Chapter 6
Tuberculosis Arthritis and Osteomyelitis

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6.1 Tuberculosis Arthritis

6.1.1 Epidemiology

Musculoskeletal tuberculosis (TB) is a rare extra-pulmonary complication of *Mycobacterium tuberculosis*. Osteoarticular tuberculosis is still a common problem in developing countries. All the cases should be questioned according to birth or resident area to state a country with high TB prevalence [1, 2]. Bone and joint TB infection is a secondary form of TB occurring most commonly due to hematogenous seeding by retrograde lymphatic and contiguous dissemination are the other less common spread from a primary focus such as the lung, kidney, or lymph node or, infrequently, through contiguous spread from adjacent tissues by direct inoculation [3]. About half of the cases involve spinal involvement and the rest involve extraspinal osteoarticular joints. Bone and joint tuberculosis accounts for 1–4.3% of all tuberculosis cases [4, 5] and 10–15% of all extrapulmonary tuberculosis cases, but the incidence of those cases has been rising due to the increasing number of immunosuppressed patients and HIV infections [5, 6]. Rarely, tenosynovitis, bursitis, or pyomyositis may occur at lower rates [7]. Commonly involved body areas are backbone and weight-bearing joints. On the other hand, joint tuberculosis may be due to direct invasion of the synovia, such as Poncet's arthritis [5, 7]. In addition, weight-bearing joints such as wrist, elbow, and the small joints of the hands may be involved. Results of joint diseases are periarticular demineralization, marginal

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erosion sites, and consequently a synovitis with impaired support structure [8]. Synovitis can be rapid in joint damage, especially in weight-bearing joints. If tuberculous tenosynovitis and arthritis become complicated due to a secondary infection such as *Staphylococcus aureus*, severe systemic symptoms and increased joint damage may be observed [5]. There is increased susceptibility to tuberculosis infection in patients with sickle cell disease and chondrocalcinosis at the bottom and other joint involvement and osteonecrosis. Additionally cases of tuberculous arthritis can be found in patients with Sjögren's syndrome, rheumatoid arthritis, seronegative arthropathies, gout, and Charcot arthropathy [5]. Immunosuppressive and/or glucocorticoids therapy, patients receiving anti-TNF therapy have suggested an increased incidence of joint infections.

Joint tuberculosis may cause severe deformation and loss of motion in the joint due to delayed diagnosis of TB in cases of low-endemic area and additional pathology [9]. TB of joints is most commonly monoarticular [5, 6]. Different findings have been reported in terms of age and gender predominance in different case series. In general TB arthritis is more common in children [5]. However Enache et al. found in a 10-year case report that 2/3 patients were over 40 years of age [10]. Two studies reported 50 and 60 years; in that study, the rate of female was generally more dominant; on the other hand, in some study it has been found that a bone joint involvement is more common in men [5, 7, 11].

6.1.2 Clinical Feature and Diagnosis

Granulomatous changes and cartilage erosion cause chronic effusion and progressive joint damage. Findings of acute inflammation are rarely seen; local deformity and movement restriction are more frequently observed. The most common symptom is chronic joint pain; it may be only minimal signs of inflammation [9]. In some cases, local swelling and a sinus tract can be seen as additional [5]. Monoarticular arthritis is common in case of joint tuberculosis [5, 6]. Strong night pain can be encountered in TB of hip and knee joints and wasting of the regional muscle, and some deformities may occur. 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, but negative results do not exclude diagnosis [12]. Although imaging features of joints and tendons TB X-ray features have been generally found nonspecific, a painless cold abscess may be reported as the only clinical presentation less common [8, 12]. Radiographic features are usually recognized 2–5 months after the onset of the disease [5, 13]. The classic triple of TB tenosynovitis and arthritis (Phemister's triad) are juxta-articular osteoporosis, peripheral bone erosion, and intra-articular space narrowing gradually in the radiological features [2, 14]. Computed tomography (CT) and magnetic resonance imaging (MRI) are useful for further identification of the disease [15–17]. MRI better defines soft tissues infections, and CT is better for bone lesions. MRI features of tuberculous

tenosynovitis and arthritis include synovitis, effusion, central and peripheral erosions, active and chronic pannus, abscess, bone fractures, and hypo-intensive synovia. MR is the preferred investigation to reveal the degree of the disease and severity of the damage [15]. MR is also non-specific but better describes the width of the lesion when compared to X-rays. These imaging features may help to diagnose tuberculous tenosynovitis and arthritis in an appropriate clinical setting [15, 18].

