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Nontuberculous mycobacterial osteomyelitis

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Abstract
Osteomyelitis caused by nontuberculous mycobacteria (NTM) can have severe consequences and a poor prognosis. Physicians therefore need to be alert to this condition, especially in immunocompromised patients. Although the pathogenesis of NTM osteomyelitis is still unclear, studies in immunodeficient individuals have revealed close relationships between NTM osteomyelitis and defects associated with the interleukin-12–interferon-γ–tumor necrosis factor-α axis, as well as human immunodeficiency virus infection, various immunosuppressive conditions, and diabetes mellitus. Culture and species identification from tissue biopsies or surgical debridement tissue play crucial roles in diagnosing NTM osteomyelitis. Suitable imaging examinations are also important. Adequate surgical debridement and the choice of appropriate, combined antibiotics for long-term anti-mycobacterial chemotherapy, based on in vitro drug susceptibility tests, are the main therapies for these bone infections. Bacillus Calmette–Guerin vaccination might have limited prophylactic value. The use of multiple drugs and long duration of treatment mean that the therapeutic process needs to be monitored closely to detect potential side effects. Adequate duration of anti-mycobacterial chemotherapy together with regular monitoring with blood and imaging tests are key factors determining the recovery outcome in patients with NTM osteomyelitis.

Keywords: *Osteomyelitis; diabetes mellitus; nontuberculous mycobacteria*

Introduction

Nontuberculous mycobacteria (NTM) comprise more than 150 species of mycobacteria (http://www.bacterio.net/mycobacterium.html), excluding *Mycobacterium tuberculosis* complex and *Mycobacterium leprae* [1]. NTM are widely distributed in the environment and can be cultured from samples including soil and lake water [2]. NTM have recently gained increased attention because of their ability to cause infections in immunocompromised patients, such as those with human immunodeficiency virus (HIV) infection, cystic fibrosis, or organ transplants, whereas NTM rarely infects immunocompetent individuals [2]. Although the skin and skeletal muscle can become infected following injection or trauma [3,4], the respiratory system is the main site of infection. There have been numerous case reports concerning either immunocompromised or immunocompetent patients with NTM osteomyelitis, but few reviews. Here, we review the status of NTM osteomyelitis and report on a patient with diabetes mellitus (DM) who developed osteomyelitis caused by multi-antibiotic-resistant *M. intracellulare* after surgery.

Species distribution and pathogenesis

NTM can be isolated from the natural environment and from hospital equipment, such as xylocaine for injection, hemodialysis water, and laparoscopic instruments. NTM show weaker virulence than *M. tuberculosis* (MTB) and *M. leprae* [4–6]. NTM are gram-positive and acid-fast-positive bacteria. They

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might be misdiagnosed as MTB, but are naturally resistant to antituberculosis antibiotics because of the complex structure of their cell wall. NTM were first identified as pulmonary pathogens in the 1950s by Runyon [7], and increasing numbers of NTM have been recognized as emerging pathogens, especially in immunocompromised individuals.

NTM infections may involve multiple organs, including the bones, and the diversity of pathogen species involved increases the difficulty of treating these infections. NTM osteomyelitis was rarely reported before the 1980s, but its prevalence seems to have increased recently, reflected by case reports and large-scale clinical research. Many slow-growing NTM species have demonstrated the ability to cause NTM osteomyelitis, including *M. avium-intracellulare* complex (MAC) [3,8–48], *M. ulcerans* [49–51], *M. marinum* [52–57], *M. kansasii* [9,33,36,58–63], *M. xenopi* [64–66], *M. gordonae* [67], *M. haemophilium* [33,68,69], *M. scrofulaceum* [45,70], *M. szulgai* [71–74], *M. longobardum* [75], and *M. flavescens* [76]. Among the rapidly growing mycobacteria, osteomyelitis can be caused by *M. abscessus* [3,77–81], *M. fortuitum* [82–94], *M. chelonae* [5,25,83,95–104], *M. smegmatis* [105], *M. peregrinum* [82], and *M. thermoresistibile* [106]. Some authors have argued that the otomastoiditis attributed to *M. fortuitum* or *M. chelonae* was actually caused by *M. abscessus* [107], though this disagreement is actually a taxonomic issue. Different strains of the same species or subspecies of NTM have shown different degrees of virulence, with complex mechanisms of resistance against the host immune system [108–110]; strains may include some genotypes with a wide host spectrum, while others are avirulent [111]. Further research is needed to establish the genetic factors related to mycobacteria virulence [111].

