



Tuberculous Arthritis: A Forgotten Diagnosis During Pandemic Covid-19



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ABSTRACT

Tuberculosis (TB) is a respiratory disease that primarily affects the lungs. The challenge is to recognize the characteristic of TB disease, including extrapulmonary presentation. TB arthritis is an extrapulmonary TB presentation in the joint, which is frequently neglected and misdiagnosed. A 41-year-old female patient was presented with a major complaint of chronic pain in her left wrist for three months. The patient had a low-grade fever without respiratory symptoms. Local examination revealed swelling, warmth and tenderness. Erythrocyte sedimentation rate (ESR) was increased and chest radiograph demonstrated pulmonary TB. She underwent arthroscopy debridement and culture examination. We initiated adjuvant anti-tuberculous treatment. On the evaluation, she reported relief from pain and showed improvement in general condition. TB arthritis is unique due to its rare incidence and unspecific clinical manifestations. A better understanding of these issues will prevent possible diagnostic errors. Prompt treatment was crucial to maintain joint function and prevent permanent destruction.

Introduction

Tuberculosis (TB), one of Indonesia's endemic diseases, remains a leading cause of morbidity and mortality. In 2001, the World Health Organization (WHO) reported 2.4 million cases, and approximately 2 billion people worldwide have latent TB infection. During 2007, an estimated 9.27 million new TB cases were diagnosed, with 13.7 million prevalent cases and 1.32 million deaths. Asia

and Africa constitute 86% of all cases in the world [1]. Musculoskeletal involvement is found in 1 to 3% of patients with TB and for approximately 10-11% of extrapulmonary TB cases [2].

Unfortunately, the world is now facing a new outbreak of emerging disease. In late December 2019, a new type of severe acute respiratory syndrome determined by a novel strain of the Coronavirinae family named Covid-19 developed from Wuhan, China

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[3]. The infection has expanded across the globe and was declared a global pandemic by WHO on March 11, 2020. Until April 30, 2021, Covid-19 has infected 151,737,995 patients, out of which 130,402,065 recovered and 3,309,008 died. The first case Covid-19 reported in Indonesia was on March 2, 2020, and as of April 30, 2021, a total of 1,668,368 cases was confirmed with a 2.73% mortality rate [4].

TB and Covid-19 are respiratory diseases that primarily affect the lungs with similarity in the initial clinical manifestations. The different characteristic of TB compared with Covid-19 is the various affected sites of infection outside the lungs (extrapulmonary TB), including skin, central nervous system, gastrointestinal, genitourinary and skeletal [5]. In 75% of extrapulmonary TB cases, the causative pathogen from a primary focus like lungs, kidney, or lymph node is spread via hematogenous way [6]. The spine is the most frequently affected site of skeletal TB, followed by the pelvis, hip and femur, knee and tibia, and ribs [2]. History of infection and evidence of active tuberculosis is essential to make a diagnosis. A negative tuberculin skin test or non-conclusive microbiological culture should not reduce the suspicion of diagnosis [2, 6]. As our intense current efforts have focused more on pulmonary TB, skeletal TB has been relatively neglected [7]. Unawareness combined with a lack of specific signs and symptoms, mainly in the rare presentation, may contribute to missed diagnosis and

inadequate treatment. The challenge is to recognize the characteristics of this disease. This paper aims to lead health providers to consider and raise awareness of the diagnosis of TB arthritis.

Case Presentation

A 41-year-old Asian female patient presented with a major complaint of chronic pain in her left wrist. The symptom was started three months earlier when the patient had a low-grade fever and generalized malaise. At that time, she reported a mild pain but no swelling, warmth, or erythema on her wrist. After two months, the patient's complaints had worsened with continuously increasing pain and swelling. She lost her appetite and weight by 4 kg in two months. She later went to a clinic and received analgesics and antibiotics therapy. However, this only provided symptomatic relief for several days. Two weeks before the admission, the pain returned and became more severe, forcing her to rest her arm completely. She also began having another complaint of pain in her right distal knee. There was no previous history of trauma and family background of tuberculosis or malignancy. The patient appeared asthenic with a body mass index of 17.8 kg/m².

Local examination revealed swelling, warmth, and tenderness over the left wrist and right distal knee. The range of motion of the wrist in all planes was



Fig. 1. Initial clinical photograph showed swelling and erythema over the left wrist

limited due to severe pain. There was no lymph node enlargement and sinus leakage from any skin sites.

Laboratory investigation revealed normochromic normocytic anemia with hemoglobin of 10.4 g/dL, elevated erythrocyte sedimentation rate (ESR) of 100 mm/h, and normal white blood cell count of $6.68 \times 10^3/\mu\text{L}$ with elevated neutrophil and monocyte presentation.

