Journal of Tuberculosis Research, 2015, 3, 107-112
Published Online September 2015 in SciRes. http://www.scirp.org/journal/jtr
http://dx.doi.org/10.4236/jtr.2015.33016

A Case of Ankle Osteomyelitis Caused by *Mycobacterium abscessus*

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Received 20 July 2015; accepted 18 September 2015; published 21 September 2015

Abstract

The proportion of non-tuberculous mycobacteria to *Mycobacterium tuberculosis* cultivated in the laboratory has been recently increasing. Numerous skin and soft tissue infections have been reported, while osteomyelitis is reported very rarely. A delayed diagnosis can cause a wide range of bone destruction and joint contracture, which highlights the importance of early recognition of osteomyelitis. Here we report a case of ankle osteomyelitis caused by *Mycobacterium abscessus* and treatment failure due to delayed diagnosis.

Keywords

Ankle, Osteomyelitis, *Mycobacterium abscessus*

1. Introduction

Non-tuberculous *Mycobacteria* (NTM) are defined as any *Mycobacterium* other than *Mycobacterium tuberculosis* and *Mycobacterium leprae*. The amount of NTM cultivated in the laboratory has been increasing [1]. NTM exists naturally in water, soil, dust, fish and non-pasteurized milk, causing localized infection in skin, soft tissue, bone, or lung, with the potential to disseminate. NTM can cause infection in both healthy and immunocompromised hosts. Depending on the host's immune status, clinical features and prognosis may vary.

Osteomyelitis caused by NTM is rare, but it has been reported in the sternum, spine, humerus, femur, tibia, and bones of the feet. Cases of skin and soft tissue infection caused by *Mycobacterium* abscesses were most often reported; however, cases of osteomyelitis have been reported very rarely [2]. Osteomyelitis caused by NTM shows clinical features similar to those of tuberculous mycobacteria infections, including nonspecific symptoms, subacute progression, and delayed diagnosis due to difficult growth of the organism in culture [3]. Early diagno-

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How to cite this paper: Seo, H.J., Son, J.H., Park, J.Y. and Kim, J.M. (2015) A Case of Ankle Osteomyelitis Caused by *Mycobacterium abscessus*. *Journal of Tuberculosis Research*, **3**, 107-112. http://dx.doi.org/10.4236/jtr.2015.33016

sis and treatment minimize pain and prevent deformation of the joint, but delayed diagnosis causes extensive bone destruction and joint contracture. Thus, an accurate early diagnosis is very important.

We report a case of osteomyelitis in the ankle joint caused by *Mycobacterium abscessus* and treatment failure due to delayed diagnosis and a discussion of related cases.

2. Case

A 67-year-old male patient presented to Kosin University Hospital due to burning pain and swelling of the left ankle after receiving acupuncture treatment at an oriental clinic for a left ankle sprain one week prior (**Figure 1**). He had no underlying disease and lived alone in unsanitary conditions. He had a history of posterior lumbar interbody fusion by spinal stenosis four years prior and left knee replacement arthroplasty six months prior.

When he presented to the hospital, his vital signs included blood pressure 130/80 mmHg, pulse rate 72 beats per minute, body temperature 36.5˚C, respiration rate 20 breaths per minute, and he was alert and conscious. His peripheral blood and biochemical examination results were as follows: hemoglobin 11.8 g/dL, WBC 6490/mm^3 (neutrophil 76.2%), platelets 258,000/mm^3, AST 50 IU/L, ALT 30 IU/L, ALP 71 IU/L, BUN/Cr 12.0/0.48 mg/dL, ESR 32 mm/hr, and CRP 7.3 mg/dL. X-ray of the left ankle suggested mild osteoarthritis with no bone destruction in the following **Figure 2**. The initial diagnosis was cellulitis in the left ankle joint. Blood culture