Multiple bone loci can be infected by NTM through direct inoculation during surgery or via insertion of a contaminated prosthesis, for example, osteomyelitis in the sternum caused by cardiac surgery [91], otomastoiditis by myringotomy tube insertion [17,25,82,96,107,112], and osteomyelitis of the mandible by dental treatment [77]. In addition to nosocomial infections, NTM osteomyelitis can be caused by trauma, fracture or animal bites during activities such as gardening, farming, fish-keeping, playing in sand pits, and swimming [5,6,51,95]. These activities might allow environmental NTM to colonize and infect individuals through a wound, as an exogenous pathogen. If the infection extends beyond the skin or soft tissue, NTM might cause transient bacteremia and colonize other organs via the bloodstream or lymphatic system, including the reticuloendothelial system in bones, where it results in osteomyelitis [113]. Studies in animal models have shown that direct injection of mycobacterial components resulted in osteomyelitis with chronic inflammation [110]. However, in patients with no history of penetrating trauma, the 'locus minoris resistentiae' (place of least resistance) theory might offer a possible explanation. NTM can colonize or invade the mucosal surface of the respiratory and gastrointestinal tracts in immunocompetent patients. Macrophages in the blood might then come into contact with the mycobacteria, such as *M. intracellulare*, which could then enter the macrophages via endocytosis. Some currently undetermined structures in the macrophages might protect the mycobacteria, allowing them to survive, while complex mechanisms may inhibit phagosome–lysosome fusion [109,114–116]. It is possible that, in the absence of penetrating trauma, abnormal levels of nitric oxide may cause bone formation [117–120] and might thus be involved in the pathophysiological progression of NTM release from macrophages mobilized to the injury site, resulting in local osteomyelitis, as in some cases of vertebral osteomyelitis [3,121]. However, the dissemination of NTM to cause osteomyelitis is not always a direct progression, which might explain the low prevalence of NTM osteomyelitis.

The pathogenesis of NTM infection is not fully understood and an ideal NTM osteomyelitis animal model is currently lacking. However, it has been suggested that the immune system plays a crucial role in NTM infection, especially multifocal NTM osteomyelitis. Multifocal NTM osteomyelitis and disseminated NTM infection have been found in different members of the same family [22,122,123]. Cases of multifocal NTM osteomyelitis have occurred in the absence of adjacent organ infection, suggesting that an impaired host immune system or inherited immune deficiency contributed to the development of infection. Studies on pathogenesis have revealed key roles for interferon (IFN)-γ, interleukin (IL)-12, and tumor necrosis factor (TNF)-α in the human immune defense against mycobacterial infection [116,124–131]. Some inherited gene defects related to the IL-12–IFN-γ–TNF-α axis have been shown to be directly linked and associated with disseminated NTM infection and multifocal NTM osteomyelitis. These include mutations in human IFN-γ receptors 1 and 2, IFN regulatory factor, signal transducer and activator of transcription 1, IL-12 receptor β1, and IL-12 p40 subunit genes [22,108,131–134]. Mutations in the genes encoding cell surface receptors impaired the functions of and cascade regulation between these cytokines [131]. Interestingly, isolated NTM osteomyelitis has been found in patients with autosomal dominant partial IFN-γ receptor 1 deficiency, but not those with recessive complete

IFN-γ receptor 1 deficiency [134], and the mechanism is unclear. IFN-γ antibodies, which are a major cause of NTM dissemination, have already been identified, although the genetic mechanisms, predisposing factors, and contributions of these antibodies remain unknown [126,133,135].

