Tuberculous and Nontuberculous Mycobacterial Infections

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G. Omondi Oyoo and Eugene Kalman Genga

Introduction

Skeletal tuberculosis (TB) refers to TB affecting the bones and/or joints. It is an ancient disease that has been found in Egyptian mummies dating as far back as 9000 years [1]. Musculoskeletal involvement TB is rare and is seen in 1–3% of patients with TB [2]. About half of these cases affect the spine, and the rest are extraspinal osteoarticular joints [3, 4]. Poncet's disease or tubercular rheumatism presents during the acute TB infection as a nondestructive polyarthritis without evidence of direct mycobacterial involvement of the joints nor any other known cause of polyarthritis detected [5, 6]. It is a different entity from tuberculosis arthritis (TB arthritis). TB arthritis is usually monoarticular and in which the organism can be isolated from the joint [5]. This chapter discusses clinical issues related to skeletal TB and those due to nontuberculous mycobacteria.

Epidemiology

More than two billion people (about 30% of the world population) are estimated to be infected with M. tuberculosis [7]. The highest rates (100 per 100,000 or higher) are observed in sub-Saharan Africa, India, and the islands of Southeast Asia and Micronesia. The major contributors in these regions are poverty, human immunodeficiency virus (HIV), and drug resistance. About 95% of TB cases occur in developing countries. Approximately one in nine new TB cases occurs in individuals who are infected with HIV [7, 8], and especially in Africa which has a higher prevalence of HIV infection, data shows that up to one-third of adults with osteoarticular infections are HIV positive [7, 8]. Data from Europe and USA have shown an increase in extrapulmonary TB (EPTB) from 7.6% to 20–40%. This has been attributed to HIV. In developed countries, the majority (58–81%) of skeletal TB cases occur in immigrants [9].

Bone and joint TB shows a bimodal age distribution: In natives of 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) [10–12]. Concomitant pulmonary and skeletal TB is diagnosed in 6.9–29% of cases [11, 12]. Pott's disease (a disease of the spine) is the most common form of skeletal TB comprising about half of musculoskeletal TB cases. This is followed by tuberculous arthritis and extraspinal tuberculous osteomyelitis, respectively [13].

Pathogenesis

Skeletal TB usually is a result of reactivation of bacilli lodged in bone during the original seeding of the primary infection. Progression of the disease happens in the background when local immune defenses fail, as in the setting of malnutrition, advancing age, HIV infection, or renal failure [14]. The bacillus tends to favor the spine and large joints due to the rich vascular supply of the vertebra and growth plates of the long bones. It is postulated that tuberculous arthritis is an extension of an initial infectious loci in the bone to the joint. Other sources of seeding include from the lungs via the lymphatic system, direct inoculation of mycobacteria following a traumatic injury, or during surgical procedures such as joint arthroplasty [15, 16].

In highly endemic regions, musculoskeletal TB usually manifests clinically in the year following primary lung infection and therefore occurs most frequently in relatively young patients. Outside endemic areas, musculoskeletal TB is more commonly associated with late reactivation of infection and occurs mainly in adults. TB-associated bone and joint involvement can either be the caseous exudative type or the granular type. The caseous exudative type is seen more

G. O. Oyoo (✉)
Clinical Medicine and Therapeutics, University of Nairobi, Nairobi, Kenya

E. K. Genga
Medicine and Therapeutics, University of Nairobi, Nairobi, Kenya

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in children and is characterized by bone destruction, local swelling, abscess formation, sinus formation, and constitutional symptoms. The granular type is more in adults and is insidious and less destructive than the caseous exudative type, and abscess formation is less common [17, 18].

Clinical Manifestations

Virtually any bone can be infected with M. tuberculosis. Musculoskeletal TB can manifest in the following forms—spondylitis (Pott's disease), arthritis, and osteomyelitis.

Spondylitis (Pott's Disease)

The most commonly affected sites are the lower thoracic and upper lumbar region. It rarely manifests in the cervical and upper thoracic region. The initial site of infection is the anterior aspect of the intervertebral joints after which it spreads to the adjacent vertebral body. Once two adjacent vertebrae are involved, infection enters the adjoining intervertebral disc space. This leads to the death of the avascular disc tissue, vertebral narrowing, and collapse [19, 20]. This leads to a Gibbus deformity, a form of structural kyphosis that eventually distorts spinal canal anatomy. Paraplegia usually results from spinal cord compression due to gibbus or late onset due to paraplegia occurs due to osteophytes and other chronic degenerative changes at a site of prior infection. Formation of a "cold abscess" (soft tissue mass) at the site is common.

