



Case Report

Mycobacterium chelonae bloodstream infection induced by osteomyelitis of toe: A case report[☆]

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ABSTRACT

Mycobacterium chelonae is a rapidly growing mycobacterium that has the potential to cause refractory infections in humans. Mycobacteremia resulting from the organism is extremely rare, and its clinical features are yet to be uncovered. We herein present a case of *M. chelonae* bloodstream infection involving an immunocompromised older patient. A 79-year-old woman, on a long-term treatment with prednisolone plus tacrolimus for rheumatoid arthritis, visited our outpatient department complaining of deteriorating pain and swelling at her right 1st toe. Laboratory parameters showed elevated C-reactive protein and leukocytosis, and magnetic resonance imaging indicated osteomyelitis at the proximal phalanx of her right 1st toe. Considering the refractory course, the infected toe was immediately amputated. *M. chelonae* was isolated from bacterial cultures of the resected tissue and blood (BD BACTEC™ FX blood culture system, Becton Dickinson, Sparks, MD, USA), leading to a diagnosis of disseminated *M. chelonae* infection. We treated the patient with an antibiotic combination of clarithromycin, minocycline, and imipenem (2 weeks), which was converted to oral therapy of clarithromycin, doxycycline, and levofloxacin. This case highlighted the potential pathogenesis of *M. chelonae* to cause mycobacteremia in an immunocompromised patient.

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1. Introduction

Non-tuberculous mycobacteria (NTM) are ubiquitously distributed across a range of environments, such as soil, natural waters, and tap water [1]. The organisms are generally non-pathogenic to humans; however, they occasionally cause a wide variety of infectious diseases, particularly in those with impaired cell-mediated immunity [2,3]. NTM bloodstream infection is a severe form of extrapulmonary NTM disease. Reports on the hematogenously-disseminated NTM diseases have been mainly described in patients with human immunodeficiency virus infection [4,5]. However, literature has suggested that various immunocompromised conditions such as organ transplantation, chronic corticosteroid therapy, oncogenic diseases, and congenital or acquired anti-IFN γ autoantibody can also expose patients to a risk of NTM bloodstream infection [6].

In this report, we illustrate a rare case of *Mycobacterium chelonae* bloodstream infection, induced by osteomyelitis at the right 1st toe of a rheumatic patient undergoing immunosuppressive therapy.

2. Case report

A 79-year-old woman presented to our hospital with a complaint of a deteriorating pain and swelling on her right 1st toe. The patient had a history of rheumatoid arthritis, interstitial lung disease, steroid diabetes, and diabetic nephropathy (stage G3b). The patient had been on a long-term treatment of 7.5 mg per day of prednisolone (3 years) and 2 mg per day of tacrolimus (2 years). She did not have symptoms of night sweat but was exhibiting weight loss. Her general status was distressed; her activities of daily living were impaired due to disuse muscle atrophy and malnutrition. She had suffered from the painful and swollen toe one month prior to admission, which was treated with oral antibiotics (250 mg of amoxicillin-clavulanate twice daily) under a diagnosis of cellulitis. However, the inflammatory manifestations did not improve (Fig. 1A), and magnetic resonance imaging (MRI) scan was indicative of osteomyelitis at the proximal phalanx of the right 1st toe (Fig. 1B). The patient was subsequently admitted to our hospital for further treatment.

Initial vital signs on admission were as follows: heart rate, 90 beats per minute; blood pressure, 138/81 mmHg; peripheral oxygen saturation, 99% on room air; and body temperature, 36.3 °C. She had an extremely low body mass index of 12.7 (Kg/m²). There were no particular findings upon physical examination, excepting conjunctival pal-

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Fig. 1. Clinical and radiographic findings of osteomyelitis at right 1st toe. A, gross appearance; Arrow indicates an inflammatory manifestation. B, T2 weighted image of magnetic resonance imaging; Arrowhead indicates a signal change suggesting osteomyelitis.

lor and her inflammatory right toe. The patient did not show any specific symptoms such as chills and rigor, or high fever, which could suggest a bloodstream infection. Laboratory data showed total leukocyte count of $7010/\text{mm}^3$ (elevated neutrophil count of $6500/\text{mm}^3$ and decreased lymphocyte count of $300/\text{mm}^3$), decreased hemoglobin (9.7 g/dL), elevated serum C-reactive protein (3.42 mg/dL) and procalcitonin (0.15 ng/mL), a decreased renal function (cystatin C 1.49 mg/L, cyst-GFR $38.9 \text{ mL/min/1.73m}^2$), hypoalbuminemia (serum albumin, 2.7 g/dL), and low hemoglobin A1c (5.8%). On admission day, we initiated intravenous antimicrobials of meropenem (1 g q12h) and vancomycin (1.5 g q24h, and 1.0 g q24h from the second day considering her body