Diagnosis

It is difficult to diagnose and differentiate NTM osteomyelitis from other diseases such as Langerhans cell histiocytosis or osteomyelitis caused by MTB and other bacteria. These difficulties arise because of a lack of specific examination methods, and the fact that the clinical presentation is variable. Furthermore, the wide cross-reactivity between mycobacteria means that the tuberculosis skin test has limited value for the diagnosis of NTM osteomyelitis [136]. However, the IFN-γ release assay can help to distinguish between some cases of NTM osteomyelitis and MTB infection, but not other bacteria, because the RD-1 region differs between most NTM and MTB [137,138]. Given the limitations of current examination methods, an accurate diagnosis of NTM osteomyelitis depends largely on imaging examinations combined with histopathologic, cytological, and microbiological examinations via surgical debridement or biopsy.

Useful imaging examinations include X-ray plain film, ultrasonography, computed tomography (CT) scan, bone nuclear imaging, and magnetic resonance imaging (MRI). X-ray plain films have the advantages of low cost and being easy to perform, even in basic hospitals, and are able to provide comprehensive imaging of the anatomy and pathologic conditions. Ultrasonography is also an easy technique for detecting involved periosteum and soft tissues, and for helping to guide surgical drainage and biopsy. CT has limited use in NTM osteomyelitis because it is less sensitive than bone nuclear imaging and MRI, although it can help to guide biopsy procedures [139]. Bone nuclear imaging can reveal multifocal infected bone lesions; this is an advantage in the case of NTM osteomyelitis, which often involves multiple bone loci. MRI can provide detailed and accurate information on both the infected bone marrow and involved periosteum and soft tissues, and it has the highest sensitivity and specificity of all the current imaging techniques; however, the cost of MRI is high [140].

Extrapulmonary NTM infection normally shows as tenosynovitis, synovitis, skin lesions, subcutaneous granuloma, or osteomyelitis, and pathological examinations without acid-fast staining (AFB) performed routinely after surgical debridement or biopsy may not provide an accurate diagnosis of NTM infection. Some samples may have no obvious inflammatory signs, whereas others might show different signs of non-specific inflammation, such as neutrophilic abscesses or spindle cell proliferation. Furthermore, some samples might have granulomas with or without necrosis, whereas others might show typical caseous epithelioid granulomas [22,54,100,141,142]. Especially if the inflammatory lesion shows a tuberculotic 'cold abscess' [143], these indeterminate characteristics and pathology might easily lead to an incorrect diagnosis and the inappropriate use of antituberculous chemotherapy. NTM-infected tissue samples do not always show AFB-positive bacteria and moreover, these bacteria are difficult to differentiate from MTB. Some case reports found that the bacteria in *M. kansasii* osteomyelitis had specific microscopic features [60,144], but it is currently not possible to differentiate the bacterial species in NTM osteomyelitis by pathological examination.

Microbiological investigation after surgical debridement or biopsy play a crucial role in the diagnosis of NTM osteomyelitis. These examinations include the traditional AFB smear test and mycobacterial culture, combined with molecular identification methods such as polymerase chain reaction (PCR) or biochip testing.

Because of their low prevalence, NTM are unlikely to be considered as the first causative pathogens in an osteomyelitis patient, leading to a delay in diagnosis and chemotherapy, which might be associated with a poor prognosis. However, NTM osteomyelitis should be suspected in patients who are negative for normal bacterial culture and tests and resistant to antibacterial therapy with routine antibiotics.

