Vijayan *et al*, 1992; Reechaipichilkul and Chuesakoolvanich, 2003) but the association between eosinophilia and tuberculosis is not conclusive. A hypersensitivity reaction to mycobacterial antigens in patients living in an endemic area with helminthes may explain this observation (Ray and Abel, 1994), but the mechanism remains unclear.

In our study, purulent synovial fluid correlated with positive acid-fast staining, better than bloody or yellow colored synovial fluid. Synovial fluid cell counts and differentials provided nominal information in our study. The synovial fluid cell count varied between 2,000 and 100,000 cells/mm^3 and polymorphonuclear cells predominated, as has been previously reported (Wallace and Cohen, 1976). Basic synovial fluid analysis may be helpful to diagnose TB arthritis if pus is present.

A limitation of this study was small sample size and the use of retrospective data. As a consequence, data regarding joint outcome was not presented. Only *M. tuberculosis* culture positive cases were included in this study, so patients with a negative culture but presenting with clinical or pathological findings consistent with TB arthritis were not included. This data, nevertheless, has value for improving patient care.

TB arthritis is frequently found in elderly, immunocompromised patients, who have underlying rheumatic disease, with systemic sclerosis being the most common. The typical presentation of TB arthritis was chronic monoarthritis; however, acute monoarthritis was not uncommon. Disseminated tuberculosis occurred in one-third of our cases and most had polyarticular involvement at onset. Pulmonary infiltration may be seen on chest radiography while blood eosinophilia might be helpful for diagnosis. Positive acid-fast staining of synovial fluid and tissue was found in 30 and 45% of cases, respectively. Tissue biopsy may show non-caseous granulomas or nonspecific synovitis.

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