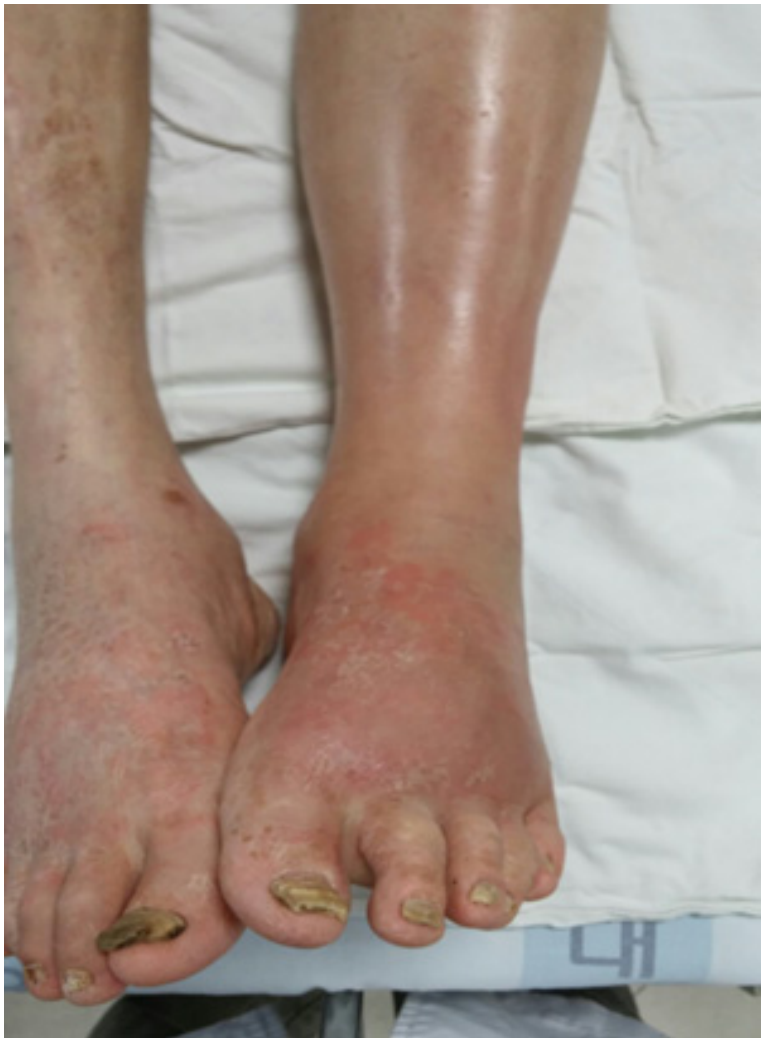

Figure 1. A 67-year-old male patient presented due to burning pain and swelling of the left ankle after receiving acupuncture treatment at an oriental clinic for a left ankle sprain.

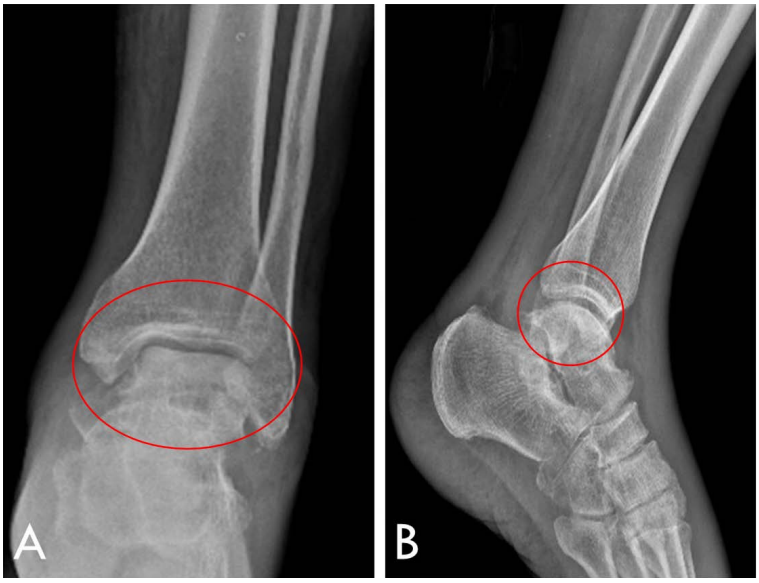

Figure 2. His initial radiograph of the left ankle showed mild osteoarthritis with no bone destruction (red circle).

