Mycobacterial Osteomyelitis and Arthritis

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*Mycobacterium tuberculosis* is by far the most common cause of mycobacterial osteomyelitis and arthritis worldwide [1]. Once a rarity, the incidence of nontuberculous mycobacteria (NTM) disease dramatically increased in the 1980s and 1990s, in parallel with the advancing AIDS epidemic. Pulmonary and disseminated disease, however, still account for most cases. Although musculoskeletal infection with *M tuberculosis* and NTM shares several characteristics, such as bone destruction and relatively slow symptom onset, there are significant differences in their epidemiology and treatment, as discussed later.

Tuberculous osteomyelitis plays a unique role in tuberculosis epidemiology, allowing medical historians to assess the presence of *M tuberculosis* in skeletal remains. Several techniques, including histologic and pathologic examination, radiography, and polymerase chain reaction, have detected tuberculosis bone disease in Egyptian mummies [2–4]. Genetic material from *M tuberculosis* has been identified using polymerase chain reaction techniques in Iron Age Southeast Asian skeletons [5], and European skeletal remains from the Dark Ages and Middle Ages [6,7]. These studies and others suggest that *M tuberculosis* has had an intimate relationship with *Homo sapiens* for millennia. Indeed, it has been proposed that the *M tuberculosis* bacillus has been present for 15,000 years [8].
Pathophysiology

Tuberculous osteomyelitis and arthritis are generally believed to arise from foci of bacilli lodged in bone during the original mycobacteremia of primary infection. Alternatively, tuberculous bacilli may travel from the lung to the spine by Batson’s paravertebral venous plexus, or by lymphatic drainage to the para-aortic lymph nodes. In most otherwise healthy individuals, the cellular immune response is able to contain the bacilli present in these sites, but not eradicate them. Given its rich vascular supply, the growth plate of long bones is the most frequent site of infection. The growth plate is in close proximity to the joint space, hence tuberculous arthritis is believed to result from an initial bone focus that extends into the joint.

Atypical mycobacterial osteomyelitis and arthritis in nonimmunocompromised individuals is secondary to direct inoculation rather than hematogenous dissemination, either from trauma or surgery [9,10]. NTM also have a predilection for causing infections associated with foreign bodies, such as prosthetic joints [11–13], although *M tuberculosis* may also cause prosthetic joint infections [14]. Hematogenous dissemination with resultant multifocal disease, including bone and joint involvement, can occur in immunocompromised individuals, and is best described in individuals with AIDS [15].

A large United States–based study of all bone and joint tuberculosis over a 4-year period revealed that the most common site of bony tuberculosis was the spine (40%); followed by weight-bearing joints (hip and knee); and lastly, other sites [16]. A British study from the same decade found a similar rate of spinal disease (43%) [17]. The proportion of spinal disease was found to be greater than 50% in more recent studies, which may be caused by demographic differences in the study populations [18,19]. The predilection for spinal disease may be explained by the fact that the vertebrae are extremely well vascularized, even in adulthood. Spinal disease is most frequently located in the lower thoracic and lumbar spine, with thoracic disease being more common in children and adolescents, whereas lumbar disease is found more commonly in adults [20–22]. Most cases of tuberculous bone and joint disease are isolated to one area, but multifocal disease has also been described [23].

Spinal tuberculosis typically involves the initial destruction of the anteroinferior part of the vertebrae. Bacilli may then spread beneath the anterior spinal ligament and involve the anterosuperior aspect of the adjacent inferior vertebra, giving rise to the typical “wedge-shaped” deformity. Further spread may result in adjacent abscesses [24]. The radiographic features of tuberculous osteomyelitis and arthritis are discussed further later.

Chronic granulomatous infection of bone by NTM is a rare but recognized clinical syndrome, and usually occurs in the setting of direct inoculation of the organism following trauma, surgical incisions, puncture wounds, or injections [25].
Epidemiology

Several factors influence the development of tuberculous osteomyelitis and arthritis (Table 1). In a large United States population-based study, age over 65 years was shown to be a significant risk factor for the development of bone and joint tuberculosis [26]. Although children up to 14 years in age were more likely to develop extrapulmonary tuberculosis than older age groups, they were overall less likely to develop bone and joint disease. This same study also showed that bone and joint tuberculosis was twofold higher in women than men. The association with older age and female gender has also been shown in a more recent study [18].