The AFB smear test is routinely used for suspected MTB or NTM infection, although *Nocardia*, *Rhodococcus*, and some other bacteria are also AFB-positive. However, the main disadvantage of the AFB smear test is its low sensitivity for detecting NTM infection [145], and the AFB test may need to be repeated several times to demonstrate a positive result if NTM infection is suspected. Mycobacterial culture of infected tissue or pus should be performed at the same time as surgical debridement or biopsy, because blood culture might be negative in most immunocompetent patients [79]. If a positive isolate is acquired, subsequent identification tests and in vitro drug susceptibility tests can then be performed easily, even if the culture result demonstrates polymicrobial infection in open fracture patients [83]. However, NTM might also be a laboratory contaminant [22], and physicians should therefore interpret positive culture results carefully to avoid misdiagnosis. Increasing numbers of NTM species have been

identified recently, and mycobacterial culture combined with PCR or other molecular tests may provide a more accurate and rapid diagnosis than conventional biochemical tests [83,112,146], given the urgency of mycobacterial identification as the key to the successful management of NTM osteomyelitis.

Therapy

Therapy for NTM infections remains difficult, and the wide range of NTM species means that there are currently no effective single anti-NTM antibiotics. Therapy for NTM osteomyelitis includes surgical debridement, abscess drainage, and long-term chemotherapy, with surgery playing a more important role in some cases.

Surgical debridement and drainage of abscesses are crucial for local NTM osteomyelitis, because the mycobacterial burden in the bone marrow is high and the dead bone might provide a storage site for mycobacteria [147]. Because the circulation does not reach dead bone, antibiotics would be ineffective, and thorough curettage, and even amputation, may be needed [56]. Surgical debridement requires the removal of all infected tissue, and multiple sequential debridements or persistent drainage may be required [79]. However, new anti-mycobacterial therapies are being developed for NTM osteomyelitis, and Kato et al. recently reported no infection recurrence in a patient with vertebral osteomyelitis treated by debridement and surgery using antibacterial iodine-supported instrumentation [78].

It has been suggested that surgical debridement is adequate treatment for NTM osteomyelitis [148], but appropriate, individualized anti-mycobacterial chemotherapy performed after debridement or abscess drainage may be beneficial [6].

Chemotherapy may limit the spread of mycobacteria and eliminate bacteria not removed during surgery, especially in cases with multifocal lesions. There are currently no guidelines for NTM osteomyelitis therapy. However, the American Thoracic Society recommends performing drug susceptibility tests before using antibiotics, using combination therapy to avoid inducing antibiotic resistance [149]. Because antibiotic resistance differs among NTM species, in vitro drug susceptibility tests should be performed as soon as possible after species identification to help physicians select the appropriate combination of antibiotics [79].

Osteomyelitis often involves deep tissue, and the decreased local concentration of antibiotics and slow growth of NTM [147] mean that anti-mycobacterial chemotherapy needs to be continued for at least 4–6 weeks after the clinical signs or cultures turn negative [6,65,79,83,100,150,151]. Chemotherapy may even need to be continued for years in immunocompromised patients, because the immune condition could affect the prognosis [152]. No guidelines or gold standards for the optimal duration of anti-mycobacterial chemotherapy have yet been developed, and associated clinical trials are lacking. Although the combination with surgical debridement might reduce the potential side effects of long-term use of combined antibiotics, the antibiotics should still be chosen carefully and monitored closely to avoid adverse drug events, such as loss of vision, rash, and hepatic or renal toxicity [153,154].

Long-term follow-up of NTM osteomyelitis patients after discharge is important for patient recovery. In addition to the use of oral antibiotics, imaging examinations and blood tests such as complete blood count (CBC), erythrocyte sedimentation rate (ESR), and liver and kidney function test should also be used to monitor the progress of the infection [155]. A significant improvement in bone imaging results could suggest the effectiveness of therapy, although bone nuclear imaging is not a useful technique for follow-up studies given that the results would take too long to become normalized [155]. In the case of slow-growing NTM like MAC, anti-mycobacterial chemotherapy should be continued for at least 1 year, whereas cases with fast-growing NTM like *M. fortuitum* and *M. abscessus* should receive chemotherapy for at least 6 months [149].

