



Clinical manifestations and outcomes of musculoskeletal nontuberculous mycobacterial infections

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Abstract

To investigate the clinical manifestations and outcomes of musculoskeletal (MSK) nontuberculous mycobacterium (NTM) infections. This study was a retrospective cohort study using the Siriraj Hospital database from 2005 to 2017. Enrolled were all patients aged 15 or older who had an MSK infection with NTM identified in synovial fluid, pus, or tissue by an acid-fast bacilli stain, culture, or polymerase chain reaction. Of 1529 cases who were diagnosed with NTM infections, 39 (2.6%) had an MSK infection. However, only 28 patients met our inclusion criteria. Their mean age (SD) was 54.1 (16.1) years, and half were male. Of this cohort, 25% had previous musculoskeletal trauma, 18% prior bone and joint surgery, 14% prosthetic joint replacement, and 11% HIV infection. The median symptom duration (IQR) was 16 (37.4) weeks. The most common MSK manifestation was arthritis (61%), followed by osteomyelitis (50%), tenosynovitis (25%), and spondylodiscitis (14%). The most common organism was *M. abscessus* (18%), and *M. kansasii* (18%), followed by *M. intracellulare* (14%), *M. marinum* (14%), *M. fortuitum* (7%), and *M. haemophilum* (7%). In addition to medical treatment, most patients underwent surgery (82%), comprising debridement, osteotomy, prosthesis removal, and amputation, while 18% received only medical treatment. The treatment outcomes were complete recovery in 46%, improvement with some residual disability and deformities in 29%, and death in 3.6%. Musculoskeletal NTM infections were uncommon. Most patients had underlying joint disease or were immunocompromised hosts. Surgical management, as an adjunct to medical therapy, was necessary.

Keywords Musculoskeletal infection · Nontuberculous mycobacterium · Risk factors · Manifestations · Outcomes

Introduction

Nontuberculous mycobacteria (NTM) are found everywhere in the environment. They are not typically spread from human to human [1]; however, infections with these organisms have been reported with increasing frequency [2], especially in patients who had penetrating trauma, surgical incisions, puncture wounds, intraarticular injections [3], defects of the interferon-gamma receptor [4, 16], or were immunocompromised hosts [5–7].

A musculoskeletal NTM infection has four distinct patterns: tenosynovitis [8–11], septic arthritis [9, 11, 12], osteomyelitis [4, 13, 14], and spondylitis [15]. Since it is an uncommon disease with an insidious onset and indolent natural history, the diagnosis of this condition is often delayed, resulting in bone or joint destruction, permanent disability, and a poor quality of life. The time from the onset of symptoms to diagnosis has been reported to be approximately 1 year [10]. Most patients present with chronic mono- or oligoarthritis. It is difficult to distinguish or to identify the causative agents from the clinical characteristics because other organisms cause similar manifestations, including *Mycobacterium tuberculosis* and *fungus*. However, it is important to determine the mycobacteria isolates to the species level because the treatment regimens for individual organisms differ [3, 11]. The gold standard for diagnosis of NTM disease is based on the results of a mycobacterial culture. While polymerase chain reaction (PCR) testing becomes a popular investigative tool due to its quick turnaround and high specificity, it is available only at university

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hospitals. Patients with NTM infections are therefore usually referred to a university hospital for diagnosis and treatment [1].

Since musculoskeletal NTM infections are uncommon, data related to the risk factors, clinical manifestations, and outcomes are scarce. We therefore investigated the clinical manifestations and outcomes of musculoskeletal NTM infections in Thailand.

Materials and methods

Study population

This study was a retrospective cohort study using the Siriraj Hospital database. The ICD-10 related to NTM infections (A31) combined with septic arthritis (M00, M01), spondylodiscitis (M46, M49), tenosynovitis (M65, M68), and osteomyelitis (M86) were searched from January 1, 2005 to December 31, 2017. Enrolled were all patients who were aged 15 years or older; were admitted to the inpatient department or visited the outpatients department; had a musculoskeletal infection; and had NTM identified in synovial fluid, pus, wound drainage, or tissue by an acid-fast bacilli (AFB) stain, culture, or PCR. The medical records of all patients who met the inclusion criteria were reviewed, and the relevant data (comprising patient characteristics, clinical manifestations, isolation of the NTM infections, investigations, treatments, and outcomes) were collected.

This study was approved by the Siriraj Institutional Review Board (COA no. Si 638/2018, Approval date: October 10, 2018). All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was not obtained from all individual participants included in the study, as this study was a retrospective chart review.