Several studies have shown that immigration affects the relative proportion of bone and joint disease in a population. A recent Dutch study showed that being of African or East Asian origin was a significant risk factor for the development of bone and joint tuberculosis compared with native Dutch [18]. The Somali population was found to be at greatest risk. Similar findings were described in a Danish study [19] and an earlier British study, although most immigrants in the British study were from the Indian subcontinent rather than Africa [17]. In the United States study, which was the largest of the group, foreign birth was not a significant risk factor for the development of bone and joint tuberculosis [26]. This finding may have been explained by the effect of the AIDS epidemic among American-born tuberculosis cases, resulting in increased extrapulmonary disease in this group.

The impact of race and ethnicity on rates of bone and joint tuberculosis when controlled for foreign birth is less clear. In the Rieder study, bone and joint tuberculosis was more closely associated with foreign birth than race, which was divided into Hispanic, black, Native American, and Asian groups, although neither variable reached significance [26].

NTM were first recognized as pathogens in the 1950s, when several large series of pulmonary disease were reported [27–29]. Most NTM organisms are ubiquitous, and have been isolated from water and soil [30,31]. There is marked geographic variability in the prevalence of disease and the specific NTM responsible for disease [32]. A history of trauma or puncture wounds, or osteomyelitis in a geographic setting where a particular NTM is known to be endemic, should raise clinical suspicion of a possible NTM bone infection.

Table 1
Risk factors for mycobacterial bone and joint infections

<table>
<thead>
<tr>
<th>Risk factors for the development of bone and joint tuberculosis</th>
<th>Risk factors for the development of atypical mycobacterial bone and joint infections</th>
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<tbody>
<tr>
<td>Age &gt; 65</td>
<td>Trauma</td>
</tr>
<tr>
<td>Female gender</td>
<td>Surgery</td>
</tr>
<tr>
<td>Country of origin</td>
<td>Compromised immune status</td>
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Clinical presentation

The symptoms of tuberculous bone and joint infections are nonspecific, and the clinical course is often indolent, usually leading to significant delays in diagnosis, and resultant bone or joint destruction. Only about 50% of patients with bone and joint tuberculosis have chest radiographs suggestive of tuberculous infection, further obscuring the diagnosis. Pain or local swelling is the most frequent presenting complaint [33,34]. Fever and weight loss are present in only a minority of patients. Cutaneous fistulae, abscesses, and obvious joint deformity may also be present, should the disease have been active for a long time. Like some other forms of extrapulmonary tuberculosis, such as lymph node disease, local symptoms are typically more prominent than systemic constitutional symptoms. Pain on ambulation in affected weight-bearing joints is common, but nonspecific. Spinal disease may be associated with neurologic deficits caused by impingement of the spinal cord, nerve roots, or nerves. Patients with thoracic spine disease are at particular risk for paraparesis or paraplegia.

In the authors’ experience, a significant number of patients have had local symptoms for greater than a year and have been treated unsuccessfully for osteoarthritis, the diagnosis only being considered when fistulae develop, or on referral to an orthopedic surgeon. The clinical presentation of NTM bone and joint disease is similar to that of tuberculosis. In these cases, a history of trauma, surgery, or immune compromise are clues that an NTM infection may be present.

Diagnosis

Tuberculin skin testing

The most significant step toward diagnosing tuberculous bone and joint infections is to consider the possibility of the diagnosis in the appropriate clinical setting. Often, a tuberculin skin test is performed. This test is of limited use in determining active disease, however, and is best used for screening for latent infection in high-risk populations. Although skin test positivity has been reported to be as high as 90% in immunocompetent patients with bone and joint tuberculosis [35], positivity neither confirms nor excludes the diagnosis. In debilitated or immunocompromised patients, the sensitivity of the test decreases substantially, making it largely irrelevant in making the diagnosis of tuberculosis disease in this population. Tuberculin skin testing is not useful in diagnosing disease caused by NTM.