was performed with initial treatment of short leg splinting, ice pack application on the left ankle and an intravenous injection of cefazedone 2 g BID. After antibiotic administration, CRP level 7.3 mg/dL increased to 9.5 mg/dL with no improvement in clinical symptoms for seven days after admission. Antibiotics were subsequently changed to cefolatam 2 g BID. Despite negative blood cultures upon admission and continuous antibiotic treatment, a fever of 38.6˚C occurred 15 days after admission. A second blood culture was also negative. Due to no effect of first- or third-generation cephalosporins, antibiotics were replaced with vancomycin 2 g BID for empirical treatment of common causative organisms of soft tissue infections. On day 17 after admission, there was fluctuation of the left ankle joint, so X-ray was performed and showed a reduction in bone density with uncertain sclerotic boundaries. CT was performed to determine the character and position of the lesion and revealed a pocket-like abscess in the following **Figure 3**. Thus, surgical debridement and irrigation were performed. Vegetation of dirty granulation tissues with yellow abscess was observed during surgery. Gram stain, culture, acid-fast stain, AFB culture, and tuberculous mycobacteria and non-tuberculous mycobacteria PCR were performed. Gram-positive bacilli were observed on Gram stain and culture. The other tests were negative, but chronic granulomatous inflammation with caseating necrosis on histological examination and acid-fast bacteria on acid-fast stain were observed in the following **Figure 4**. These results suggested tuberculous osteomyelitis. Vancomycin was stopped after one month from initial presentation, and isoniazid 300 mg, rifampin 600 mg, ethambutol 1200 mg, and pyrazinamide 1500 mg PO were started. A transient decrease and subsequent increase in CRP and continuous drainage of the lesion were observed, prompting curettage treatment. Trimethoprim/Sulfamethoxazole(TMP80 400 mg/SMX 80mg) 2T BID was administered for possible secondary bacterial infection. A second acid-fast stain of the lesion was negative, but a second AFB culture was positive. Species identification tests were then ordered. Due to severe weakness and severe mucus discharge, the patient had difficulty taking oral medications. Concomitant symptoms were nausea and vomiting, and fever lasted for two days. MDR *Acinetobacterbaumannii* was identified on culture, and medications were changed to tigecycline in addition to antituberculous agents for the superimposed infection. At 52 days after admission, *Mycobacterium abscessus* was identified by acid-fast bacterium identification test, and it was susceptible to amikacin and clarithromycin on antimicrobial susceptibility test (**Table 1**). Antituberculous agents were stopped, as *Mycobacterium abscessus* was resistant to the initial drug therapy, and the patient's general weakness was becoming more severe. Antibiotics were replaced with intravenous augmentin 1.2 g TID. Despite continuous antibiotic treatment, on day 58 after admission, clouded consciousness, decreased blood pressure, septic shock with atelectasis and pulmonary edema were all observed. On day 58 after admission, the patient expired from pneumonia with respiratory failure.

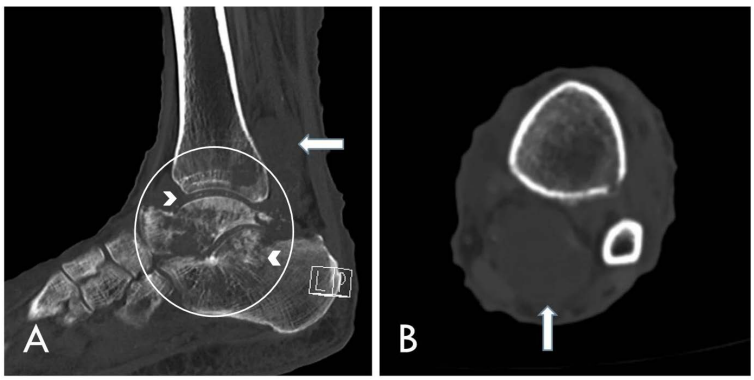

Figure 3. Seventeen days after admission. CT was performed to determine the character and position of the lesion and revealed a pocket-like abscess behind distal tibia (white arrow), multiple osteolytic lesionin his left ankle (white circle) and pathologic fracture of the talus and calcaneus (white arrow head).