Chest radiograph demonstrated patchy infiltrate on both lungs, which showed evidence of pulmonary tuberculosis (Figure 2). Plain radiograph of the left wrist showed soft tissue swelling, rarefaction, and thinning of the head ulna and distal radius. An overall decrease in the joint space of the wrist was noted (Figure 3).

Suspicious of septic arthritis was made, and the patient underwent arthrotomy debridement and soft tissue biopsy of the left wrist and right knee under general anesthesia. Histopathology examination of the debrided tissue material revealed cell necrosis with infiltration of polymorphonuclear and mononuclear inflammatory cells suspecting a nonspecific inflammation.

While waiting for culture and biopsy results, the patient was treated with empiric broad-spectrum

antibiotic therapy for one week. By the end of the treatment period, the response was not typical. The patient reported intermittent pain and sinus leakage from the wrist and knee. Despite the unclear culture and biopsy results, however, the clinical, laboratory, and radiograph findings were suggestive of polyarthritis TB of the wrist and knee. The patient then was commenced on combination adjuvant anti-tuberculous therapy consisting of rifampicin, pyrazinamide, isoniazid, and ethambutol for the first two months with supplementation vitamin B₆. The wrist joint was immobilized in a neutral position for about two weeks till the swelling was reduced. Afterward, the wrist was gradually mobilized until the full range of motion was achieved to restore strength and range of motion. Following this treatment for six months, the symptoms were significantly improved. The patient reported relief from pain and swelling with increased wrist and knee movement. She showed improvement in general condition and was able to return to work without any complaints. The patient was suggested to have physical therapy to maintain the range of motion of the joint.

Discussion

Tuberculosis (TB) manifestations are classified as either pulmonary or extrapulmonary. Skeletal TB accounts for up to 35% of extrapulmonary TB and may



Fig. 2. The chest radiograph showed patchy infiltrate on both lungs



Fig. 3. The plain radiograph anteroposterior (AP) and lateral (L) view of the left wrist showed soft tissue swelling, joint space narrowing, and rarefaction of the head ulna and distal radius



Fig. 4. Clinical photographs two days after arthrotomy debridement showed productive discharge



Fig. 5. Clinical photographs after six months follow-up showed improvement range of motion (ROM) a) dorsal flexion, b) palmar flexion, c) pronation, d) knee extension, e) knee flexion

involve any part of the body's skeleton [8]. In an adult, the spine is the most commonly affected site known as Pott's disease, which responsible for 51% of total skeletal TB cases, followed by weight-bearing bone and joints such as the pelvis (12%), hip and femur (10%), tibia and fibula (10%), and ribs (7%) [2, 6]. When joint involvement occurs, it is usually monoarthritis, and only 10-15% of cases being polyarthritis [2]. Non-weight bearing joint infection is rare, moreover in an upper extremity.

TB arthritis generally arises from the reactivation of bacilli lodged in adjoining bone during the original mycobacteremia of primary infection or a hypersensitivity reaction to the tubercle bacilli (Poncet's arthritis). The predilection of the bacillus for the spine and large joints can be explained by the rich vascular supply of the vertebra and growth plates of the long bones [9].

Pathogenesis of TB arthritis involves reactive hyperemia resulting in marked juxta-articular bone demineralization, local bone destruction, and periosteal new bone formation [2]. TB infection in a joint starts as synovitis, causing joint effusion, progressing to periarticular demineralization, marginal erosions, and finally joint destruction [2,

9]. As an inflammatory reaction to infection, the synovium generates granulation tissue production, which invades and ultimately erodes the articular cartilage by forming "pannus" [9]. When the process reaches the subchondral region, the articular cartilage gets detached from the bone resulting in necrotic bodies [2]. Fibrin in the synovial fluid and the articular cartilage may precipitate, forming "rice bodies" [9]. Periarticular soft tissue masses, cold abscesses and sinus tracts may develop in late disease [2].

The earliest manifestation is local pain and swelling followed by mild restriction of movement of the affected joint [9]. Pain may precede signs of inflammation for weeks or months. The main characteristic of all TB infections is slowly progressive. In the later stage, worsening chronic pain, wasting regional muscle, progressive loss of function, and joint deformity may appear [2]. Enlargement of regional lymph nodes and the presence of an abscess is also a great diagnostic significance clinically. Systemic symptoms such as fever, night sweat, or weight loss may or may not be present during TB arthritis [9]. Chest x-ray pulmonary foci are only seen on less than 50% of patients presenting with skeletal TB [8].

Hematological data can contribute to the diagnosis

of TB arthritis. Leukocyte count is usually normal, but erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) concentration are often raised [10]. Acid-fast smear examination has low sensitivity to diagnose TB arthritis because Ziehl-Nielsen stain can reveal acid-fast bacillus only if the sample contains greater than 10,000 bacilli/ml³. Tuberculin skin test and polymerase chain reaction (PCR) test may also help make the diagnosis, but a negative result does not by itself exclude the possibility of TB [11]. Indeed, in the tuberculin test, a false-negative rate of 14% was reported [12].

