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REVIEW

Extrapulmonary Comparisons Between *Mycobacterium Tuberculosis* and Non-Tuberculous Mycobacteria: From Manifestations and Diagnosis to Treatment

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Abstract: The incidence of tuberculosis (TB) and non-tuberculous mycobacteria (NTM) diseases and the number of deaths from these diseases are steadily increasing worldwide. However, the pathologic diagnosis of NTM disease is similar to that of tuberculosis, and it is often difficult to distinguish between the two, which can lead to misdiagnosis and treatment aversion. Therefore, differentiation between the two can help in accurate diagnosis and treatment planning. This review compares the presentation, diagnosis, and treatment of common extrapulmonary sites of involvement in tuberculosis and non-tuberculous mycobacterial disease.

Keywords: *Mycobacterium tuberculosis*, non-tuberculous mycobacteria, extrapulmonary, manifestations, diagnosis, treatment

Introduction

Backgrounds

Tuberculosis (TB) is a chronic infectious disease mainly caused by the *Mycobacterium tuberculosis*. The lungs are the main site of involvement. TB that occurs outside the lungs is called extrapulmonary tuberculosis (EPTB) and accounts for about 15–20% of cases. EPTB can occur in almost any part of the body, usually including lymph nodes, pleura, and bone and joint sites.[1] Tuberculosis (TB) has long been a significant threat to public health and continues to be a major challenge worldwide.

Non-tuberculous mycobacteria (NTM) is a disease in which the body is infected by non-tuberculous mycobacteria, resulting in associated tissue and organ lesions. Non-tuberculous mycobacteria (NTM), formerly known as atypical mycobacteria, are a group of mycobacteria in the genus Mycobacterium, except *Mycobacterium tuberculosis* and *Mycobacterium leprae*.[2] More than 200 subspecies have been identified.[3,4] They are conditionally pathogenic and only a few can cause serious disease.[4] The most frequently affected organ is the lungs. NTM can also manifest as a localized disease affecting extrapulmonary sites, including lymph nodes, skin, soft tissues, and, in rare cases, bones. Extrapulmonary NTM disease accounts for about 20–30% of cases.[5–7] The global incidence of non-tuberculous mycobacteria (NTM) infections has increased and is now one of the most significant public health threats.[8,9]

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Epidemiology

According to the World Health Organization's Global Tuberculosis Report 2024, the number of new tuberculosis (TB) cases diagnosed in 2023 is projected to reach 8.2 million. This figure represents the highest number the World Health Organization recorded since global TB detection began in 1995. Of the total tuberculosis (TB) cases, 55% are in men, 33% are in women, and 12% are in children and adolescents.[10] The high number of new tuberculosis cases is influenced by five major risk factors: malnutrition, HIV infection, alcohol abuse, tobacco use (especially among men), and diabetes.[10] Although the lungs are the initial site of infection, the disease can spread to many organs.[11] TB can be transmitted by inhalation of aerosolized droplets containing *Mycobacterium tuberculosis* produced by symptomatic patients or by transmission of *Mycobacterium bovis* to the gastrointestinal tract via unpasteurized dairy products. While uncommon, there have been documented instances of congenital transmission, sexual transmission, vaccination-related transmission, and the involvement of therapeutic devices.[12] Extrapulmonary tuberculosis(EPTB) is primarily due to *Mycobacterium tuberculosis* infection forming and circulating through the blood or lymphatic system or to direct transmission of tuberculous lesions in neighboring organs and sites.

The incidence of nontuberculous mycobacteria (NTM) is rising globally. This increase may be linked to a greater number of individuals at risk, such as those undergoing organ transplantation, orthopedic surgery, or receiving immunosuppressive therapies. Additionally, heightened awareness of the disease and advancements in diagnostic techniques contribute to this trend.[5] Women outnumber men, particularly among patients over the age of 70.[13] Risk factors include organ transplantation, plastic surgery, and the use of immunosuppression.[14] NTM can involve several sites, mainly the lungs, lymph nodes, skin and soft tissues, bones, and joints.[15] NTM are conditionally pathogenic organisms present in water and soil and are transmitted mainly through aerosols in the environment. NTM disease is rarely transmitted from person to person and from animal to animal. In most cases, it is transmitted from pathogenic microorganisms in the environment to humans or animals, partly through the digestive tract and through wounds exposed to NTM, resulting in direct contact transmission[16] (Table 1).

Pathogenesis

People with tuberculosis pass *Mycobacterium tuberculosis* to uninfected people through respiratory transmission routes, such as coughing and sneezing, usually through small aerosol droplets 1–5 micrometers in diameter.[32] First, the first line of defense comes into play—the cup cells of the respiratory tract trap MTB and prevent it from entering. Some MTB bypasses this line of defense and reaches the lungs, initiating a second line of defense. MTB passes through cell surface molecules into macrophages, which phagocytose MTB and secrete various hydrolytic enzymes and cytokines. When the phagocytes fail to stop the MTB, the bacteria are released into the internal environment, where other macrophages engulf them in a continuous cycle. With the initiation of cellular immunity, Th1 cells in the T-lymphocytes are activated, and Th1 cells release a variety of cytokines, such as gamma-interferon. Lymphocytes are recruited to the site of infection and surround the infected macrophage, leading to granuloma formation, a key feature of TB.[33] Granulomas can inhibit progression to active TB in immunocompetent individuals.[34] If the body is immunocompromised, the infection may lurk in the lungs or spread to extrapulmonary sites of the body through bloodstream dissemination and directly from the trachea and bronchi. (Figure 1).