Usually the diagnosis of Pott's disease is delayed due to its low incidence and slow, subacute course. Commonly it presents with local pain which increases with severity over time associated with muscle spasm and rigidity [19, 20]. Some patients develop an erect posture with "aldermanic gait" in which the patient walks in short, deliberate steps to compensate for the pain around the infection site. In about 40–70% of the cases may present with symptoms and signs of cord compression at the time of diagnosis. Constitutional symptoms such as fever and weight loss are present in less than 40% of cases [19].

Arthritis

Tuberculous Arthritis

Tuberculous Arthritis is usually monoarticular and can affect any joint. The most commonly affected joint is the hip followed by the knee. It presents with a "cold joint" without any signs of an acute infection. It can also present with swelling, pain, and/or loss of joint function that progress over weeks to months. Constitutional symptoms, fever, and weight loss occur in only about 30% of cases. Some advanced cases manifest as discharging sinuses. Over time the joint undergoes progressive destruction, disorganization of its architecture with joint deformity. Histopathology reveals granulomatous changes with synovial proliferation with joint effusion and erosion of cartilage [21, 22]. There are five stages of TB arthritis [23, 24]. Stage 1 manifests as soft tissue swelling, localized osteoporosis and has good outcomes on treatment. Stage 2 has early arthritis with bone erosions; treatment is good but leaves behind joint stiffness. Stage 3 Stage has advanced arthritis with subperichondral cyst and loss of joint space. This complicates after treatment with loss of joint motion and flexibility. Stage 4 has advanced arthritis with joint destruction and no motion at the joint after treatment. Stage 5 is ankylosis of joint [23, 24].

Poncet's Disease

Poncet's disease is an acute symmetrical polyarthritis involving large and small joints associated with active extrapulmonary, pulmonary, or miliary TB but no evidence of active TB [25, 26]. It's a rare entity of unknown pathogenesis thought to be immune mediated. HIV has been identified as a risk factor. Generally, it resolves within a few weeks of start of TB treatment. It leaves no residual joint destruction [25, 26].

Diagnosis

Diagnosis of skeletal tuberculosis (TB) is a challenge especially considering that in more than half the cases there is no evidence of active chest disease. The indolent nature of the disease also contributes to its delays. Clues from history including prior TB contact, the systemic B-symptoms of TB, and countries of origin of the patient can help raise the level of suspicion for TB. The diagnosis of musculoskeletal TB is established by microscopy and culture of infected material.

Bacteriology

The gold standard for diagnosis of tuberculosis is demonstration of acid fast bacillus from any body tissue or fluid [27]. Tissue may be obtained by needle aspiration and/or biopsy. CT guidance is useful in regions where available. Tuberculous arthritis can be diagnosed from a synovial biopsy. The findings can be non-specific but raised or low white cell count with predominantly neutrophils or lymphocytes is suggestive [27–29]. Cases of draining sinuses culture of this material may be collected for culture. Examples of culture methods available include Lowenstein-Jensen medium, radiometric (Bactec 12B liquid medium), and non-radiometric (Bactec MGIT 960 system) [27]. The major drawback is the long length required to grow the culture. There are newer rapid automated growth systems and nucleic acid detection methods that have been limited in use due to high cost and technical demands required.

Radiology

It usually takes 2–5 months after onset of the disease to note any radiological changes [30]. The classic triad for TB arthritis is juxta articular osteoporosis, peripheral osseous erosion, and gradual narrowing of intraarticular space. This can be confused for rheumatoid arthritis which has similar findings apart from preserved joint space especially in early TB arthritis [30]. Children may present with enlarged epiphysis. Computerized tomography (CT) and magnetic resonance imaging (MRI) can be used to characterize the disease further. MRI defines soft tissues better, while CT is good for bony lesions. Between the two MRI is the investigation of choice when you want to see the extent and severity of damage. Characteristic findings of TB arthritis on MRI are synovitis, effusion, central and peripheral erosions, active and chronic pannus, abscess, bone chips, and hypointense synovium [31]. These are illustrated in Figs. 18.1, 18.2, 18.3, and 18.4.