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used for one-dimensional distributions. For the quantitative data, descriptive statistics were shown as mean \pm standard deviation (SD), or median (IQR) values. Counting was in number and percent (%) for the qualitative data.

Results

Demographic data, clinical manifestations, and laboratory findings

Of 1529 cases who were diagnosed with NTM infections (ICD-10 A31), 39 (2.6%) had a musculoskeletal infection.

However, only 28 patients met our inclusion criteria. Their mean age was \pm SD of 54.14 ± 16.05 years, and half were male. The most common occupation was housewife (21%). This was followed by farmer and private business (18% each); fisherman (7%); government officer (4%); and other occupations (32%), comprising student, monk, employee, and self-employed. The median duration from the onset of symptoms to diagnosis (IQR) was 16 (37.4) weeks. The common risk factors for the musculoskeletal NTM infections were previous musculoskeletal trauma (25%), prior bone and joint surgery (17.9%), prosthetic joint replacement (14.3%), human immunodeficiency virus (HIV) infection (2/19 or 10.5%), and anti-interferon (IFN)-gamma autoantibodies (7/10 or 70%; Table 1).

Regarding the clinical manifestations, the most common presentation was pain at the affected part (93%), followed by restricted or painful joint movement (89.3%), and localized swelling (85.7%). Extra-articular involvements were found in 11 out of 28 cases (39%). The most common extra-articular involvement was the lymph nodes (28.6%), followed by skin and soft tissue (21.4%), and lungs (10.7%), while the liver, spleen, and pericardium were reported in two cases each (Table 2).

The most common musculoskeletal manifestation was arthritis (61%), followed by osteomyelitis (50%), tenosynovitis (25%), and spondylodiscitis (14%).

A total of the four patients with spondylodiscitis, the cervical and lumbar spines were affected in two patients each. Three out of the four patients had consecutively involved segments of the vertebral body. Skipped vertebrae were found in one patient, which involved the second, fifth, and sixth cervical spines.

The majority of patients with arthritis manifested with monoarthritis (11/17; 65%), followed by oligoarthritis (5/17; 29%), and rarely with polyarthritis (1/17; 6%). In the monoarthritis group, the knee (37%) was frequently affected, followed by the hip and the shoulder (18% each). Other involved joints were the elbow (9%), ankle (9%), and wrist (9%). In the oligoarthritis group, the affected joints included the knees, shoulders, ankles, metacarpophalangeal (MCP) joint, proximal interphalangeal (PIP) joint, and distal interphalangeal (DIP) joint. Only one case presented with polyarthritis, involving the small joints of the hands (the MCP joint, PIP joint, and DIP joint).

Fourteen patients (50%) had osteomyelitis. The most common infected site was the tibia (21.4%), followed by the humerus (14.3%), radius (14.3%), femur (14.3%), carpal bones (7%), metatarsal bones (7%), and other bones (21%; e.g., the manubrium of the sternum, base of the skull, and mandible). One-quarter of the patients in the tenosynovitis group (25%) had a previous history or co-morbidity predisposing to NTM infections, such as prior musculoskeletal

Table 1 Characteristics of patients with musculoskeletal NTM infections

Characteristics	N=28
Demographics	
Age (years), mean \pm SD	54.14 \pm 16.05
Male, N (%)	14 (50)
Body mass index, mean \pm SD	21.69 \pm 2.88
Occupation	
Officer, N (%)	1 (3.6)
Farmer, N (%)	5 (17.9)
Fisherman, N (%)	2 (7.1)
Housewife, N (%)	6 (21.4)
Private business, N (%)	5 (17.9)
Other, N (%)	9 (32.1)
Duration from onset to diagnosis (weeks), median (IQR)	16 (37.4)
Rheumatic diseases	
Previous septic arthritis, N (%)	3 (10.7)
Prosthetic joint replacement, N (%)	4 (14.3)
Prior bone and joint surgery, N (%)	5 (17.9)
Prior joint injection/arthrocentesis, N (%)	3 (10.7)
Osteoarthritis, N (%)	3 (10.7)
Crystal-induced arthritis, N (%)	2 (7.1)
Rheumatoid arthritis, N (%)	1 (3.6)
Systemic lupus erythematosus, N (%)	1 (3.6)
Comorbid conditions	
Central venous catheter, N (%)	1 (3.6)
Prior musculoskeletal trauma, N (%)	7 (25.0)
Diabetes mellitus, N (%)	2 (7.1)
Malignancy, N (%)	1 (3.6)
Steroid, N (%)	2 (7.1)
Immunosuppressive drugs, N (%)	1 (3.6)
Chemotherapy, N (%)	1 (3.6)
HIV infection, N (%)	2/19 (10.5)
Anti IFN-gamma autoantibodies, N (%)	7/10 (70.0)

HIV human immunodeficiency virus, IFN interferon, SD standard deviation

trauma or prior arthrocentesis. All cases with tenosynovitis were affected only at their hands and fingers.