Prophylaxis

There are currently few prophylactic options for NTM osteomyelitis, especially in patients with IFN-receptor deficiency [22]. Bacillus Calmette–Guerin (BCG) vaccination was suggested to protect patients from osteomyelitis caused by *M. ulcerans* [113,146,156], but the value of BCG vaccination as a prophylaxis against other species is undetermined. Furthermore, BCG vaccination should be contraindicated in immunocompromised patients because of the potential to cause *M. bovis* infection [157]. Macrolides and rifabutin have been suggested as prophylactic agents for MAC infection in HIV patients with decreasing $CD4^+$ T-cell counts [21,158–160]. However, there is currently no recommended drug for NTM osteomyelitis prophylaxis.

Immunocompromised patients

HIV-infected patients

NTM osteomyelitis is a rare complication in HIV patients, even though *M. intracellulare* and *M. avium* are major opportunistic pathogens responsible for dis-

seminated infection among patients with acquired immune deficiency syndrome (AIDS) [161,162], and osteomyelitis in HIV patients caused by *M. kansasii*, *M. haemophilum*, *M. fortuitum*, *M. terrae*, and *M. xenopi* has also been reported [33,36,59,61,64,90,144,163]. NTM osteomyelitis often develops late in AIDS patients, when it involves multiple sites of the bones or joints related to cutaneous lesions, and is co-infected with other opportunistic fungi or bacteria. The spine is the most commonly involved location, with both arteries and veins providing hematogenous sources of infection [15]. The widespread use of highly active antiretroviral therapy (HAART) in patients with HIV infection seems to be associated with an increased prevalence of local NTM infections such as NTM osteomyelitis [18,21]. However, although the prevalence of NTM osteomyelitis in HIV-infected patients is higher than in healthy individuals, it is still lower than in injecting drug users [33,164]. Although $CD4^+$ T cells play an important role in controlling NTM infection together with elevated IFN-γ and macrophages [165], NTM osteomyelitis is often seen in patients with immune reconstitution inflammatory syndrome after effective HAART, even when $CD4^+$ T-cell counts were ≥ 100 cells/μl [21,64]. This could be explained if localized NTM infection or undetectable mycobacteremia already existed before HAART and effective T-cell revival. This phenomenon highlights the need for physicians to be aware of the possibility of NTM infection at all stages of AIDS, although the optimal time for prophylaxis remains to be determined [21].

Various immunosuppressive conditions

In addition to immune defects caused by mutations related to the IL-12–IFN-γ axis, steroids, anticancer chemotherapy, immunosuppressive drugs, and various conditions such as leukemia, organ transplantation, and hepatic and renal failure also impair immune function and may lead to NTM osteomyelitis [22,81,88,99,121,166]. These underlying diseases and drugs are also risk factors related to prognosis, with possible implications for therapeutic progress [6,166].

Diabetes mellitus

Diabetes mellitus (DM) can cause immune impairment, thus increasing the risk of multiple opportunistic infections, and DM is strongly associated with tuberculosis in developing countries [167]. Although NTM osteomyelitis has been reported in DM patients, it appears to be rare and its prevalence is not clear. Serum IFN-γ levels were found to be decreased in DM patients [168,169], which might contribute to the increased risk of NTM infections in these patients. IFN-γ may help to combat pathogens by contributing to the production of nitric oxide and maturation of intracellular phagosomes [170,171]. Although superoxide anions and nitric oxide have been shown to play significant roles in host resistance to MTB infection [172–176], studies of MAC showed that NTM had a strong ability to inhibit the activity of superoxide anions, and nitric oxide could only prevent the proliferation of some strains, although it could take part in the post-infection pathophysiology progress and granuloma formation [171,177,178]. DM patients produce subnormal levels of superoxide anions and nitric oxide as the result of impaired and abnormal immune function [179–181]. Still it should be remarked that effector mechanisms in macrophages active against NTM have not been fully clarified [182–184].