Severe clinical suspicion is required. In the case series by Enache et al., clinically delayed due to the absence of specific clinical findings were found as 26% and cause a delay in diagnosis of joint TB infection [6, 10]. On the other hand, on a retrospective evaluation, clinically suggestive findings were found in only 26% of joint TB infections.

Clinically, TB tenosynovitis and arthritis are evaluated at five stages [15, 19]:

- Stage I or synovitis: tissue edema, bone lesions, and localized osteoporosis are present, and the outcome of the treatment is excellent.
- Stage II results in early arthritis with marginal erosions (one or more erosions or lytic lesions in the bone, reduced joint space) and mild joint stiffness.
- Stage III is advanced stage arthritis with cyst formation and loss of joint space; the result is a serious loss of motion.
- Stage IV is arthritis at a more advanced level with limited joint disruption and post-joint therapy and limited mobility.
- Stage V is ankylosis of the joint.

General laboratory findings are also neither specific nor reliable. Raised ESR has been observed [5]. PPD has a limited role in adults in high prevalence area but can be useful in children under 5 years.

Synovial fluid aspiration: Synovial fluid is usually nonhemorrhagic, with moderate elevation of the white blood cell count, below 50.000 cells/mL with a predominance of polymorphonuclear leukocytes or lymphocytes. AFB smear and culture for *M. tuberculosis* should also be planned. A direct smear of synovial fluid or operative specimen can show positivity for AFB in as low as 27% of cases [6]. During AFB investigation, it is recommended to obtain at least two, preferably three, samples, and if the bacteria are more than 10,000 per ml in the sample, AFB can be revealed. Different culture methods such as Lowestein-Jensen medium and radiometric (Bactec 12B fluid medium) and non-radiometric (Bactec MGIT 960 system) culture can be used to confirm in the paucibacillary state [15].

Diagnosis can be classified into three categories [5]:

1. Definitive confirmed TB diagnosis – had positive culture
2. Suspected TB – had positive AFB smear/chronic granulomatous inflammation
3. Possible TB – favorable radiological and clinical response to antituberculosis treatment

Culture is the gold standard, and the specimens t are biopsy specimen, aspiration from joint space, or sinus tract specimen should be examined by AFB smear and histopathologic method as well as cultures [5, 6]. Generally culture positivity has been found low percentages. In this situation, histological evaluation is one of the

important diagnostic tests. Biopsy of bony lesion/synovium/soft tissue masses may help to clear up diagnostic confusion [6, 20]. Possibly diagnosed patient in area of high prevalence with limited resources can be treated by clinical features, and X-ray suggests without biopsy. If a case is unresponsive to chemotherapy, and there is suspicion of resistant infection or other diseases, a synovial biopsy is recommended [5]. The most important findings of histologic evaluation are epithelioid granulomas and caseous necrosis. In some cases TB PCR positivity can be leading non-specific granulomatous response [5, 10]. PCR technique can increase the sensitivity and help exclude non-tuberculous mycobacterial infection of soft tissue [6]. Diagnostic rate of PRC is reported 33.3% in a study [7]. In the case of elbow joint TB reported by Sagoo et al., when initial treatment did not bring complete relief, a synovial biopsy with debridement was done (along with smear, culture and PCR) [8]. This could be a good approach to diagnosis but expensive and complex and may not always be practicable.

Early diagnosis of osteoarticular TB is important to prevent advanced destruction of the joint and bone structure and suffering from systemic spreading infection.

The tuberculin skin test (TST) is recommended standardly, but sensitivity and specificity are known to be low. If the prevalence of TB infection were high, the positive predictive value of TST would be higher [21]. In additionally interferon-gamma release assays (IGRAs) are blood-based assays that have recently become available and have good diagnostic values for chronic inflammatory arthritis; however, indeterminate results may be difficult to use of them [22].

6.1.3 Management and Treatment

Splints can be used briefly to reduce acute symptoms or can be used for long periods in selected cases to prevent deformities of the infected extremities and joints [15, 23]. Surgical treatment is usually limited and does not require, except biopsy to obtain infected tissue, open or arthroscopic debridement, abscess drainage, and synovectomy [15]. However, surgery appears to be beneficial and may be indicated. Such situations include failure to respond to chemotherapy with evidence of ongoing infection, the patients with persistent of recurrence of neurological complications. It is not recommended that surgical procedures should be performed in the joints with severe cartilage destruction, deformities, large abscess, and multidrug-resistant TB [15, 24].