Interferon Gamma Release Assays (IGRAs)

These are T-cell assays that measure production of interferon γ in response to stimulation by host blood cells. There are two assays, T-Spot TB and QuantiFERON-TB Gold, that are available. Unfortunately, they can detect active disease and latent tuberculosis infection so interpretation should be done using the clinical scenario [32, 33]. The costs and technical demands of IGRAs have limited their use in resource-poor settings, where better tests are the most needed.

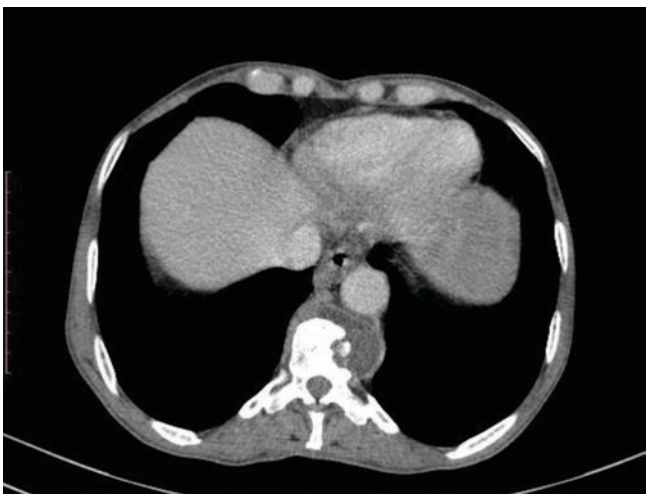

Fig. 18.1 Left paravertebral abscess elevating the aorta in a patient with TB spine adjacent to a Brodie's abscess in T10 vertebra. (Image courtesy of Dr Elijah Kwasa, Radiologist, Stratus Medical, Kenya)

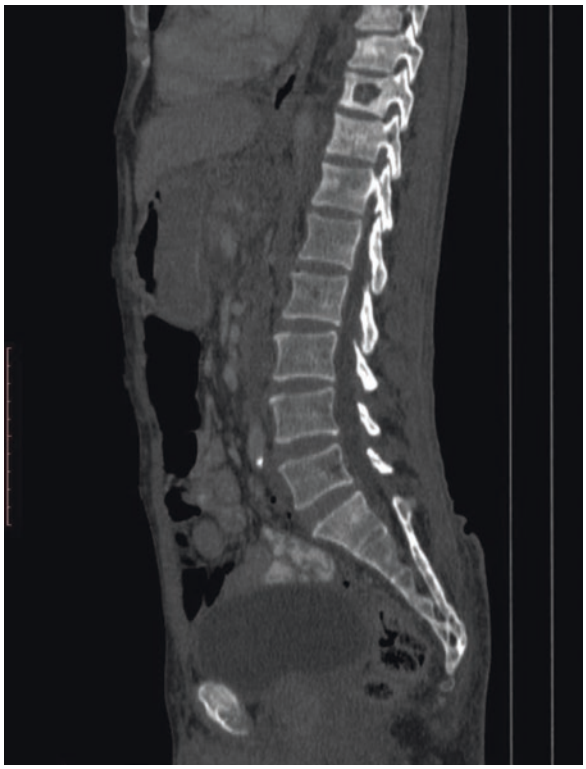

Fig. 18.2 A Brodie's abscess in T10 vertebral body in a patient with TB Spine with paravertebral abscess. (Image courtesy of Dr Elijah Kwasa, Radiologist, Stratus Medical, Kenya)

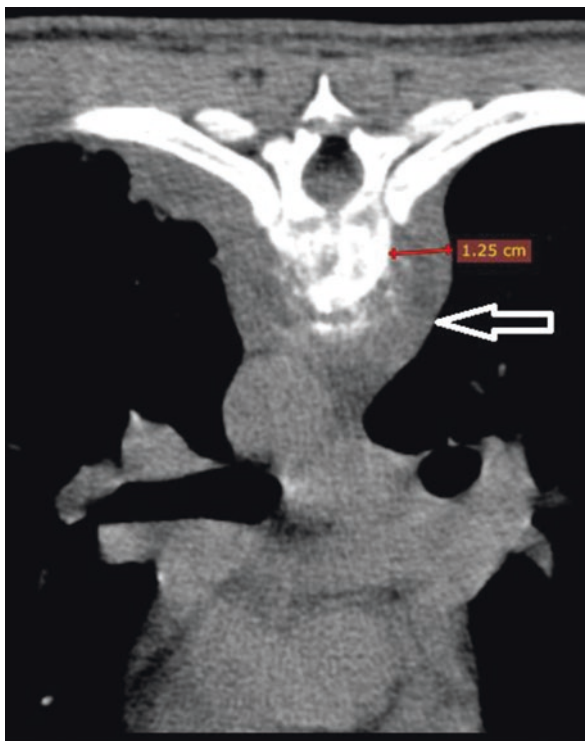

Fig. 18.3 Thoracic spinal TB with paravertebral abscess and vertebral body lysis. (Image courtesy of Dr Elijah Kwasa, Radiologist, Stratus Medical, Kenya)