weight of 26.5 kg). Shortly after the hospitalization, the patient was sent for a surgery to debride the infected toe. During the debridement, however, we found a necrotic change of the tissue and finally performed an amputation of the right 1st toe. Gram staining (Favor G “Nissui”; Nissui Pharmaceutical Co., Ltd., Tokyo, Japan) of the resected tissue detected Gram-positive microbes implying *Mycobacterium* species (Fig. 2A). We additionally performed Ziehl-Neelsen staining and found numerous acid-fast bacilli (Fig. 2B). A PCR test for *Mycobacterium tuberculosis* was negative. Two sets of blood culture samples drawn from different peripheral veins on hospitalization became positive after 5 days of incubation period (BD BACTEC™ FX blood culture system, Becton Dickinson, Sparks, MD, USA). Gram staining and Ziehl-Neelsen staining of the blood culture smears also revealed acid-fast bacilli (Fig. 2C and D).

Under a diagnosis of disseminated mycobacterium infection, specifically caused by a rapidly growing mycobacterium, we administered a combination of oral clarithromycin (400 mg q12h), oral minocycline (100 mg q12h), and intravenous imipenem-cilastatin (0.5 g q8h). The organism detected from both the resected tissue and blood were identified to be *M. chelonae* using mass spectrometry (MALDI Biotyper, Bruker Daltonics Inc., Billerica, MA, USA). Also, the organism was identified as *M. chelonae* by *rpoB* sequence analysis using following primer sets; Forward 5'-CGA CCA CTT CGG CAA CCG-3' and Reverse 5'-TCG ATC GGG CAC ATC CGG-3'; 99.7% (297/298 bases) similarity to *M. chelonae* subsp. *gwanakae* strain MOTT36W chromosome [7]. Antimicrobial susceptibility testing showed the organism to be susceptible to clarithromycin (minimal inhibitory concentrations (MICs): 0.25 $\mu\text{g/mL}$), minocycline, imipenem-cilastatin, levofloxacin (MICs = 2 $\mu\text{g/mL}$), gentamycin, and linezolid, depending on Frozen broth microdilution panels (Eiken Chemical Co., Ltd., Tokyo, Japan).

A result of gallium scintigraphy was negative for any secondary infected lesions. After two weeks of the combination therapy, the patient showed gradual improvements; she became afebrile and her physical activity ameliorated. In parallel, laboratory testing revealed normalized level of serum C-reactive protein. The patient was transferred to another hospital with oral antimicrobials of clarithromycin, doxycy-

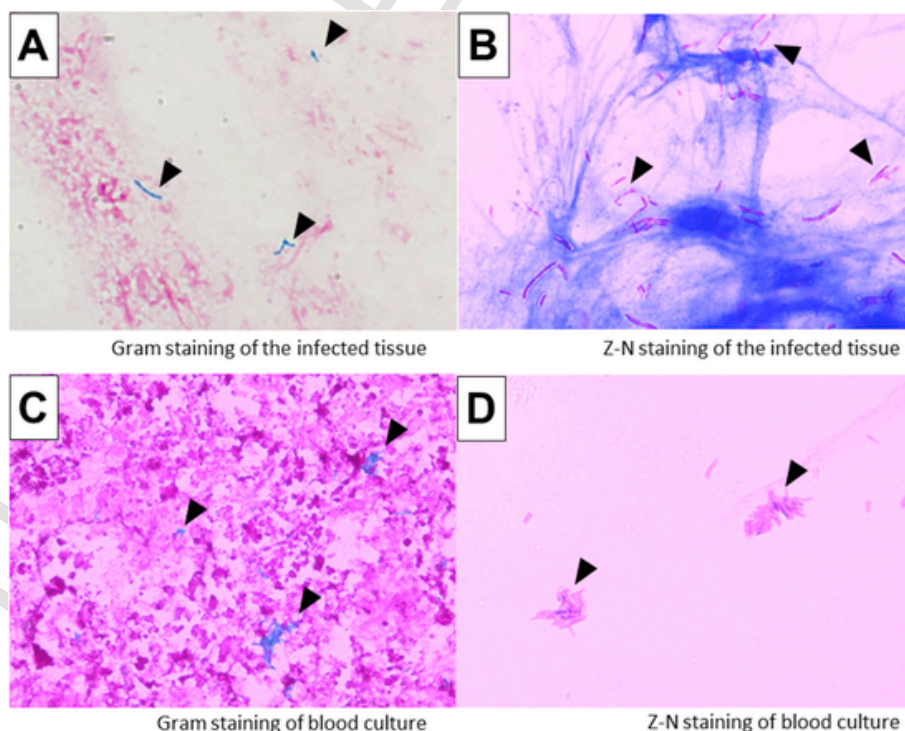


Fig. 2. Gram staining and Ziehl-Neelsen staining of the resected tissue and blood culture sample. Arrow heads showing organisms which were identified as *Mycobacterium chelonae*.

cline (100 mg q12h), and levofloxacin (500 mg q 24 h). The patient has remained on the triple therapy for 6 months with a good clinical course.