Water and soil are important routes of transmission of NTM disease, and NTM can invade the body through the respiratory tract, gastrointestinal tract, and skin.[35] At the onset of NTM infection, neutrophils capture and kill most of the NTM. Macrophages phagocytose the remaining NTM and grow and multiply within the macrophage, where lysosomal enzymes lyse some of the NTM. Its antigenic products and its bacterial constituents are transported to localized lymph nodes, where they activate a variety of effector cells to release a variety of cytokines through a series of pathways that result in the production of, among other things, a CD4+ T cell- CD4+ T cells mainly secrete IFN-γ and IL-12 to activate macrophages to kill NTM. At the same time, natural killer cells also play an important role in the early activation and enhancement of the body's natural and acquired immune responses to NTM infection through IFN-γ production (Figure 2).

Table 1 Comparison Between MTB and NTM

	Tuberculosis	Non-Tuberculous Mycobacterial Disease	Reference
1 Causative agent	Mycobacterium tuberculosis	Non-tuberculous mycobacteria	
2 Mode of transmission	Transmission is mainly through inhalation of aerosolized droplets containing Mycobacterium tuberculosis. Gastrointestinal transmission, congenital transmission, sexual transmission, and vaccination transmission are rare cases.	NTM is spread mainly through aerosols in the environment (water and soil), partly through the digestive tract, and by direct contact with wounds. Person-to-person transmission is rare	[12,16]
3 Affected area	All organs of the body can be involved, lungs are more common.	It can involve several sites, mainly the lungs, lymph nodes, skin and soft tissues, bones, and joints.	[11,15]
4 Sex with higher disease burden	55% of TB cases are men, 33% are women, and 12% are children and adolescents.	Women outnumber men, especially in patients over 70 years of age.	[10,13]
5 Predisposition/Co-morbidities	Major risk factors: malnutrition, HIV infection, alcohol abuse, tobacco use (especially among men), and diabetes	Organ transplantation, plastic surgery, and use of immunosuppression.	[10,14]
6 Diagnosis 6.1 Clinical diagnosis	The clinical course is mostly chronic. There are often systemic symptoms such as low-grade fever, malaise, night sweats, and respiratory manifestations such as coughing and coughing up blood.	Similar to Mycobacterium avium conjugatum, but with milder systemic symptoms. Varies by species and organ involved.	[17,18]
6.2 *Samples for the diagnostic test*	Sputum, alveolar lavage, lung tissue, cerebrospinal fluid, lymph nodes, joint fluid, and urine.	Sputum, induced sputum, bronchial lavage fluid, bronchoalveolar lavage fluid, lung biopsy tissue, lymph node biopsy tissue, liver biopsy tissue, kidney biopsy tissue, spleen biopsy tissue, blood, bone marrow secretions, body fluids, and feces.	[19,20]
6.3 Microbiological test	Smear antacid staining (Ziehl-Neelsen) is positive but detects only 50–75% of active tuberculosis. Fluorescent staining is positive.	Smear antacid staining (Ziehl-Neelsen) is positive, but the detection rate is low Fluorescent staining is positive.	[21]
6.4 Culture	No growth in the PNB medium	Growth in PNB medium	[22]
6.5 Molecular biological test	PCR DNA testing is recommended only in areas with a high prevalence of NTM disease to distinguish MTB from NTM quickly. RNA testing is the only molecular biology test on the market today that can differentiate between MTB and NTM. XpertMTB/RIF is positive and it can accurately distinguish between MTB and NTM.	PCR LAP Genechip MALDI-TOF MS Sanger sequencing mNGS whole-genome sequencing	[23–25]

(*Continued*)

Table 1 (Continued).

	Tuberculosis	Non-Tuberculous Mycobacterial Disease	Reference
6.6 Immunological test	TST results are generally of little significance and usually only indicate infection with TB. IGRA is highly specific and is not interfered with by BCG vaccination and most NTM.	TST may be positive IGRA is negative in most non-tuberculous mycobacteria	[26,27]
7 Treatment	Commonly used anti-tuberculosis drugs: are isoniazid, rifampicin, ethambutol, and pyrazinamide. Adjustments are made on a case-by-case basis, and in the case of tuberculous meningitis, glucocorticoids are used to reduce inflammation and lower intracranial pressure. In some cases, such as lymph node tuberculosis, surgical treatment may be required.	Appropriate antibiotics are selected based on drug sensitization results; commonly used drugs include: clarithromycin, azithromycin, ethambutol, amikacin, and ciprofloxacin in combination. Surgery may be required in some cases.	[28–31]