A case of NTM osteomyelitis associated with diabetes mellitus

A 69-year-old man found a soft, soybean-sized lump on his right upper arm on September 6, 2011. He was a retired resident living in Shaoxing, Zhejiang province, on the southeast coast of China. He had an 18-year history of DM and injected insulin daily, with good blood glucose control. Before his presentation, he had felt fatigued and the lump had enlarged slowly over a 10-day period. He underwent surgery at a local hospital to excise the lump. The pathology report indicated a sebaceous cyst, but AFB test and culture were not performed. After surgery, he started to sweat and became febrile, and small lumps appeared under the skin of his arms. The local hospital suspected tuberculosis and started antituberculosis therapy with isoniazid (INH), ethambutol (EMB), and rifampin (RIF). However, the therapy was stopped after 15 days because of rashes all over his body, and because a T-SPOT.TB test was negative. Four months later, he developed chest tightness and shortness of breath. A CBC revealed high levels of white blood cells, and a CT scan showed exudative lesions in the lung and multiple lesions on both humerus bones and the ribs. He developed respiratory failure and was transferred to the intensive care unit with tracheal intubation and ventilation. A biopsy of one rib was performed without culture and an AFB test was positive (Figure 1a). He was diagnosed with osteomyelitis caused by NTM. Caspofungin, linezolid (LZD), and moxifloxacin (MXF) were used, but changed to minocycline and clarithromycin (CLR) as a result of exfoliative dermatitis. His fever resolved after 2 months and the antibiotics were therefore stopped. However, 6 months later, the

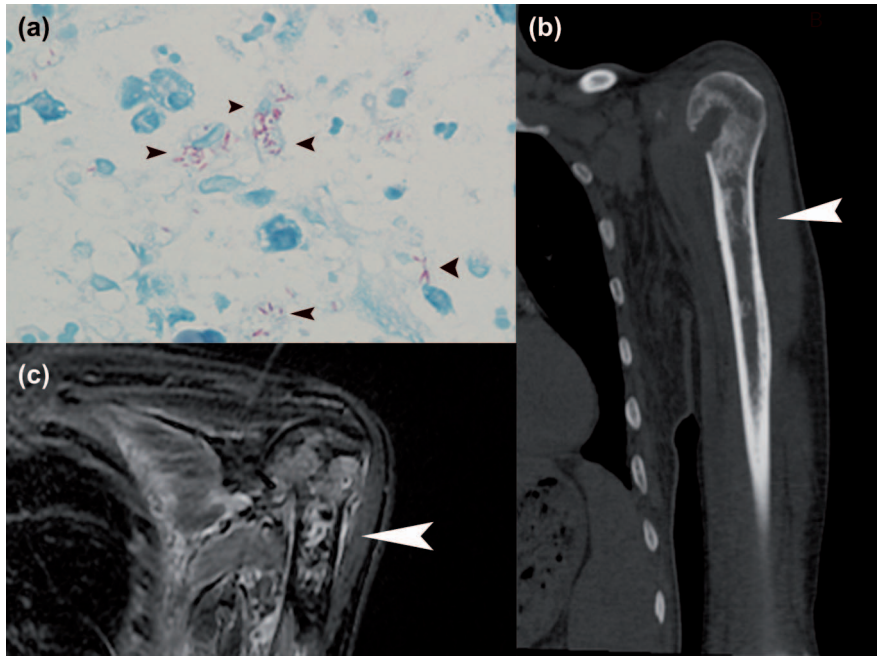

Figure 1. (a) Acid-fast staining (AFB) test showing acid-fast bacilli in the monocytes (arrowheads). (b) CT scan of left humerus, with multiple vermiform destructions (arrowhead). (c) MRI of left humerus, T2-STIR, showing abnormal signal in the marrow (arrowhead).

rashes and fever re-emerged, and his temperature peaked at 40°C. CLR, MXF, and 40 mg methylprednisolone once a day were then initiated, with a decrease in temperature but residual low fever.