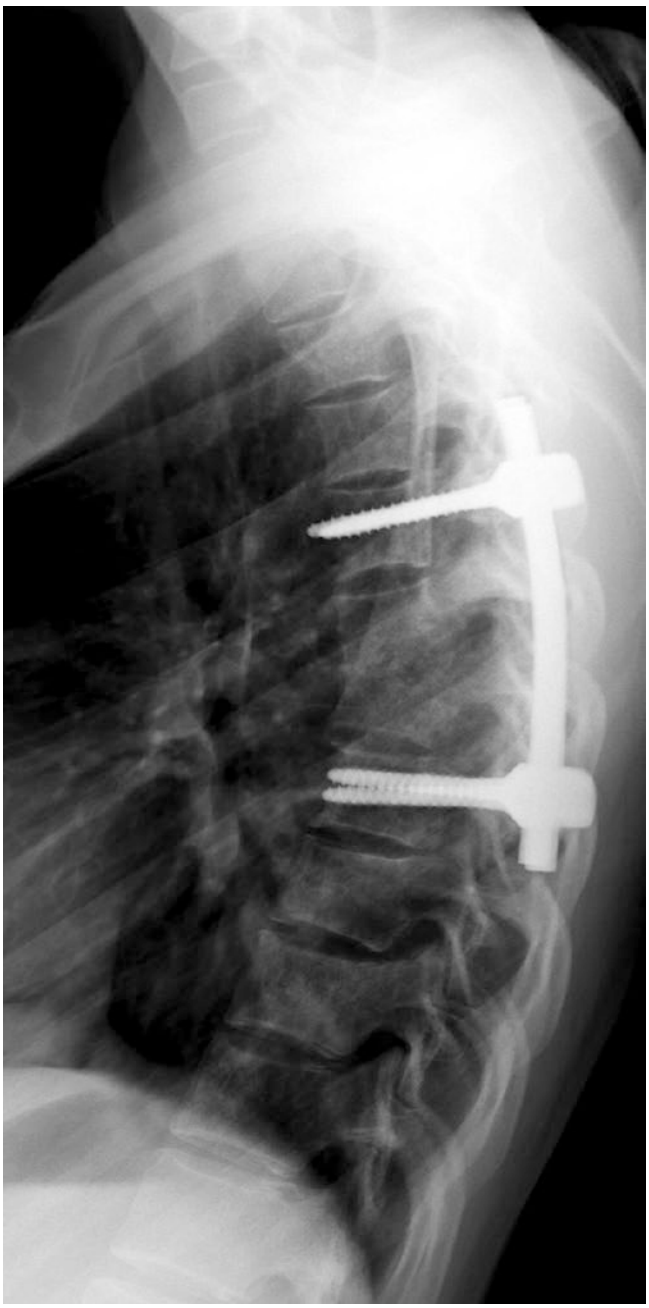

Fig. 18.4 Harrington rod placement to stabilize T5 and T6 vertebrae following collapse fractures secondary to tuberculous spondylodiskitis. (Image courtesy of Dr Elijah Kwasa, Radiologist, Stratus Medical, Nairobi, Kenya)

Tuberculin Skin Test

The Mantoux test is the recommended standard tuberculin skin test [TST]. Tuberculin is commercially available in 1, 2, and 5 Tuberculin Unit (TU) PPD (purified protein derivative, RT23 equivalent) forms. The test is read 48–72 hours after an injection, with raised wheal of about 6 mm identified as positive [34]. In areas of high TB prevalence, the positive predictive value of TST is higher [34]. It is important to note that prior BCG vaccination depending on age at vaccination and time after vaccination when TST was done can influence the results [35].