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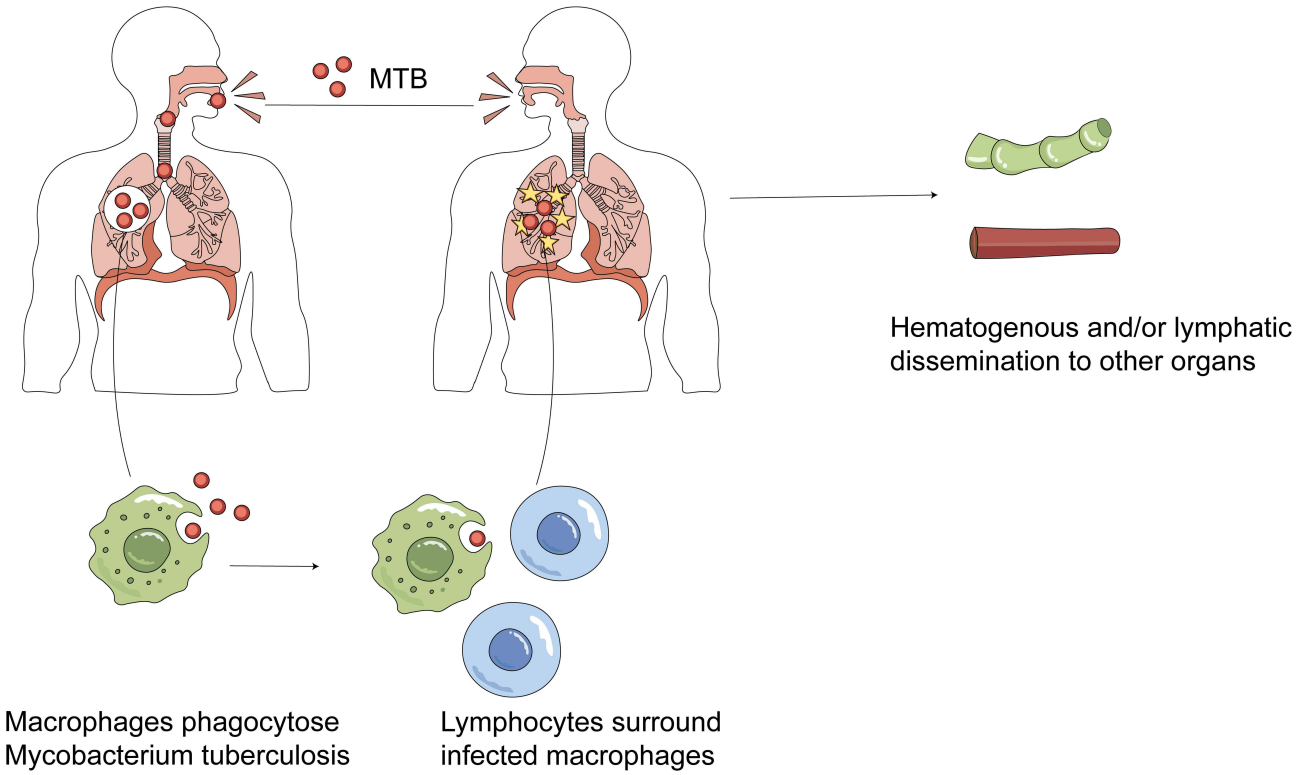

Figure 1 Pathogenesis of MTB.

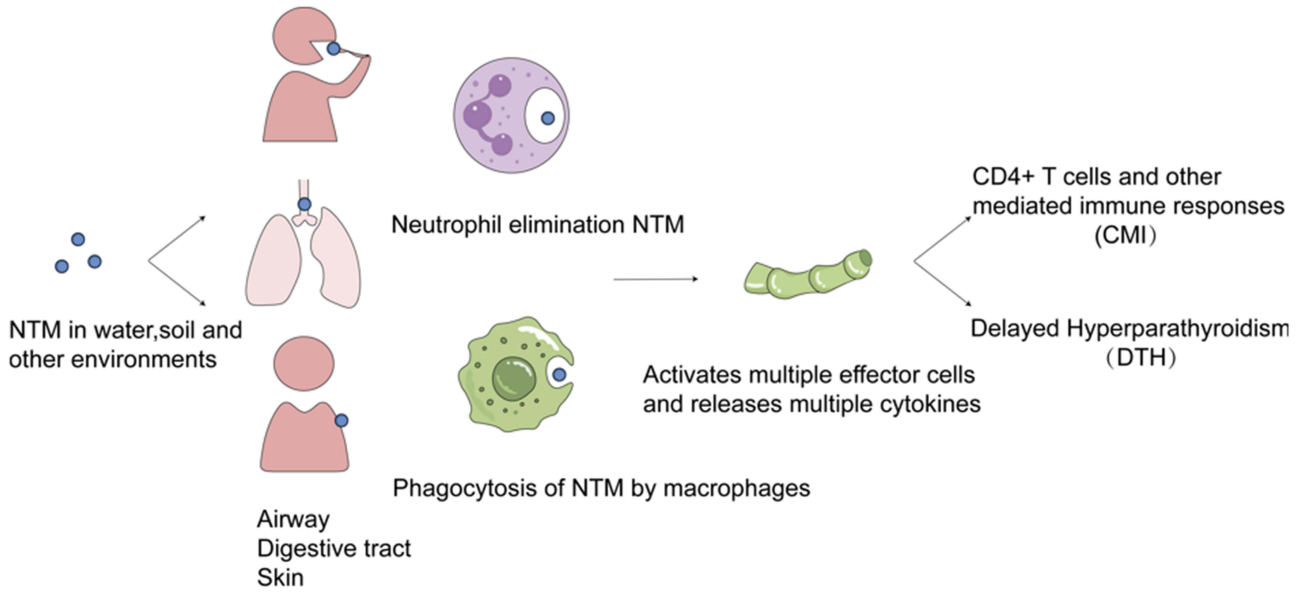

Figure 2 Pathogenesis of NTM.

