Mycobacterial Musculoskeletal Infections

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KEYWORDS

• *Mycobacterium tuberculosis* • Nontuberculous mycobacteria • Septic arthritis
• Pott's disease • Osteomyelitis • Tenosynovitis

KEY POINTS

- Patients may be predisposed to mycobacterial musculoskeletal infection by virtue of geographic exposure to *Mycobacterium tuberculosis*; cell-mediated immunosuppression, including use of immunomodulatory therapies; or traumatic or postsurgical inoculation of environmental mycobacteria.
- Mycobacteria often cause paucibacillary disease and may be fastidious in their growth characteristics. Diagnosis usually requires culture confirmation but newer molecular technologies offer the potential to identify infecting organisms more rapidly. Sensitivity testing is recommended whenever possible.
- Mycobacterial musculoskeletal infections remain challenging to treat, requiring combination antimycobacterial therapy generally for a minimum of 6 months. Surgical therapy is often required for infection caused by nontuberculous mycobacteria.

INTRODUCTION

Mycobacterial musculoskeletal infections have contributed to significant morbidity for millennia. Researchers have extracted *Mycobacterium tuberculosis* (MTb) DNA from bone lesions of humans who lived more than 9000 years ago.[1] Despite significant advances in modern medicine, these infections remain challenging to manage. Host deficiencies, antibiotic resistance, drug toxicities, limited medication penetration into bone, and complex surgical considerations can all complicate management of these infections. Additional difficulties stem from limited clinical data to guide therapy for patients with severe mycobacterial infections of bones and joints. This article therefore

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offers a framework for the approach to musculoskeletal mycobacterial infections, acknowledging that when data are lacking, expert opinion guides much of the management of these infections.

PATHOGENESIS AND HOST RISK FACTORS

Mycobacteria have evolved alongside humans for millennia. Over this period of coevolution, agents of mycobacterial disease have developed a variety of molecular mechanisms that allow them to evade immune detection, avoid destruction within the host, and eventually propagate to effect clinical disease if left unchecked. On initial inhalation, MTb adheres to complement, Fc receptors, and mannose receptors present on the surfaces of macrophages.[2] Like other mycobacteria, the initial stage of infection with this pathogen is characterized by an early transition to the intracellular space. MTb and nontuberculous mycobacteria (NTM) actively infect the same cells that are instrumental in their clearance, and on moving into the intracellular space, they avoid detection by other arms of the immune system. Once inside the macrophage, MTb interferes with the expression of various proteins involved in pH regulation and produces a urease that prevents acidification of the phagosome.[2,3] Other NTM adopt a similar strategy.[4] Mycobacteria, including MTb, are also known to express superoxide dismutase, catalase, and thioredoxin to mitigate the reactive oxygen species produced by phagocytic cells.[5] Even if multiple intracellular mechanisms fail to control the intracellular propagation of mycobacteria, macrophage apoptosis mediated by tumor necrosis factor (TNF)–alpha can limit the propagation and viability of mycobacterial species like MTb.[6] However, virulent strains of MTb may still interfere with macrophage apoptosis, thus enhancing their propagation.[7] After becoming established in the intracellular space, cellular immunity becomes essential in clearing mycobacterial infections. TNF-alpha, interleukin (IL)-12, and interferon (IFN)-gamma help to facilitate control of these primarily intracellular pathogens.

Patients with certain inherited and acquired immunodeficiencies or other medical comorbidities are known to be at higher risk of mycobacterial infection in general (**Box 1**). In addition, use of corticosteroids and other immunomodulatory medications has now become one of the most common factors predisposing to invasive mycobacterial disease. In particular, TNF-alpha modulators confer a significant risk of reactivation of tuberculosis, and a growing number of reports suggest that these agents can also increase the risk of invasive NTM infections.[8–10] Although infliximab and adalimumab seem to confer greater risk than etanercept, all three of these immunomodulators may increase the risk of new or reactivated musculoskeletal infections with acid-fast bacilli (AFB).

RISK FACTORS FOR MUSCULOSKELETAL INVOLVEMENT

In a susceptible host, mycobacterial musculoskeletal infections may occur via several different mechanisms. Tuberculosis generally spreads to osteoarticular sites via the hematogenous route. During primary infection with MTb, bacillemia may occur, although it is usually contained by cell-mediated immunity. When cellular immunity is impaired, bacillemia may lead to seeding of sanctuary sites, including bones and joints. Osteoarticular tuberculosis may manifest during primary infection, although more commonly it represents reactivation of latent bacilli well after an initial bout of primary disease.

Although osteoarticular infection caused by NTM may occur via hematogenous spread in immunodeficient hosts, contiguous and lymphatic spread of NTM infection after percutaneous inoculation provides another route of infection for NTM. NTM are