Differential Diagnosis

Skeletal TB can be confused for subacute or chronic infections due to pathogens or diseases such as *Staphylococcus aureus* osteomyelitis, brucellosis, melioidosis, actinomycosis, candidiasis, and histoplasmosis, depending upon epidemiologic factors. In the setting of Pott's disease, the differentials include degenerative disc and facet joint disease, spondyloarthropathy, vertebral body collapse due to osteopenia (due to a variety of causes such as osteoporosis and chronic corticosteroid therapy), pyogenic spinal infection, and malignancy. The use of imaging will help distinguish these from skeletal TB.

Treatment

The mainstay treatment of tuberculosis arthritis is appropriate anti-TB drug therapy. Early antimicrobial intervention can lead to a near complete resolution and preservation of function. The principles that define treatment of pulmonary tuberculosis also apply to extrapulmonary forms of the disease. However, there is paucity of data on the optimal duration of treatment [36]. For a long time, longer treatment duration was recommended. This was due to concerns about poor drug penetration into osseous and fibrous tissues. However, several studies have shown that 6- to 9-month regimens containing rifampin are at least as effective as longer courses without rifampin [36, 37]. A study from United Kingdom comparing 6 versus 9 months showed a higher rate of relapse (62%) with 6 months; no relapse was observed among patients who received 9 months of treatment [38]. A Chinese study in selected patients combined surgical intervention and shorter duration of therapy of 4.5 months and was as successful as the 9-month course with fewer adverse events reported [39].

Surgical interventions are also used in treatment. They include decompression, use of hardware for stabilization of spine, abscess drainage, and/or debridement of infected material [40, 41].

Indications for surgical intervention include [40, 41]:

- Patients with spinal disease and advanced neurological deficits
- Patients with spinal disease and worsening neurological deficits progressing while on appropriate therapy

- Patients with spinal disease and kyphosis >40 degrees at the time of presentation
- Patients with chest wall cold abscess

Monitoring Clinical Response

This is quite difficult as role of inflammatory markers is limited in skeletal TB. Utilization of clinical symptoms like pain, mobility, constitutional symptoms, and neurological findings is more useful. There is no role to perform serial radiographs since radiographic findings may appear to progress during appropriate treatment [42].

Nontuberculous Mycobacterial Infections

Mycobacteria other than *Mycobacterium tuberculosis* and *Mycobacterium leprae* are generally free-living organisms that are ubiquitous in the environment. There are about 60 of the more than 125 nontuberculous mycobacterial (NTM) species that can cause disease in humans [16]. These can be broadly classified into four clinical syndromes [43]:

1. Progressive pulmonary disease especially in older persons caused primarily by *Mycobacterium avium* complex (MAC) and *Mycobacterium kansasii*.
2. Superficial lymphadenitis, especially cervical lymphadenitis, in children caused mostly by MAC, *Mycobacterium scrofulaceum*, and, in northern Europe, *Mycobacterium malmoense* and *Mycobacterium haemophilum*; the most common cause in adults, however, is *M. tuberculosis*.
3. Disseminated disease in severely immunocompromised patients.
4. Skin and soft tissue infection usually as a consequence of direct inoculation.

NTM rarely affects skeletal tissue; it more commonly affects soft tissue [16]. Soft tissue infections are due to direct inoculation occurring during penetrating trauma, open surgery (such as mediastinitis and sternal wound infections after cardiothoracic surgery), after injection of steroids or local anesthetics, or following cosmetic surgery, such as abdominoplasty and liposuction [16, 44]. The most commonly isolated mycobacteria are the rapidly growing types, for example, *M. abscessus*, *M. chelonae*, and *M. fortuitum* [44]. The disease an indolent course and presents with painful red to violaceous nodules that can drain serosanguineous material, ulcerate, or spread to deeper tissues and form fistulous tracts. Histology may reveal non caseating granulomas with abundant neutrophils. The acid-fast bacilli test is usually negative [16, 44].

NTM skeletal infections are rare. Risk factors are transplant patients, invasive procedure like in cardiothoracic surgery (sternal osteomyelitis due to *M. fortuitum* or *M. abscessus*) or in isolated cases of *M. xenopi* arthritis after joint arthroplasty [45]. Treatment duration for a minimum of 6 months of specific antimycobacterial chemotherapy is recommended, and the regimen can be extended to 12 or more months in patients with disseminated disease [43]. Surgery is recommended for NTM osteoarticular infections where surgical excision of the infected tissue and/or prosthetic joint removal should be performed [43].

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