Lymphatic Node

Manifestations

Tuberculous lymphadenitis, alternatively referred to as TBLN, represents the most prevalent form of EPTB, comprising between 20% and 40% of all EPTB cases.[36,37] The peak incidence is between 20–40 years of age and is more common in the female population. Most cases present with unilateral cervical lymph node enlargement.[38] Severe cases with systemic

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symptoms such as low-grade fever, malaise, night sweats, and weight loss are more common in HIV-positive patients. *M. tuberculosis* usually involves the cervical lymph nodes, posterior deltoid lymph nodes, or supraclavicular lymph nodes. Tuberculous lymphadenitis can occur either in the setting of a pulmonary infection or through lymphatic dissemination through the mediastinal lymph nodes after an incubation period.[39]

Non-tuberculous mycobacterial lymphadenitis usually occurs in children 1 to 5 years of age and is a painless, subacute, or chronic lymphadenitis.[40,41] Adult cases are rare unless immunosuppression is present. The most common nontuberculous mycobacterium is *Mycobacterium avium* complex (MAC), and others include *Mycobacterium haemophilum, Mycobacterium intracellulare*, and *Mycobacterium marinum*.[42,43] The oropharyngeal mucosa is one of the sites of invasion for NTM cervical lymphadenitis, and some children may have a history of odontogenic infection and/or recent dental manipulation.[44] The clinical picture is characterized by a localized, unilateral, painless, or mildly painful mass, mostly without systemic signs and symptoms, with only local lymph node involvement, mainly in the submandibular, cervical, or parotid lymph nodes.[45] The clinical course of NTML can be divided into four phases: slow enlargement of lymph nodes in Phase I, liquefaction of affected lymph nodes and fluctuating masses in Phase II, skin discoloration (violet) and marked thinning of the skin in Phase III, and rupture of the lymph nodes in Phase IV, resulting in a parchment-like mass in Phase IV. Stage III is characterized by discoloration of the skin (violet color) and marked thinning of the skin or parchment, and stage IV is characterized by rupture and formation of sinus tracts.[46]

Diagnosis

Differentiating tuberculous lymphadenitis from nontuberculous mycobacterial lymphadenitis is often a major challenge. Regarding histologic features, NTM lymphadenitis is similar to *Mycobacterium tuberculosis* lymphadenitis in that both result in granuloma formation.[47] A positive antacid stain does not distinguish NTM from *Mycobacterium tuberculosis* infection, and a negative antacid stain does not exclude *Mycobacterium tuberculosis* infection. Atypical mycobacterial infection should be suspected if the patient has documented antacid bacilli on the smear and has not responded to multidrug therapy.[48] The tuberculin skin test (TST) contains many antigens common to both *Mycobacterium tuberculosis* and nontuberculous mycobacteria so the TST may be positive in patients with nontuberculous mycobacterial lymphadenitis. There were differences in the size of mycobacteria-induced TST sclerotomies between NTM-infected and Mycobacterium tuberculosis-infected individuals; however, the high inter-individual variability and significant overlap between the study groups rendered sclerotomy size insufficient to be used as a biomarker.[49] It has been shown that simultaneous detection of T cell reactivity to two mycobacterial antigenic proteins (tuberculin and sensitizer) improves the differential diagnosis in pediatric patients. Notably, the proportion of tuberculin-reactive T cells was significantly higher in children with tuberculosis, whereas the proportion of sensitizer-reactive T cells was much higher in children with nontuberculous mycobacterial lymphadenitis (NTM-L).[50] Positive cultures confirm the diagnosis of NTM lymphadenitis, and excisional biopsies of lymph nodes are more likely to be culture-positive than needle aspiration biopsies. Fine needle aspiration cytology (FNAC) provides rapid insight into cytopathology and is an accurate and reliable method of diagnosing nontuberculous mycobacterial lymphadenitis, especially in cases where the diagnosis of nontuberculous mycobacterial lymphadenitis is difficult. In addition, it has evolved as a direct outpatient diagnostic tool for the assessment of tuberculous lymphadenitis, thereby replacing histopathological examination of lymph node biopsies.[51] PCR can also be used to diagnose NTM disease, but it takes longer, especially for slow-growing NTM strains that take more than 6 weeks to culture and are susceptible to contaminants such as the environment.