Mycobacterial culture

Once considered, a clinical diagnosis should be supported by mycobacterial culture from the affected area. Culture is also crucial to provide antibiotic sensitivities to guide therapy. It is important to culture material
from deep structures, such as bone, abscesses, synovial fluid, or synovial tissue rather than culturing drainage fluid, because these specimens may grow colonizing organisms, such as bacteria or fungi, which may cloud the diagnosis. An older review of the use of synovial fluid culture for \textit{M. tuberculosis} reported a sensitivity of 79\%, whereas synovial tissue culture had a sensitivity of 94\% [36]. Acid-fast smears are positive in a minority of patients. The use of molecular diagnostic tests in the assessment of smear-negative or culture-negative patients with suspected extrapulmonary tuberculosis remains unclear [37,38].

\textit{Histology}

In cases where a biopsy was performed but material was not sent for mycobacterial culture, histology can be very useful in suggesting the diagnosis. Histologic evidence of mycobacterial infection has been reported in 94\% of synovial biopsy specimens [36], although the presence of granulomatous inflammation is not specific for mycobacterial infection [39]. The detection of mycobacterial genetic material from pathology specimens may aid in diagnosis, although the positive and negative predictive value of these techniques is not well defined [40].

\textit{Cell counts and fluid biochemistry}

The cell count and biochemistry findings from tuberculous joint fluids, although typical of inflammatory arthritis, are not specific for a mycobacterial infection [34]. Moderately elevated leukocyte counts with a neutrophilic predominance, low glucose, and increased protein are typical [36].

\textit{Radiology}

Multiple imaging modalities, such as plain radiographs, CT, MRI, and ultrasound, may all play a role in suggesting the diagnosis and aiding in the recovery of culture material through directed biopsies (Figs. 1–3). Imaging of extraspinal bones may show soft tissue swelling, evidence of bone destruction with relative preservation of the joint space, and osteopenia [24]. Osteomyelitis without involvement of the adjacent joint is unusual. In advanced stages, gross bone destruction and soft tissue calcification may be evident (see Figs. 1 and 2). These changes, however, can be seen with other causes of chronic osteomyelitis.

Spinal imaging may reveal findings that favor tuberculosis over other causes of bone destruction, such as malignancy (see Fig. 3). Typically, infection starts at the anteroinferior aspect of the vertebral body, and spreads to contiguous vertebrae along the anterior longitudinal ligament of the spine. The infection, however, may also track down the posterior aspect of the spine [24]. The infection may also “skip” vertebrae. The disks and posterior elements are typically spared, at least early in the course of disease.
As the disease progresses, collapse of the anterior portion of the vertebrae can lead to a kyphotic wedging deformity of the spine, the gibbus of Pott’s disease. Fusiform cold paraspinal abscesses, with or without calcification, occur in roughly 70% of cases [20].

Treatment

Medical therapy

Antituberculous chemotherapy for bone and joint tuberculosis does not differ significantly from that recommended for most other forms of the disease. Large clinical trials have confirmed that standard short-course therapy for drug-sensitive disease consisting of 6 months of isoniazid and rifampin, and 2 months of pyrazinamide, is effective [42–44]. Concerns regarding tissue penetration and difficulty in measuring a microbiologic response to treatment have led some experts to recommend prolonging therapy to 9 months; however, there are little clinical data to support this. The American Thoracic Society recommends 6- to 9-month duration of therapy for patients with drug-sensitive disease [45]. Prolonged therapy should be considered for patients slow to respond to otherwise adequate treatment. The treatment of drug-resistant disease follows the same principles for treatment of other sites.
Adjunctive corticosteroids

The use of corticosteroids in tuberculous osteomyelitis and arthritis is generally not recommended [45]. The authors have occasionally used steroids (40–60 mg prednisone per day followed by tapering doses) in situations where significant swelling has developed, resulting in severe pain and immobilization of the joint. This situation may infrequently occur several weeks after the start of appropriate therapy, and is typically considered a paradoxical reaction resulting from effective therapy, rather than an indication that treatment is ineffective.

Fig. 2. (A, B) Plain radiographs of a 37-year-old man of Indian origin who presented to the hand clinic with a several year history of pain and swelling of the right wrist. Cultures obtained at the time of bone debridement grew *M. tuberculosis*. Imaging reveals extensive destruction of the wrist with pancarpal erosive changes. Erosion is also noted at the distal radius and ulna, and at the metacarpal bases. There is a significant amount of soft tissue calcification, typical of long-standing tuberculous infection. The patient’s treatment course was complicated by the development of worsening swelling and fistulae while on therapy. The degree of drainage required several episodes of surgical debridement.