Antituberculosis treatment is a multidrug complex [5]. The results of appropriate treatment are good with low morbidity and mortality. Even in the advanced cases, good response can be seen. Early antimicrobial therapy provides near-complete cure and preservation of function. Antituberculosis therapy in general should be of at least 9–12 months but to be continued longer in children and immunocompromised hosts [3, 12]. The basic principles for the treatment of pulmonary tuberculosis are also applied for extrapulmonary disease [13]. Two months of isoniazid (INH)

and rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) followed by 7–10 months of INH and RIF are recommended as an initial therapy unless the organisms are known or strongly suspected resistant TB to the first-line drugs.

6.1.4 Special Joint Infections

Prosthetic joint infection (PJI) due to *M. tuberculosis* is rare and was reported as case in few studies [25, 26]. A misdiagnosed patient has knee or hip osteoarthritis after joint arthroplasty, with culture negativity [26]. The diagnosis is often difficult and should be suspected in culture-negative PJI with histological features of granulomatous lesions with or without caseous necrosis. The diagnosis may be confirmed by isolation of the microorganism on Löwenstein culture or by molecular techniques (PCR). Resection arthroplasty or arthrodesis has been used to treat of PJI, but when there is no loosening of the prosthesis, the patient may cure with debridement, exchange of the polyethylene components while retaining the prosthesis, and prolonged antituberculous therapy (9–12 months).

Multifocal osteoarticular tuberculosis Four to six bones or joints are affected, and there are some cases that have more focus. It occurs mostly in the hands and feet of flat bones in children and may also have spinal involvement [25]. Whole body scintigraphy may be useful in detecting lesions in different regions. Although the duration of antituberculosis treatment in clinical features is not known due to this uncommon bone involvement, most patients are treated for 24 months.

Tuberculous sacroiliitis The sacroiliac joint is affected in 4–9.5% of patients. The diagnosis cannot be delayed (92%). Tuberculous sacroiliitis may be confused by septic arthritis, inflammatory diseases (such as rheumatoid arthritis), ankylosing spondylitis and Reiter's disease, gut and pseudograft, tumorlike conditions (e.g., pigmented villonodular synovitis), and endemic that may be miscible with the brucella sacroiliitis in the regions [25]. Arthrodesis is used in patients with large periarticular apse and persistent aches. Treatment of this involvement requires 6–9 months of antibiotic therapy.

6.2 Tuberculosis Osteomyelitis

6.2.1 Epidemiology

Tuberculosis osteomyelitis accounts approximately 10% of all extrapulmonary TB cases and is the third most common type of extrapulmonary TB after pleural and lymphatic disease. The presentation of TB may be insidious over a long period, and the diagnosis may be elusive and delayed. The diagnosis is often confused with

malignancy [27]. In a series of 194 patients from India with TB, 30% of cases occurred during the second decade of life, 22% in the first decade, 18% in the third decade, and 14% in the fourth decade [5]. Tuberculosis osteomyelitis shows a bimodal age distribution: in developed countries, the disease commonly affects people older than 55 years, whereas in immigrants, it is more common in younger individuals (20–35 years old). In patients with skeletal tuberculosis, concomitant pulmonary involvement is diagnosed in 6.9–29% of cases [28].

6.2.2 Pathophysiology

Tuberculous osteomyelitis pathophysiology generally arises from reactivation of bacilli lodged in bone during the original mycobacteria primary infection. In adults, the lesion may be single and affect any bone, including long bones, the pelvis, ribs, and skull. In children, multiple lesions in long bones dominate, but the bones of the hands and feet may be affected.

The tendency 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. Tuberculous arthritis is believed to result from extension of an initial infectious focus in the bone to the joint. Infrequently, tuberculous bacilli travel from the lung to the spine along the Batson paravertebral venous plexus or by lymphatic drainage to the para-aortic lymph node [29].

Osteoarticular lesions result from hematogenous spread of a primary infection. Any bone, joint, or bursa can be infected, but the spine, hip, and knee are the preferred sites of infection, representing 70–80% of infections [30]. Hematogenous dissemination can occur in immunocompromised patients with bone infections, such as individuals with AIDS or transplant recipients [25].

The growth plates (metaphyses) receive the richest blood supply and are most often the initial site of infection. Tubercle bacilli invade the end arteries, causing endarteritis and bone destruction through the epiphysis. After crossing the epiphysis, bacilli can drain into the joint space, resulting in tuberculous arthritis, or form a sinus tract after being released from the destroyed bone. *M. tuberculosis* does not produce any cartilage destroying enzymes as are seen in pyogenic infections.

A closed cystic form of skeletal TB can occur, especially in the long bones, and may not have associated sclerosis, osteopenia, or abscess/sinus tract formation as in other forms of skeletal TB. This form of TB is more likely to occur in children and may be misdiagnosed as a malignancy.