Treatment

The recommended regimen for the treatment of tuberculous lymph node enlargement in children and adults is daily rifampicin, isoniazid, ethambutol, and pyrazinamide for the first two months, followed by rifampicin and isoniazid daily or three times weekly for the next four months.[52] Cervical lymph node tuberculosis responds well to antituberculosis drugs. Surgical treatment should generally be avoided in the absence of serious complications. The role of surgery is limited to guided fine needle aspiration, incision and drainage, incision, and limited excisional biopsy.[53] A retrospective cohort analysis showed that surgical intervention for lymph node tuberculosis could be considered in cases of abscesses 3 cm or more in diameter, the presence of abscesses and fistulas, recurrent cases, resistance to antibiotics, and paradoxical reactions of escalating severity 40.

There are three main strategies for the treatment of NTM lymphadenitis, including observation, antibiotic therapy, and surgery.[54] A retrospective study showed that lymphadenitis usually subsided within one year. In addition, 97% of pediatric patients developed fistulas in the affected lymph nodes during the observation period.[55] In addition, some of the patients' families were not satisfied with the scarring.[56] The use of antibiotics such as clarithromycin does not have a statistically significant difference in the time to lymph node regression compared to the observation group, but it decreases the incidence of fistulae.[57,58] Pharmacological treatment of non-tuberculous mycobacterial (NTM) lymph node enlargement is usually based on a two-drug combination therapy in which a macrolide antibiotic is paired with another drug with antimycobacterial activity (eg, rifampicin, rifabutin or ethambutol). Clarithromycin is usually the drug of choice because of its strong in vitro inhibition of the *Mycobacterium avium complex* (MAC), but some studies have shown that clinical response does not correlate with in vitro susceptibility. In pediatric patients, azithromycin is preferred for its convenience of once-daily dosing. Macrolides alone carry the risk of developing MAC resistance.[59]

Surgery is considered the treatment of choice for nontuberculous mycobacterial lymphadenitis despite the high risk.[60] Complete removal of the infected lymph nodes results in the highest cure rate but may carry a risk of at least 2% permanent mandibular marginal nerve palsy.[58] Surgical treatment has demonstrated that the long-term esthetic results obtained with surgical treatment are superior to those obtained with nonsurgical treatment. In addition, surgery after failure of the initial nonsurgical treatment strategy resulted in worse aesthetic outcomes than initial successful surgery.[43] In 2015, Zimmerman et al reported adjusted mean cure rates of 98% following complete resection, 73.1% with antibiotic therapy, and 70.4% under observation.[42] Treatment decisions for nontuberculous mycobacteria in children should be individualized.

Skin and Soft Tissue

Manifestations

The incidence of cutaneous tuberculosis (CTB) has been increasing since Mid- to late twentieth century as the number of patients on immunosuppressive therapy and multidrug-resistant tuberculosis (MDR-TB) has increased.[61] Cutaneous tuberculosis (CTB) is a rare manifestation of mycobacterial infection, with *Mycobacterium tuberculosis* as the main pathogen, and occasionally *Mycobacterium bovis* and BCG (BCG is an attenuated strain of *Mycobacterium bovis*), and accounts for 1%-1.5% of extrapulmonary tuberculosis.[62] Cutaneous tuberculosis (CTB) is commonly observed in young adults, especially among females. In contrast, tuberculosis verrucosa cutis is more prevalent in males, and erythema induratum of Bazin is predominantly seen in females.[63] The prevalence of CTB is influenced by several factors, including the burden and virulence of the infecting Mycobacterium strains, the mode of transmission, and the individual's prior susceptibility to tuberculosis. Based on the bacterial load, CTB cases can be classified into two categories: polymicrobial (low immunity to BK, including tuberculous chancre, artificial tuberculosis, scrofulous dermatophytosis, acute granulomatous tuberculosis, and tuberculous dendritic); and paucibacillary (high immunity to *Mycobacterium tuberculosis*, including verrucous tuberculosis, lupus vulgaris, and TB-like tuberculosis).[63]

The more widely accepted method of classifying cutaneous TB is to divide it into the following five categories: exogenous cutaneous TB (including tuberculous soft chancre and tuberculous cutaneous warts), endogenous cutaneous TB (which can occur through self-inoculation, the lymphatic system, and hemorrhagic and secondary dissemination, and results in scrofulous dermatosis, metastatic tuberculous abscesses, lupus vulgaris (LV), granulomatous TB, and artifacts of TB). Cutaneous tuberculosis due to BCG (BCG vaccine); postvaccination lupus vulgaris Tuberculosis (papillary necrotizing tuberculosis; lichenoid tuberculosis); TB-like tuberculosis and allergic tuberculosis.[63] A variety of slowly progressive lesions usually characterize the clinical picture, and in addition, recurrent lesions may lead to tissue destruction or long-term cancer.[64]