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Surgery

The role of surgery for bone and joint tuberculosis, for sites other than the spine, is relatively straightforward. Surgery is not necessary for cure, but can play a supportive role in draining abscesses and decompressing vital structures, such as nerves. Joints that are significantly damaged may require debridement and possible fusion or replacement. Placement of a prosthetic joint into a previously infected space is possible, provided the patient has received adequate therapy before the replacement [14,34].

Spinal tuberculosis can also be cured by medical therapy [44]. Patients treated medically, however, have a tendency to develop late neurologic and musculoskeletal complications from progressive kyphosis and spinal instability. Given the close proximity of vital structures, such as the spinal cord and nerve roots, it has been argued that aggressive surgical treatment should be used to stabilize the spine and prevent kyphosis, unless only very mild disease is present [46]. There is evidence to suggest that radical debridement and bone grafting may be superior to simple debridement in improving kyphosis and preventing late deterioration [47–49].

Although there have been no large randomized trials studying the treatment of bone infections caused by NTM, a combination of surgery and antibiotics is usually advocated. Aggressive surgical intervention has been emphasized, particularly in the setting of abscess formation. In general, NTM are more resistant to antituberculous drugs than \textit{M tuberculosis}, and in vitro resistance testing may not correlate with clinical response [25].

Fig. 3. MRI and CT scan of a 47-year-old man of Jamaican origin who presented with a several month history of lower back pain. (A) The MRI reveals marked destruction of the L4-L5 disk, with marked irregularity of the end plates. No impingement on nervous structures was noted. (B) The CT revealed partial anterior collapse of the L4 vertebrae, and destruction of the L4-L5 end plate. A CT-guided biopsy revealed chronic inflammation, but mycobacterial cultures were negative. A clinical decision was made to treat the patient for vertebral tuberculosis, and he rapidly recovered.
Although the combination of agents used is based on the particular mycobacterium species or group isolated, agents used for treating NTM infections have included macrolides (clarithromycin, azithromycin); rifampin or rifabutin; ethambutol; doxycycline; minocycline; quinolones (ciprofloxacin, moxifloxacin, gatifloxacin); sulfonamides; amikacin; streptomycin; isoniazid; ethionamide; cefmetazole; and imipenem [50]. The number of agents required for effective treatment is not clear, although three-drug regimens are often adopted. Furthermore, the optimal duration of therapy is unknown, although courses of 6 to 12 months are generally used. Severely immunocompromised patients may require treatment for years [51].

**Follow-up during treatment**

As per any type of tuberculosis, regularly scheduled follow-up, at least monthly, is essential. Patients must be warned of the possible side effects of therapy and questioned regarding suspicious symptoms at each visit. The authors perform liver function tests at the initial visit, repeated monthly for the first 3 months, and then as needed based on patient symptoms, until therapy is completed. Baseline measurement of visual acuity and color vision, followed by regular assessments thereafter, is necessary for patients receiving prolonged ethambutol therapy, especially at doses > 15 mg/kg.

Similarly, the prolonged duration of therapy and use of toxic agents demands that patients with NTM bone infections be followed closely for adverse drug events. Although little evidence exists on the management of these patients, clinical and radiologic improvement on therapy can direct the frequency of follow-up and intervention.

Proof of cure is not easily available for mycobacterial bone and joint disease, unlike pulmonary disease. Repeat cultures of the affected area are typically difficult to obtain and generally not required, unless there is a suspicion that the patient is not responding to therapy. Repeat imaging is helpful to show resolution of symptoms; however, the patient’s ongoing history and physical examination findings are likely the most relevant.

**Summary**

Physicians can expect to see more mycobacterial bone and joint disease in North America as a result of increased travel, immigration, and use of immunosuppressive medications. The first step in treating infections caused by these organisms is to consider the diagnosis early in the course of illness. Long-standing untreated mycobacterial infections typically cause significant bone destruction and loss of function. The treatment of mycobacterial bone and joint infection requires prolonged antibiotic therapy, often in conjunction with surgical intervention, particularly for spinal tuberculosis.
References