As to the laboratory findings, inflammatory markers were detected at a high level, with a mean erythrocyte sedimentation rate (ESR) \pm SD of 72.40 \pm 31.25 mm/h and a median C-reactive protein (IQR) of 32.10 (112.29) mg/l. However, the complete blood counts revealed non-specific results, including mild anemia (mean hemoglobin \pm SD: 10.49 \pm 2.33 g/dl) with no leukocytosis (median white blood cell count [IQR]: 9465 [7777.5] mm³/ml).

A synovial fluid culture was performed for 13 out of the 28 patients (46%), while a tissue biopsy culture was isolated to identify the causative pathogen in 25 out of the 28 patients (89%). The most common organisms were *M. abscessus*

Table 2 Clinical manifestations of patients with musculoskeletal NTM infections

Chief complaint	No. of patients N (%)
History of fever	13 (46.4)
Fever	10 (35.7)
Pain at affected part	26 (92.9)
Localized swelling of affected part	24 (85.7)
Redness of affected part	9 (32.1)
Warmth of affected part	6 (21.4)
Restricted/painful joint movement	25 (89.3)
Mass/tumor	7 (25.0)
Unhealed wound/ulcer	7 (25.0)
Neurological deficit	4 (14.3)
Constitutional symptoms	12 (42.9)
Other organ involvement	11 (39.3)
Lungs	3 (10.7)
Lymph nodes	8 (28.6)
Skin and soft tissue	6 (21.4)
Liver/spleen	2 (7.1)
Pericardium	2 (7.1)

and *M. kansasii* (17.9% each), followed by *M. intracellulare* and *M. marinum* (14.3% each; Table 3). Anti-IFN-gamma autoantibodies were identified in seven out of the ten patients for whom this test was performed. In this group, *M. abscessus* was identified in three patients, and *M. kansasii*, *M. haemophilum*, *M. scrofulaceum*, and *M. NTM* spp. in one patient each. *M. kansasii* and *M. intracellulare* were detected in both of the two patients with an HIV infection from the 19 patients who underwent a serologic evaluation.

Treatments and outcomes

All patients received regimens of antibiotics that depended on the causative pathogens and the patients' drug sensitivities. The antibiotics selected for the rapidly growing mycobacteria (RGM) were imipenem, amikacin, cefoxitin, macrolides (azithromycin and clarithromycin), fluoroquinolone (ciprofloxacin, levofloxacin, and moxifloxacin), and linezolid. On the other hand, the drugs used for the slowly growing mycobacteria (SGM) were isoniazid, rifampicin, ethambutol, macrolides, fluoroquinolones, doxycycline, and sulfamethoxazole/trimethoprim. In addition to medical treatment, most patients underwent surgery (82%), consisting of debridement (70%), prosthesis removal (17.4%), incision and drainage (4.3%), amputation (4.3%), and osteotomy (4.3%), while 18% received only medical treatment. The median duration of the medical treatment (IQR) was 55 (88.7) weeks.

Table 3 Nontuberculous mycobacteria isolations

Species	All (N=28)	Synovial fluid culture (N=13)	Tissue biopsy (N=25)
<i>M. abscessus</i> , N (%)	5 (17.9)	–	5/25 (20.0)
<i>M. fortuitum</i> , N (%)	2 (7.1)	1 (7.7)	2/25 (8.0)
<i>M. kansasii</i> , N (%)	5 (17.9)	1 (7.7)	4/25 (16.0)
<i>M. marinum</i> , N (%)	4 (14.3)	2 (15.4)	4/25 (16.0)
<i>M. intracellulare</i> , N (%)	4 (14.3)	3 (23.0)	2/25 (8.0)
<i>M. haemophilum</i> , N (%)	2 (7.1)	–	2/25 (8.0)
<i>M. scrofulaceum</i> , N (%)	1 (3.6)	–	1/25 (4.0)
<i>M. simiae</i> , N (%)	1 (3.6)	1 (7.7)	1/25 (4.0)
<i>M. NTM</i> spp., N (%)	4 (14.3)	1 (7.7)	4/25 (16.0)

M., *Mycobacterium*; NTM, nontuberculous mycobacterium; spp., species

As to the outcomes of the treatment, 46% of the patients recovered completely, 29% experienced improvement with some residual disability and deformities, and 3.6% died. The remaining 22% had unknown outcomes due to their being lost to follow-up.