Research revealed a notable rise in the prevalence of skin and soft tissue NTM (SST NTM) infections, possibly due to the use of immunosuppressive drugs, an increase in cosmetic surgery, or an increase in NTM detection.[65] SST NTM infections usually occur when wounds come into contact with water contaminated with these organisms or hospital-acquired infections, such as plastic surgery.[66] The prevalence of skin infections caused by Non-Tuberculous Mycobacteria (NTM) rises as individuals age, exhibiting no statistically discernible gender disparity between males and females.[67] Rapidly growing Mycobacteria (RGM) tend to manifest as infections confined to a single site, whereas

slowly growing Mycobacteria (SGM) are more inclined to present as infections spanning multiple sites.[67] The most common species was *Mycobacterium marinum*.[68] Manifestations of symptoms may emerge within a range of days to years post-trauma and are not definitive for diagnosis.[66] Mycobacterium marinum-induced infections, commonly termed "fish-tank granuloma", are frequently acquired through exposure in contaminated swimming pools or during the cleaning of aquariums. These infections are distinguished by the presence of a solitary papulonodular lesion, which may be verrucose and/or ulcerated, and localized to the site of inoculation.[69] *Mycobacterium ulcerans* is commonly found in tropical rain forests, with most cases occurring in West Africa, and can cause Buruli-ulcer disease.[70] Childhood is the most common age for patients with Buruli ulcer.[71] Lesions are most common in exposed areas such as limbs.[70] It goes through three stages, starting with a pre-ulcerative lesion (such as a papule, nodule, or plaque) that extends to deep necrosis and leads to the formation of a destructive ulcer, followed by scar formation and spontaneous healing of the ulcer.[66] Healing may result in severe contractures, scars, and deformities.

Diagnosis

The clinical presentation of Mycobacterium cutaneous infections lacks specificity, so it is crucial to correctly diagnose them early to avoid misdiagnosis. It can be differentiated based on history as well as pathogenetic examination. Acid-fast bacilli smears are often performed on skin lesions, but because the results are related to the number of bacteria in the specimen and the detection level, the positivity rate is low, and it is impossible to identify CTB and NTM.[72] Culture is considered the definitive method for diagnosing the infection; however, it is time-consuming and prone to environmental disruptions. In recent years, PCR-nucleic acid sequencing (which has become the gold standard for identifying Mycobacterium species), PCR-restriction fragment length polymorphism (RFLP) analysis, and genome sequencing techniques such as second-generation sequencing of the macro-genome have been used to help diagnose strains at an early stage, and whole-genome sequencing has been used to help further identify the NTM species and subspecies.[73]

Treatment

Current treatment options for CTB caused by *Mycobacterium tuberculosis* include conventional anti-tuberculosis therapy and occasional surgical intervention.[62] Treatment of CTB consists of two therapeutic phases. Initially, an intensive phase involving isoniazid, rifampicin, and pyrazinamide is employed to decrease the bacterial burden and minimize the emergence of drug-resistant organisms. Subsequently, a continuation phase follows, utilizing isoniazid and rifampicin alone to eradicate any drug-sensitive bacilli that may have become dormant during the initial stage.[74] The initial phase spans approximately 8 weeks, followed by a second phase that extends from 9 to 12 months. The efficacy of the treatment hinges on multiple factors, including the patient's immune system strength, general health status, the disease stage, the classification of skin lesions, adherence to treatment by the patient, the length of the therapeutic intervention, and any encountered adverse effects. Debridement can provide a biopsy of the diseased skin to aid in diagnosis.[74] In localized areas of scrofuloderma and TVC, surgical excision may be used.[75] To date, although most topical therapies have been useful for cutaneous tuberculosis, they have not been completely effective.[62]

There are no specific guidelines for nontuberculous mycobacterial skin infections, and medication regimens are often based on the particular species of mycobacteria, drug sensitivity profile, and the patient's immune status.[76] By the treatment protocols established by the American Thoracic Society (ATS), the Centers for Disease Control and Prevention (CDC), and the Infectious Diseases Society of America (IDSA), the standard management of skin and soft tissue infections (SSTIs) caused by nontuberculous mycobacteria (NTM) involves an antibiotic regimen spanning from 3 to 6 months.[77] In some cases, surgery is also an important treatment option.[78] A regimen consisting of clarithromycin, administered at a dosage of 500 mg twice daily, in combination with either ethambutol at 15 mg/kg per day or rifampicin at 600 mg per day, is typically prescribed for the treatment of *Mycobacterium marinum* infections. This dual-drug therapy is recommended for 2 to 3 months, followed by an additional 1 to 2 months of continued treatment once symptoms have resolved.[79] For less severe *Mycobacterium marinum* infections in the marine environment, monotherapy with clarithromycin, doxycycline, minocycline, or TMP-SMX may be a suitable treatment for superficial manifestations.[76]

In the initial stages of *Mycobacterium ulcerans* infection, fosfomycin and clarithromycin are recommended at 500 mg twice daily for 8 weeks. Surgery is necessary if the ulcer continues to enlarge after 4 weeks of antibiotic treatment, if the

patient is intolerant of antibiotics, or if there is extensive necrosis of the skin or soft tissues.[80] A paradoxical worsening of symptoms may occur after antibiotic therapy, which may be due to a reversal of the immunosuppressive effects of mycolactones due to decreased levels of mycolactones and a rapid increase in the local cellular immune response.[81] In such cases, treatment should be continued and supplemented with systemic corticosteroids.[82] For infections caused by *Mycobacterium fortuitum, Mycobacterium chelonae, and Mycobacterium abscessus* (collectively known as rapid-growth mycobacteria or RGM), treatment recommendations include the use of at least two antimicrobial drugs to which the organisms are sensitive for a period of four to six months. This approach aims to minimize the risk of developing resistance. Typical treatment regimens include: ciprofloxacin at a dose of 750 mg twice daily; or levofloxacin at a dose of 500 mg twice daily; TMP-SMX (trimethoprim-sulfamethoxazole) at a dose of 160 mg/800 mg twice daily; doxycycline at a dose of 100 mg twice daily; or clarithromycin at a dose of 500 mg twice daily. Twice a day.[83] Surgical excision may be considered if the infection involves a single lesion.[79]