If the infection progresses without treatment, abscesses surrounding the joint or bone may develop. These are often described as being “cold” abscesses. Calcifications are also frequently seen in healed lesions. As the area of infection enlarges, the center becomes necrotic, resulting in an area of caseating necrosis. This caseation may progress to cause bone expansion and eventually destruction of the cortex. A pathological feature of tuberculous osteomyelitis is that there is usually no bone regeneration (sclerosis) or periosteal reaction.

Although uncommon, TB can also involve the ribs and skull. The skull contains little cancellous bone, which is usually affected by *M. tuberculosis*. Disease involving the skull occurs more often in children and anecdotally may be associated with head trauma [31].

Several reports have noted an association between mechanical factors such as trauma and the development of skeletal TB. In a Canadian study of 99 patients with skeletal TB, 30 had a history of trauma preceding their presentation and 7 had a recent history of intra-articular steroid injection. This may also explain why weight-bearing joints are most frequently involved. Trauma may be associated with skeletal TB because of resulting increased vascularity, decreased resistance, or unmasking of latent infection [32].

6.2.3 Clinical Feature and Diagnosis

Tuberculous osteomyelitis often occurs in conjunction with tuberculous arthritis, but it can occur as a distinct entity without joint involvement. In adults, tuberculous osteomyelitis without joint involvement usually presents as a single lesion, usually in the metaphysis of long bones (e.g., femur and humerus), although the ribs, pelvis, skull, mastoid, and mandible can be affected. In children, older adults, and immunocompromised persons, including those with HIV infection, the lesions may be multiple [33]. In children, the lesions may affect the short bones of the hands and feet; tuberculous dactylitis has been reported to occur in adults but is unusual. Patients with widespread lesions may be misdiagnosed as having a malignant process [34]. Bacterial superinfection can also mask the diagnosis and presentation, as there are reports of infection due to coexisting *Staphylococcus aureus* infection and TB [35]. Tuberculous osteomyelitis usually manifests with pain and swelling adjacent to the bone, with eventual limitation of movement of the affected limb. Symptoms may be present for 6–24 months before a diagnosis is made. Fever, weight loss, and night sweats are often present. Abscesses and sinus tracts may occur, often later in the course [36]. Tuberculous involvement of the skull may be associated with headaches and soft tissue masses. TB involving the ribs manifests with chest pain and sometimes with a “cold” chest wall mass. Infection of bones of the head and neck, especially the mastoid and mandible, has been reported to result from tuberculous otitis and disease involving the oral cavity. Facial paralysis can occur secondarily to tuberculous mastoiditis [37]. TB of the temporomandibular joint has also been reported as a cause of chronic temporomandibular joint pain [38]. TB of the sternum can manifest as anterior chest pain [39].

A high index of suspicion is needed for the diagnosis of TB, especially given the insidious onset of symptoms and reports of a long duration between onset of symptoms and diagnosis of disease. In countries with a high burden of TB disease, musculoskeletal complaints may be attributed to TB correctly based on clinical and radiologic examination. In the developed world with a lower incidence of TB, the diagnosis may not be initially considered, and the diagnosis is frequently delayed.

Any bone or joint may be involved, but the spine and weight-bearing joints are the most common sites of infection. Pain is the most common complaint that leads a patient to seek medical care, and TB should be considered in the differential diagnosis of the cause of skeletal pain. Interestingly, local pain, swelling, and limitation of movement may even on occasion precede radiographic findings by up to 8 weeks [40]. Cold abscesses can occur and sometimes with draining sinus tracts, but this is usually seen in advanced, untreated disease or among patients with HIV infection. The differential diagnosis of tuberculosis osteomyelitis includes other infectious causes of musculoskeletal disease (bacterial, fungal, and other mycobacterial pathogens), as well as malignancy, rheumatologic conditions, and sarcoidosis. Imaging techniques, which include conventional radiography, CT, and MRI, are useful in evaluation of patients with suspected tuberculosis osteomyelitis and other skeletal diseases. The use of newer techniques such as CT, MRI, and CT-guided fine-needle aspiration biopsy has revolutionized the diagnostic approach and has resulted in more accurate results and much less invasive procedures than when only plain radiography and open biopsy were available [15]. Previously, conventional radiography had been the mainstay in the diagnosis of tuberculous osteomyelitis.