The patient was transferred to our hospital on March 3, 2013. He seemed weak, with scattered rashes on his arms and legs, and multiple lumps identified by ultrasound as lymph nodes at the neck, groin, left ear, and right arm. The lumps were not tender and were about 1 cm in diameter. CBC showed neutrophils 7.2×10^9/L, eosinophils 0.65×10^9/L, hemoglobin 96 g/L, albumin 27.2 g/L, C-reactive protein (CRP) 92.2 mg/L, and ESR 103 mm/h. A CT scan showed no lung infection and multiple vermiform destructions of the left humerus (Figure 1b). MRI showed signal abnormalities of the marrow in the left scapula, and right and left humerus bones (Figure 1c).

Biopsy of the left humerus was performed and the specimen was cultured for mycobacteria. AFB-positive isolates were found 10 days later and tested by CapitalBio Mycobacterium identification microarray (CapitalBio Corp., Beijing, China) according to the manufacturer's instructions [155]. The isolate was identified as *M. intracellulare*. Microdilution drug susceptibility testing was carried out according to Clinical Laboratory Standard Institution recommendations [185], using MXF, levofloxacin (LVF), CLR, azithromycin (AZM), LZD, RIF, EMB, and rifabutin (RFB). Minimum inhibitory concentration (MIC) results showed that the strain was resistant to CLR (MIC > 64 μg/ml), AZM (MIC > 64 μg/ml), LZD (MIC > 64 μg/ml), RIF (MIC 4 μg/ml), EMB (MIC > 64 μg/ml), and RFB (MIC 16 μg/ml), but susceptible to MXF (MIC 0.5 μg/ml) and LVF (MIC 2 μg/ml).

PCR of the 23S rRNA gene was performed using LA Taq enzyme (Takara, Shiga, Japan) and primers 23.1 (5′-AATGGCGTAACGACTTCTC AACTGT-3′) and 23.2 (5′-GCACTAGAGGTTC GTCCGTCCC-3′) and the products were sequenced to detect mutations [148]. Sequence analysis identified an A to T substitution at the resident position 2274, and a T to C substitution at the resident position 1636 in the 23S rRNA gene. The sequence was uploaded to the GenBank database with the accession number KJ400964.

Following species identification and drug susceptibility testing in vitro, the patient was administered oral CLR 500 mg twice daily, oral EMB 750 mg once daily, and oral MXF 400 mg once daily. The patient's condition had improved 1 month later, and his temperature, CBC, and CRP were normal. However, 5 months after the therapy he complained of poor vision, and fundus examination by an ophthalmology physician showed retinal damage to both eyes. Diabetic retinopathy was considered. EMB was stopped and vitamin B was supplied daily. One month later, he again developed a low fever and his neutrophils and CRP started to increase. Despite retinal laser photocoagulation therapy in both eyes, his vision was not improved. EMB was added again to control the infection, and 1 month later his fever was controlled and his blood tests returned to normal. The patient

continued to take CLR, EMB, and MXF, but his condition slowly deteriorated. MRI indicated improvements in his osteomyelitis, but after receiving anti-mycobacterial chemotherapy for 18 months, the patient suddenly died of respiratory failure. No autopsy was performed.

Reports of NTM osteomyelitis in DM patients are rare, but given the recent increase in identification of NTM as pathogens, the possibility of NTM osteomyelitis in DM patients is worthy of more attention. DM can affect cytokine levels, chemotaxis and phagocytosis of monocytes and macrophages, and can cause an abnormal delayed-type hypersensitivity response [186]. These effects are particularly serious in elderly patients with DM, and may increase the risk of intracellular infections with pathogens such as NTM and tuberculosis [186]. Osteomyelitis is a complication of DM, and is associated with increased mortality, as well as increased costs [187]. We performed a search of the English literature for reports of NTM osteomyelitis in DM patients (Table I) and identified eight cases, none of whom was HIV-positive [8,70,84,95,188–191]. The infection sites varied, but were mostly in the extremities. Three patients took immunosuppressive agents and had other serious underlying diseases, including end-stage renal disease and rheumatoid arthritis. Not all patients had a clear history of trauma or wounding, suggesting that the immunocompromised condition induced by DM might be a major risk factor for NTM infection.