Skeletal and Muscular

Manifestations

Musculoskeletal tuberculosis is a secondary manifestation of primary infection with TB in the lungs or digestive tract. It is the third most prevalent type of extrapulmonary TB.[84,85] Musculoskeletal tuberculosis (TB) occurs in areas that are heavily loaded, active, and prone to trauma. The spine is the most common site of bone and joint tuberculosis, accounting for about 50% of all cases, followed by the knee, hip, and elbow.[86] Most joint tuberculosis lesions present as solitary, with only a few being multiple. Moreover, the vast majority of these lesions are asymmetrical. Prior to onset, adolescents frequently report a history of joint trauma. The onset of the disease is usually slow and accompanied by mild fever, malaise, night sweats, lethargy, anorexia, and anemia. However, there are cases of acute onset, characterized by high fever and toxemia, mostly in children and immunocompromised patients. Tuberculosis of bones and joints initially presents as exudative inflammatory changes, followed by proliferative or necrotic lesions. The disease can be divided into three types: pure synovial TB, pure bone TB (which is the most common), and total joint TB.[87] In the early stages of TB of the joints, the lesions are limited to bone or synovial tissue, the articular cartilage remains intact, and joint function is relatively unaffected. As the disease progresses, the TB lesions may penetrate the joint surface and invade the joint cavity, causing varying degrees of damage to the articular cartilage, a condition known as total joint TB. Thus, total joint tuberculosis can lead to varying degrees of joint dysfunction.

Musculoskeletal (MSK) infections are a rare occurrence of NTM infections, usually occurring as a result of trauma, surgery, skin puncture, or direct inoculation following injection.[88] Non-tuberculous mycobacterium strains acquired by trauma are *Mycobacterium fortuitum, Mycobacterium chelonae*, and *Mycobacterium marinum*. A study showed that the most commonly isolated mycobacteria in immunocompetent patients were *Mycobacterium marinum, Mycobacterium avium*, and other fast-growing mycobacteria, including M*ycobacterium occasionalis, Mycobacterium abscessus*, and *Mycobacterium chelonae*. In contrast, certain mycobacteria, particularly *Mycobacterium chelonae* and *Mycobacterium haemophilum*, are isolated primarily from immunocompromised patients.[89] Patients aged 50 years and older are more susceptible to musculoskeletal (MSK) infections caused by nontuberculous mycobacteria (NTM).[90] Arthritis is the most common manifestation of musculoskeletal (MSK) infections, accounting for 61% of cases, followed by osteomyelitis (50%), tenosynovitis (25%), and discitis (14%).[91] In orthopedics, NTM infections occur mainly in the hand and wrist. Typically, patients present with symptoms such as swelling, drainage, or the presence of a palpable mass.[92] The most common clinical presentation is flexor tenosynovitis of the fingers, with magnetic resonance imaging showing marked hypertrophy of the synovium around the flexor tendons and fluid in the tendon sheaths.[93] Initial imaging findings may include mild soft tissue edema and proximal joint bone demineralization, but these are not diagnostic of the specific condition. In severe cases, the condition may progress to extensive necrosis of the synovial tissue with direct extension to the adjacent periosteum and ultimately to osteomyelitis. If milia are found in the tendon sheath or bursa, a nontuberculous mycobacterial infection should be considered immediately.[90] One study found that the average duration between symptom onset and diagnosis was 20.8 months.[94]

Diagnosis

To differentiate between *Mycobacterium tuberculosis* and non-tuberculous mycobacterial (NTM) infections in osteoarticular tissues, it is important to look at the clinical presentation, imaging features, microbiological analyses, and response to treatment.[95] Accurate diagnosis depends on meticulous history taking, physical examination, and laboratory evaluation.[96] A combination of clinical data, such as a history of open wounds, surgical procedures, or injections, can help establish a presumptive diagnosis of NTM infection.[97] Combining this clinical information with other diagnostic methods can help make a presumptive diagnosis of NTM infection.