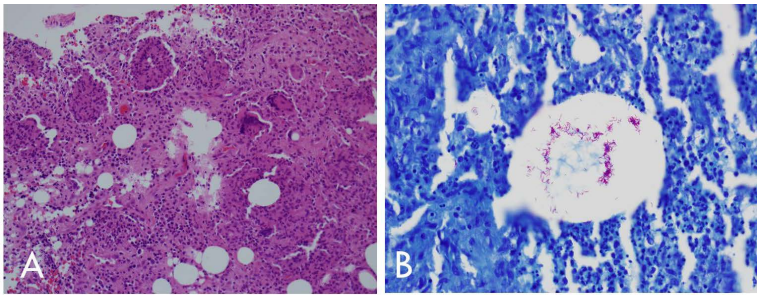

Figure 4. (A) Chronic granulomatous inflammation with caseating necrosis stained with hematoxylin and eosin and (B) acid-fast bacteria on acid-fast stain were observed.

Table 1. Antimicrobial susceptibility of the isolated *Mycobacterium abscessus.*

Antibiotic	Susceptibility	Concentration range tested (μg/mL)	MIC
Amikacin (AMK)	S	1 - 128	16
Cefoxitin	I	2 - 158	32
Ciprofloxacin	R	0.125 - 16	16
Clarithromycin	S	0.5 - 64	2
Doxycycline	R	0.25 - 32	>32
Imipenem	I	0.5 - 64	8
Moxifloxacin	I	0.125 - 16	8
Rifampincin	R	0.125 - 16	>16
Sulfamethoxazole	R	1 - 128	>128
Tobramycin	I	0.25 - 32	16
Ethambutol	R	0.25 - 32	>32
Linezolid	I	2.0 - 64	16

MIC, minimum inhibitory concentration; S, susceptible; I, intermediate; R, resistant.

3. Discussion

Most NTM are weakly pathogenic bacteria with low mortality on infection. They are widely distributed in nature and the environment in contrast with tuberculous mycobacteria, which have no natural host reserves. The

exact incidence and prevalence of non-tuberculous mycobacterial infection are not known. According to data from the US, the ratio of NTM to tuberculous mycobacteria has increased from 30% to greater than 50%; according to a national report, the ratio of NTM to tuberculous mycobacteria is reaching 20% - 30% [4]. Reasons for this increase in NTM are unknown, although transmission through a liquid medium, increasing recognition of NTM by medical staff and the development of treatment methods are thought to contribute. Immune weakness in the elderly due to increased average life span, increased water usage (c.f. shower), and a decrease in cross-immunity due to decreased tuberculosis infection could also be reasons.

Disease due to NTM can be classified into lung disease, lymphadenitis, cellulitis and bone infections and disseminated diseases. Smoking, chronic lung disease, AIDS, alcoholism, immunosuppressive therapy, cancer, leprosy, history of tuberculosis infection, connective tissue disease, and diabetes are all known risk factors.

Diagnosing osteomyelitis caused by NTM is very rare [5]-[7]. Although a vertebral osteomyelitis and epidural abscess caused by *Mycobacterium abscessus* were reported in several literatures, there is no article regarding an ankle osteomyelitis cause by *Mycobacterium abscessus*. Our significance of this study is to report it and to alarm the musculoskeletal infection of none-tuberculosis Mycobacterium. It has a similar pattern of presentation to osteomyelitis caused by tuberculous mycobacteria, including a chronic lapse in symptoms, lack of bone tissue near the joint, and swelling of the soft tissues [8].

Also there is growing incidence of procedure related-infection due to increased frequency of invasive injections in pain clinics or oriental clinics [9]. The presented case is considered to be a systemic infection preceded by local infection from an invasive acupuncture procedure since the patient had a history of oriental medicine treatment.