Since there are no pathognomonic radiographic findings, the diagnosis is usually made by tissue biopsy and/or culture [41]. Needle aspiration and biopsy can confirm the diagnosis with the findings of caseating granuloma and the presence of acid-fast bacilli (AFB) [5]. A positive culture for *M. tuberculosis* provides definitive evidence of tuberculous disease and allows antimicrobial susceptibility testing to be performed, which is essential for helping to prescribe optimal therapy. Fine-needle aspiration biopsy of involved bone (often CT directed) to obtain specimens for culture is useful diagnostically [42]. In addition to modern culture techniques performed on specimens obtained by biopsy of involved tissues, the use of molecular diagnostics to detect the presence of *M. tuberculosis* has the potential to improve the ability to diagnose skeletal and other types of musculoskeletal TB. While nucleic acid amplification for AFB smear-positive respiratory specimens, there are limited data on the utility of these tests for extrapulmonary TB [43]. This is especially the case for the use of these molecular diagnostic tests for tuberculosis osteomyelitis. The currently commercially available and FDA-approved nucleic acid amplification tests are not approved for use in extrapulmonary TB, including tuberculosis osteomyelitis. While further data are needed on the utility of these tests in the aid of diagnosis of tuberculosis osteomyelitis, recent reports from South Africa appear promising and suggest that Xpert MTB/RIF may be a valuable diagnostic test for tuberculosis osteomyelitis in both adults and children [44].

Recent TB diagnostic guidelines published by the American Thoracic Society, Infectious Diseases Society of America, and CDC suggest that the quality of data for the utility of nucleic acid amplification tests performed on specimens from patients with suspected extrapulmonary TB is low: the test results are specific but may lack sensitivity [45]. This suggests that a positive Xpert MTB/RIF is valuable but that a negative test does not rule out extrapulmonary TB. Radiographically, tuberculous osteomyelitis is often confused with malignancy, especially if the lesions are diffuse and lytic. Plain radiographs may show osteoporosis, lytic lesions,

sclerosis, and periostitis. Sequestra may appear as spicules of increased radiodensity within the area of destruction. Cystic lesions may be seen, especially in children and young adults. The lesions in children are less well defined than in adults, in whom well-defined margins of sclerosis are usually present [5]. Multifocal disease is an uncommon presentation and occurs primarily in children and the immunocompromised [46]. MRI is useful in detecting osteomyelitis early because of changes in the bone marrow. Tuberculous lesions are rarely seen in the hands and feet, but tuberculous dactylitis occurring in children is a well-recognized entity. The typical radiologic appearance is a ballooned-out configuration of "spina ventosa" in which the dissolution of bone causes absorption of trabeculae and expansion of the affected digit [47].

6.2.4 Management and Treatment

There are no controlled trials assessing treatment of tuberculosis osteomyelitis. Based on experience from treating tuberculous spondylitis and the experience with treating other forms of extrapulmonary disease, it is recommended that treatment of drug-susceptible tuberculous osteomyelitis be carried out using rifampin-based short-course regimens like those that are used for the treatment of pulmonary disease. Surgery is generally reserved for diagnosis and when necessary to drain an abscess that is not responding to medical therapy or to drain a large abscess to relieve pressure. Curettage and bone grafting followed by medical therapy yields good result [48]. Late treatment or inadequate treatment results in ankylosis of the affected joint by fibrosis or bony fusion. There are no formal recommendations, but some experts have suggested that patients requiring total arthroplasty for quiescent TB receive perioperative chemotherapy for at least 3 weeks before and at least 6–9 months after surgery to minimize the risk of reactivation. A total of 6–9 months of a rifampin-based regimen, like treatment of pulmonary TB, is recommended for the treatment of drug susceptible musculoskeletal disease.

6.3 Conclusions

Osteoarticular tuberculosis is a very rare form of tuberculosis. It is estimated that osteoarticular TB constitutes about 1.7–2% of all TB cases [49]. The rarity of the disease makes the general physician less aware of its presentation. Therefore, it is essential to educate and increase awareness of all physicians of the presentation of this disease in order to diagnose this disease promptly. Prompt diagnosis and treatment are important to avoid the development of skeletal deformities and finally long-term functional disabilities. The introduction of newer imaging modalities, including MRI and CT, has enhanced the diagnostic evaluation of patients with osteoarticular tuberculosis and for directed biopsies of affected areas of the

musculoskeletal system. Obtaining appropriate specimens for culture and other diagnostic tests are essential to establish a definitive diagnosis and recover *M. tuberculosis* for susceptibility testing.

Positive microbiological and histological yields can be obtained in 64–90% of all patients. Studies have shown that microbiological testing is less sensitive than the importance of biopsy [50]. In conclusion, it is important to have a high index of clinical suspicion of tuberculosis osteomyelitis and arthritis affecting any parts of the body. Patients suspected of having osteoarticular tuberculosis should be thoroughly investigated, and biopsy should be done if necessary.

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