Histologically, infections of the musculoskeletal system caused by atypical mycobacteria usually present as chronic granulomas, similar to those caused by *Mycobacterium tuberculosis*.[98] A history of trauma or surgery is helpful; however, a definitive diagnosis depends on the isolation of the mycobacterial species by culture.[98] Traditional culture methods for diagnosing musculoskeletal infections caused by NTM have limited positivity. Next-generation sequencing (NGS) technology provides a rapid and accurate method for diagnosing NTM pathogenesis, especially in fast-growing NTM strains.[99,100] With improved culture strategies, positive culture results can be obtained to guide clinical treatment modifications. Magnetic resonance imaging (MRI) is the method of choice for the evaluation of tuberculosis (TB) of the spine and musculoskeletal system.[101]

Treatment

Treatment of spinal tuberculosis in the absence of neurologic deficits, instability, and deformities, with or without paravertebral abscesses, antituberculosis drugs, and other conservative therapies is effective, and appropriate early drug therapy can prevent serious complications.[102] A combination of rifampicin, isoniazid, ethambutol, and pyrazinamide for 2 months, followed by a combination of rifampicin and isoniazid for a total of 6, 9, 12, or 18 months is the most commonly used regimen for the treatment of spinal tuberculosis.[103,104] The American Thoracic Society recommends using the same primary medication for the first two months of treatment, followed by a consolidation phase consisting of seven months of isoniazid and rifampicin therapy, for a total of nine months of treatment. In contrast, the Canadian Thoracic Society recommends a treatment period of 9 to 12 months. Surgery for Pott's disease is indicated for patients with neurological deficits, paravertebral abscesses, spinal instability due to deformities (especially those with deformities of 50 to 60 degrees or greater, which tend to worsen), resistance to current anti-tuberculosis medications (which are increasingly occurring in conjunction with HIV infection), and to alleviate or resolve complications such as delayed paraplegia. Delaying surgical treatment of Pott's disease can lead to severe kyphosis and ultimately respiratory insufficiency, painful subglottic compression, and paraplegia. Therefore, we advocate early surgical treatment to prevent severe spinal instability and neurological deficits.[103] Currently, the following techniques are used in the treatment of tuberculous spondylitis: 1) posterior decompression and fusion using an autologous bone graft; 2) anterior debridement and decompression followed by fusion with an autologous bone graft; 3) anterior debridement and decompression followed by fusion with simultaneous or subsequent posterior instrumented fusion; and 4) posterior instrumented fusion with anterior debridement and decompression followed by fusion either prior to or concurrently with this technique.[105]

For most musculoskeletal infections, antimicrobial chemotherapy combined with surgery is usually recommended.[88] The long-term outcome of musculoskeletal nontuberculous mycobacterial infections depends on host factors, the extent of infection, the success of surgical source control, and the pathogen itself.[94] Treatment of mycobacterial osteomyelitis usually involves surgical debridement, abscess drainage, and long-term chemotherapy. Several studies have shown that surgical debridement is adequate for the treatment of nontuberculous mycobacterial osteomyelitis, but appropriate individualized antimycobacterial chemotherapy following debridement or abscess drainage may be beneficial. Depending on the clinical response and the pathogens involved, postoperative therapy should be administered for 6 months to 2 years. Because of the variability of nontuberculous mycobacteria and the high rate of drug resistance in some nontuberculous mycobacteria, drug therapy should be decided after culture results yield drug sensitivity.[89,90] Osteomyelitis usually involves deeper tissues and requires continuation of antimycobacterial chemotherapy for at least 4 to 6 weeks, even after the onset of clinical symptoms or negative cultures.[106] Immunocompromised patients may even require chemotherapy for up to several years, as immune status may affect prognosis. The prognosis for spinal osteomyelitis due to NTM is relatively good.[107] The combination of rifampicin, ethambutol, and clarithromycin (REC)

has been reported to achieve favorable clinical outcomes in the treatment of *Mycobacterium avium complex* (MAC) infections, but the optimal duration of dosing (usually more than 12 months[108]) and a suitable alternative regimen have not yet been determined, and relapses have been observed.[109]

Conclusion

Tuberculosis is more prevalent in men than in women, while non-tuberculous mycobacterial (NTM) disease is slightly more prevalent in women than in men. TB is transmitted primarily through aerosols and droplets containing *Mycobacterium tuberculosis*. In contrast, non-tuberculous mycobacterial disease is transmitted primarily through respiratory, gastrointestinal, or dermal contact with non-tuberculous mycobacteria in the environment. A comprehensive patient history should be considered, and smear microscopy, culture, molecular biology techniques, and immunological testing should be differentiated. It is important to note that various NTM strains have different susceptibilities to drugs, and it is necessary to adjust the drug regimen based on the results of drug sensitivity testing.

Currently, there is no definitive medical regimen for extrapulmonary tuberculosis (EPTB), and the treatment used is similar to the standard 6–18 months regimen for TB. In cases of TB meningitis, anti-tuberculosis chemotherapy is usually used together with corticosteroids to prevent fibrotic sequelae. Surgery may be considered when drug therapy fails. Lymph node tuberculosis usually does not require surgery, except for a definitive diagnosis. In patients with EPTB, a second biopsy or bacteriological evaluation is generally not considered necessary to assess response to treatment, as efficacy is usually assessed based on clinical and radiological observations.

Drug selection for extrapulmonary non-tuberculous mycobacterial (EP-NTM) infections usually relies on insights, clinical expertise, and expert advice gained from pulmonary non-tuberculous mycobacterial infections. The standard course of therapy for EP-NTM infections is usually 6 to 18 months. An experienced healthcare team should make adjustments if adverse effects occur. Surgical interventions, including debridement, resection, and drainage procedures, play a key role in the treatment of extrapulmonary NTM disease.

Disclosure

All authors report no conflicts of interest in this work.

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