AFB smear and culture test used to detect tuberculous mycobacteria can also be applied to detect NTM. When *Mycobacteria tuberculosis* is cultured, one must distinguish whether it is tuberculous mycobacteria or NTM. It is important to obtain a proper tissue sample in order to diagnose rapidly growing bacteria, including *Mycobacterium abscessus*. When the tissue is cultured on blood or chocolate agar, it forms achromic colonies after 3 - 5 days, and Gram-positive bacilli can be observed in the Gram stain. Traditional biochemical tests take several weeks or longer; however, recent methods such as DNA markers, high-pressure liquid chromatography, rpo B, hsp 65 gene-targeted polymerase chain reaction restriction fragment length polymorphism allow for faster bacterial identification [10].

It is not easy to distinguish osteomyelitis caused by NTM from infection due to *Mycobacterium tuberculosis*, resulting in an average time span for diagnosis of 10 months or longer. The presented case took 52 days for a final diagnosis, during which the patient proceeded to septic shock and death. Microscopy of NTM rarely distinguishes the infection from tuberculous mycobacteria. When AFB smear tests for tuberculosis are positive in high-prevalence TB areas (such as Korea), tuberculosis nucleic acid amplification tests should be used for diagnosis. If positive, the case should be provisionally diagnosed as tuberculosis; if negative, NTM infection should be considered. A final diagnosis should be made based on the culture results.

Mycobacterium tuberculosis nucleic acid amplification test is useful since it requires a small number of bacteria and provides results in a short time. It also has the advantage of early detection and is used widely due to high sensitivity and specificity. However, the drawbacks include the risk of false-positive results and the inability for direct detection of NTM, which have been increasing in prevalence. Despite the drawbacks mentioned above, because the ratio of NTM isolation is increasing, it is rational to consider this infection on AFB-positive culture [11]. In the presented case, since multiple blood smears and *Mycobacterium tuberculosis* nucleic acid amplification tests showed repeated negative results, there was a delay in diagnosis and a failure of treatment. Although *Mycobacterium abscessus* requires both rapid and accurate bacterial identification and an antimicrobial susceptibility test for early diagnosis, the lack of appropriate initial diagnosis and treatment was thought to be a major cause of fatality.

The extent of the disease and immune status of the patient affect treatment of *Mycobacterium abscessus*; although treatment guidelines exist, the use of intravenous antibiotics such as cefoxitin, imipenem, amikacin and oral antibiotics such as clarithromycin or new a macrolide is widely accepted. Intravenous tigecycline, which was used in this case, is reported to have excellent antibacterial activity in *in vitro* drug susceptibility tests. However, there have been no clinical trials to assess its application in medical fields [12]. The long-term effects of antibiotic treatment are recommended to be combined with surgical treatment for *Mycobacterium abscessus* infection due to high resistance to IV antibiotics, the need for long-term treatment, and insufficient effect [13].

This is a case of non-tuberculous mycobacterial infection in a patient without risk factors that progressed to

non-tuberculous osteomyelitis from cellulitis due to an invasive procedure. The use of early antibiotics tends to delay diagnosis of non-tuberculous mycobacterial infection. Local cellulitis should be included in the differential diagnosis when there is evidence of infection in topical skin or soft tissue, and tissue biopsy and AFB stain must be executed. Considering that different bacterial species require different types of antibiotics, aggressive culture, identification and antibiotic susceptibility test are needed, although there is no known duration of treatment for non-tuberculous mycobacterial infection in the skin, soft tissue or bone. Delayed diagnosis due to negative results of the AFB smear and *Mycobacterium tuberculosis* nucleic acid amplification tests and overlooking the possibility of non-tuberculous mycobacterial infection are thought to be reasons for treatment failure. Non-tuberculous mycobacterial infection should always be considered, even if AFB smear, culture test, and *Mycobacterium tuberculosis* nucleic acid amplification tests show negative results. We present a case of failed treatment for septic shock due to systemic infection of non-tuberculous mycobacteria and hope that our experience will help to prevent such failures in the future.

Conflict of Interest

No funds were received in support of this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

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