Discussion

Musculoskeletal NTM infection is an uncommon disease. We found the mean age and the sex profile of the patients in our study were similar to those reported by other studies [4, 10]. The majority of the occupations of the patients in the current study may be associated with prevalent infections because of the high chance of acquiring traumatic wounds or accidental injury through exposure to the environment. The median duration from the onset of symptoms to diagnosis in our study was noticeably shorter than those reported elsewhere, viz, 10 months [7] and 1 year [10]. This may be due to a more heightened physician awareness, a better quality of investigation and technology, and an increased knowledge of the risk factors.

The risk factors and characteristics of patients identified in our study were similar to those reported by other studies: a history of musculoskeletal trauma or joint replacement surgery [7, 9]; underlying systemic diseases, especially HIV infection [10, 14]; and anti-interferon-gamma autoantibodies [16].

Moving on to the clinical manifestations of the musculoskeletal NTM infections, we found arthritis of the large joints was the most common presentation, followed by osteomyelitis, tenosynovitis, and spondylodiscitis. By contrast, Piersimoni and Scarparo [7] found that osteomyelitis (63%) was the most common manifestation, followed by arthritis (21%) and tenosynovitis (16%). This difference may be caused by the differences in the study population. The population in the study by Piersimoni et al. consisted of immunocompromised hosts, whereas most patients in

the current study were immunocompetent hosts who had undergone joint replacement surgery (such as a total knee arthroplasty or total hip arthroplasty), or who had prior joint trauma leading to an increased risk of septic arthritis.

With regard to the other features of musculoskeletal NTM infections, the cervical and lumbar regions were the most common sites of spondylodiscitis, which corresponded with the findings of a prior study [15]. These vertebral segments are the weight-bearing sites of the human body, so they have an increased risk of wear-and-tear and are susceptible to infection. Additionally, the site of tenosynovitis was similar to the finding of a study that found that the distal upper extremities were particularly involved because injury frequently occurs at this site [11]. The data relating to osteomyelitis were not distinguished from another study [14]. The sites of infection in the current study depended on the area of direct trauma or bone manipulation (for example, the sternum after cardiac surgery, the mandible following dental procedures, and open fractures or wounds).

The most common organisms were *M. abscessus* and *M. kansasii*. These were followed by *M. intracellulare*, which has been associated with cell-mediated immune defects (e.g., anti-IFN-gamma autoantibodies) and HIV infections; therefore, evaluation of NTM patients' immune status should always be performed. Moreover, history taking regarding musculoskeletal trauma, prior bone and joint procedures, prosthetic joint replacement, and arthrocentesis should be undertaken.

Treatment for a musculoskeletal NTM infection consists of multiple drug therapy based on the pathogens and patient drug susceptibility, combined with surgical interventions, such as open or arthroscopic joint debridement, and abscess drainage [11, 12, 14]. In the present study, medical treatment was provided in all cases. Furthermore, most patients underwent surgery for adequate drainage, debridement, and prosthesis removal. The clinical outcomes were generally favorable with some residual disability. The mortality rate in this study was quite low, mostly due to nosocomial

infections with multi-organ failure. Our study has some mentionable limitations. First, using data obtained by ICD-10 identifications may have resulted in the omission of some patients who had been diagnosed with a musculoskeletal NTM infection but were recorded using different ICD-10 codes. In addition, due to the nature of retrospective studies, there might have been missing or incomplete information in the medical records. Lastly, as the study population was very small, our results and outcomes might not be similar to previous reports.

In conclusion, musculoskeletal NTM infection was an uncommon disease. Most patients had preexisting joint disease or were immunocompromised hosts. Surgical management, as an adjunct to medical therapy, was necessary. A high index of suspicion in high-risk patients is the key to early diagnosis and leads to favorable outcomes.

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Author contributions CN and WK made substantial contributions to the conception, design of the work, the acquisition, analysis, interpretation of data, drafted the work or substantively revised it, approved the submitted version and take full responsibility for the integrity of the study and the final version of the manuscript.

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Compliance with ethical standards

Conflict of interest Author Wanruchada Katchamart and Author Chai-kiat Napaumpaiporn declares that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standard (Siriraj Institutional Review Board, COA no. Si 63812018, Approval date: October 10, 2018).

Informed consent Informed consent was not obtained from all individual participants included in the study because this study is a retrospective chart review.

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