Imaging findings in skeletal TB are often nonspecific and only indicative of an infective etiology, rather than an exact causative organism. A plain x-ray of the affected joint includes periarticular bone destruction, subchondral erosions, and gradual narrowing of the intraarticular space known as “Phemister triad” [2, 12]. In the initial stages, a plain x-ray may be typical. CT scan can be used to assess the degree of bone destruction, soft tissue extension, and sequestrum formation in the joint space [2]. MRI scores more than other modalities in showing all tubercular pathology features, including synovitis, effusion, articular erosions, active and chronic pannus, abscess, tenosynovitis, bursitis, bone chips, and marrow edema [7].

The gold standard diagnostic tools were established through synovial biopsy and mycobacterial culture. Histopathological examination of the specimen taken from the lesion, which is positive in 80% of cases, shows cessation granulomas, specific chronic inflammation cells, or giant cells with cessation are very characteristic of TB arthritis [7]. Microbiological culture test of the synovial fluid can identify mycobacterium in 60-80% of samples [13].

We reported an uncommon presentation of skeletal TB. The incidence of TB arthritis of the wrist and knee is less than 1%. Considering the risk factors, physical examination, laboratory and radiograph findings, we concluded this case as polyarthritis TB of the wrist and knee. Identification of *M. tuberculosis* is essential for diagnosing TB arthritis, which can be achieved through culture and histopathologic examinations. According to the principal diagnosis procedure, we performed arthrotomy debridement and tissue biopsy under general anesthesia. Moreover, we did a microbiological culture examination of the debrided specimen. Unfortunately, we got unclear results of biopsy and culture. These results can occur due to low-quality sampling or the effect of previous empiric antibiotics.

In a study conducted by Piccazzo et al., clinical and chest radiographs in high-risk populations demonstrate high consistency of case finding TB infection with the false-negative examination is about 1% in adult immunocompetent and increasing to 7-15% in adult immunocompromised. Different studies of chest radiograph findings for TB diagnosis found an overall sensitivity of 96% and specificity of 47% in a high-risk population [14]. Moreover, an Indonesian study conducted by Saktiawati et al. found that the TB routine examinations, including clinical, bacteriological sputum, and chest radiography examination had a sensitivity of 85-90% and specificity of 86-99% [15]. Our patient comes from a TB endemic area and low socioeconomic status. She experienced a chronic progressive pain and low-grade fever with an elevation of ESR level and patchy infiltration in her lungs. Although all of these findings indicated TB's diagnosis, TB arthritis has a great number of clinical variants and can mimic many other diseases. Similar to TB infection in the initial stage, Covid-19 symptoms such as dry cough and fever may confuse TB's diagnosis, especially during the pandemic period³.

Adjuvant anti-tuberculous therapy was initiated and the patient showed clinical improvement. In Yang et al.'s study in Taiwan, 87% of smear-negative patients clinically diagnosed with TB were positively confirmed to have TB based on their excellent response to therapy [16]. Anti-tuberculous chemotherapy is the cornerstone in the management of extrapulmonary TB. In TB arthritis, some experts recommend more than 12 months or until radiological or pathological evidence of regression occurs. There is a tendency that over-treatment is preferable to under-treatment [5]. A standard first-line anti-tuberculous chemotherapy is defined as a four-drug regimen of isoniazid, rifampicin, ethambutol, and pyrazinamide for two months as initiation phase followed by isoniazid and rifampicin for another 7-10 months as continuation phase [5]. The outcomes are categorized as successfully treated, relapsed, defaulted, transferred, or died.

Splints and immobilization may help to relieve acute symptoms and to prevent deformities for a long time. Operative treatment is usually limited and includes obtaining a biopsy, performing open or arthroscopic debridement, incision drainage of the abscess and synovectomy [7].

Conclusion

Tuberculosis is a common disease entity in Indonesia, but its presence in the wrist and knee joint is unusual. The insidious onset, atypical clinical manifestations, and the low index of suspicion may result in a missed

diagnosis. Diagnosis of TB arthritis is possibly made through history taking, clinical, laboratory and radiographs examination. A prompt treatment with an anti-tuberculous therapy was crucially required to maintain useful joint function and prevent permanent bone destruction. Health providers should be familiar with the diagnosis of TB arthritis and prevent possible diagnostic errors.

Ethical approval

This study has been reviewed by the authors' Institutional Review Board.

Informed consent statement

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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CRedit authorship contribution statement

Thomas E. C. J. Huwae: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing - original draft, Writing - review & editing. Alva Pribadi: Conceptualization, Data curation, Formal analysis, Resources, Visualization, Writing - original draft, Writing - review & editing.

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