The clinical manifestations of NTM infection among DM patients vary and include fever, painless mass, fistula, and local pain [8,70,84,95,188–191]. According to his history, our patient may have initially suffered from NTM granulomatous panniculitis, with osteomyelitis developing secondary to the surgery. He had no history of trauma or wounding, but did live near a river and liked to fish, and may therefore have become infected by touching the pathogen.

The isolate from the current patient showed resistance to macrolides in vitro, and the base substitution at 2274/2275 in the 23S rRNA gene was confirmed to be associated with macrolide resistance [192,193]. Because of drug allergies, we used CLR in combination with MXF and EMB, which successfully inhibited the infection, although some side effects occurred. The current case demonstrates three points. First, macrolides might be useful in combination therapy, despite the existence of drug resistance. Second, an adequate duration of anti-mycobacterial chemotherapy is important in DM

Table I. English language articles on nontuberculous mycobacteria (NTM) osteomyelitis in patients with diabetes mellitus (DM).

Reference	Age/sex	Pathogen	Anatomic site	Underlying condition	Surgical treatment	Anti-NTM therapy	Outcome
Phoa et al. [70]	66/M	*M. scrofulaceum*	Wrist	DM	None	KAN, EMB, and ETH	Improved clinically
Satti et al. [84]	52/M	*M. fortuitum*	Bone marrow	DM	None	AMK and CIP	Cured
Argiris et al. [188]	37/M	MAC	Bone marrow	DM, ESRD, renal transplant	None	AZM and EMB	Died
Baylor et al. [189]	39/M	MAC	Humerus, tibia, and fibula	DM, schizophrenia	Surgical debridement	STR, CFZ, INH, EMB, RFP, PZA, CLR, and AMK	Cured
Iyengar et al. [95]	58/F	*M. chelonae*	Finger metacarpal heads	DM, ESRD	Incision for drain, surgical debridement	CFZ and CLR	Cured
Conejero et al. [190]	76/F	*M. chelonae*	Metatarsal and calcaneus	DM and RA	None	Intravenous IPM, CLR, and LVX	Cured
Halleran et al. [191]	61/M	MAC	Wrist	DM, hypertension	Aspiration	INH and RFP	Unresolved
Suzuki et al. [8]	67/M	MAC	Spine, ribs, and pelvis	DM	Surgical debridement	RFP, EMB, CLR, CS, and STR	Cured
This study	69/M	*M. intracellulare*	Humerus and ribs	DM	Anti-mycobacterial chemotherapy	CLR, EMB, and MXF	Died

AMK, amikacin; AZM, azithromycin; CFZ, clofazimine; CIP, ciprofloxacin; CLR, clarithromycin; CS, cycloserine; EMB, ethambutol; ESRD, end-stage renal disease; ETH, ethionamide; INH, isoniazide; IPM, imipenem; KAN, kanamycin; LVX, levofloxacin; MAC, *M. avium-intracellulare* complex; MXF, moxifloxacin; PZA, pyrazinamide; RA, rheumatoid arthritis; RFP, rifampicin; STR, streptomycin.

patients with NTM osteomyelitis. Third, the antibiotics used for anti-mycobacterial chemotherapy should be chosen carefully and monitored closely to avoid adverse drug events.

Conclusions

NTM osteomyelitis can have a poor prognosis and physicians should thus be aware of its clinical significance. However, the mechanisms of NTM pathogenesis remain poorly understood, and prophylactic options are currently limited. In patients with osteomyelitis caused by undetermined pathogens, care is needed to differentiate NTM infection from normal pyogenic infection or tuberculosis, through blood tests, imaging examinations, pathological examination and AFB tests, and mycobacterial culture and identification of biopsy specimens during or before surgery. In vitro drug susceptibility testing is important for anti-NTM chemotherapy, and the long duration of combined antibiotic anti-mycobacterial chemotherapy means that physicians need to monitor adverse drug events and infection progress closely.

Consent

Written informed consent was obtained from the patient and his kin for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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