3. Discussion

We described a rare case of NTM bloodstream infection that occurred in an immunocompromised patient. The patient had steroid-related diabetes mellitus as underlying condition, which was well controlled on admission, and long-term use of prednisolone and tacrolimus could be mainly responsible for the occurrence of disseminated disease. *M. chelonae* was detected from both the infected toe and the blood specimen, leading to a final diagnosis of disseminated NTM infection. Among various NTM species, *M. chelonae* has been infrequently reported as a bacteremic pathogen of NTM [6,8]. Due to the slow-growing and poor-staining nature of the pathogen, microbiological diagnosis of the disease is challenging. In addition, due to the infrequency of the disease, clinical features of *M. chelonae* bloodstream infection are yet to be elucidated. Nevertheless, we successfully diagnosed the case and treated the patient with surgical amputation and antibiotic combination therapy.

Clinical characteristics of NTM bloodstream infection are well summarized in a case series with literature review published in 2016 [6], followed by additional case reports [8–10]. According to this research, the majority of cases involved those with immunocompromised conditions, and our patient was presumably vulnerable to the rare infection due to long-term use of immunosuppressive agents. The severe disease shows a wide variety of clinical manifestations involving multiple organs, such as the lungs, endocardium, brain, spinal cord, and soft tissues. Additionally, osteomyelitis is reportedly a possible infectious focus of the NTM bloodstream infection as well [11,12]. According to the preceding literature, the median time to positive blood culture results was 11.5 days (interquartile range of 6.8–18.8 days), including non-rapidly growing mycobacteria [6]. Rapidly growing mycobacteria can be detected from blood culture in a shorter incubation period, such as 5 or 6 days [8,10], as demonstrated in our case. However, reliable data on blood culture positivity and prognosis of NTM bloodstream infection remains unclear due to the rarity of the disease.

Early recognition of NTM infection leads to a good outcome with less recurrence [13]. Because NTM is barely unstained by Gram-staining [11], diagnosis of the disease is generally challenging. In our case; however, the organism was initially suspected via Gram-staining, leading to a successful identification of the pathogen by additional Ziehl-Neelsen staining.

The treatment strategy for NTM bloodstream infection includes a combination of antibiotic therapy and surgical debridement. Focusing on *M. chelonae*, the organism is reportedly susceptible to macrolides (clarithromycin and azithromycin), aminoglycosides (tobramycin and amikacin), tetracyclines (minocycline and doxycycline), and imipenem [14]. Of these, macrolides are considered a key drug for NTM infection, and a combination of these antimicrobials in the initial phase of the disease can yield a better outcome [15,16]. Antimicrobial susceptibility testing in this case (frozen broth microdilution panel) is not recommended by Clinical & Laboratory Standards Institute (CLSI) guideline (M24-A2) [17], and thus, our results may be unreliable. Sensitiser kit (Thermo Fisher Scientific, Waltham, MA, USA) is reportedly well equivalent with the CLSI standard, which is, however, commercially unavailable in Japan [18]. No guidelines or gold standards for the optimal duration of anti-mycobacterial chemotherapy have yet been developed. However, at least 4–6 weeks of multiple antibiotic therapy after improvement of clinical signs is suggested for NTM osteomyelitis [11], and 12–36 months of the anti-NTM drugs successfully treated patients with NTM bloodstream infection [6]. We administered antibiotic combination therapy on the basis of clarithromycin without using aminoglycosides because of her renal dysfunction. In addition to antibiotic therapy, surgical debridement is often essential to treat such

cases [11]. According to a recent report on NTM musculoskeletal infections, all the fourteen patients required surgical interventions in combination with antibiotics to control the diseases [12]. Thus, we believe the early amputation of the infected toe combined with long-term antibiotic treatment in this case could have contributed to the good outcome of the patient.

In summary, we illustrated a clinical course of *M. chelonae* bloodstream infection. A growing number of immunocompromised patients are exposed to a risk of severe NTM disease, especially the current ageing society. This case highlighted that physicians should consider the possibility of this rare but refractory infection, especially in older people who are under immunocompromised conditions.

Declaration of Competing Interest

None to declare.

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