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DISSEMINATED NONTUBERCULOUS MYCOBACTERIAL INFECTION SIMULATING A METASTATIC DISEASE

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ABSTRACT
Nontuberculous mycobacteria (NTM) are ubiquitous in the environment, and seldom considered as the potential pathogens for disseminated infections in clinical practice. We herein report a pyrexial woman presented with abnormal lung findings, lymphadenitis and disseminated bone foci on radiologic and radionuclide images, which were suggestive of a metastatic disease. Subsequent CT-guided biopsies of the lung and bone lesions showed mycobacterial histopathologic features and grew *Mycobacterium gordonae*. The diagnosis of NTM infection was achieved. Establishing the diagnosis of NTM infection requires the awareness of NTM as potential pathogens. Our case highlights that NTM infection should be included in the list of differential diagnosis of metastatic diseases.

INTRODUCTION

Nontuberculous mycobacteria (NTM) are ubiquitous organisms found in city water, aerosols, soil and dust [1]. NTM are seldom considered as causative agents of disease. Disseminated NTM infection is seldom reported, which may mimic malignancy on CT or radionuclide scan. Because of their fastidious nature, NTM are notoriously difficult to isolate and diagnosis of such infections is a challenge. Clinical symptoms and radiology often provide non-specific information. Positive cultures and staining for mycobacteria remain the gold standard for a firm diagnosis [2].

CASE REPORT

A 47-year-old woman was referred to our hospital due to chronic cough, vague bone pain, an enlarged node in the right submandibular area and abnormal lung findings for one month duration. Previous evaluation at another institution was inconclusive. The biopsy of the submandibular node showed inflammatory and hyperplastic changes. Past medical history was significant for Legionnaires' disease treated successfully with antibiotics one year earlier.

At the initial evaluation, the patient was pyrexial at 38.3°C, with WBC 12,600/μL, Hgb10 g/dL, ESR 76 mm/hr (range ≤25 mm/hr), CRP 0.7 mg/dl (range ≤0.5 mg/dl). Serology for Legionella, Mycoplasma, Chlamydia, Toxoplasma and Epstein-Barr virus were negative. Blood cultures were negative for bacterial growth, likely due to prior administration of antibiotics, and initial acid-fast bacillus (AFB) smear was negative from sputum specimens. Chest radiograph and computed tomography (CT) revealed mediastinal lymphadenitis, interstitial infiltration in bilateral lower fields and subpleural consolidation over left lower lung (Figure 1, A & B). Histopathological appearance from the mediastinoscopy biopsy revealed reactive lymph nodes. In view of the evidence of infection, levofloxacin was initiated for a broad covering.

At the follow-up visit after a week of antibiotic therapy, persistent fever, subsequent development of

pleural effusion, and CA-125 rising at 54 U/mL (range <35 U/mL) were noticed. Thereupon, a further search for occult disease was arranged. Numerous lesions disseminated in the rib cage, spine, pelvis and long bones were disclosed on Tc-99m MDP bone scan (Figure 2A, *arrows*). Mixed osteoblastic and osteolytic lesions over visible bony structure were also found on her abdominal CT (Figure 2B, *arrows*). A tentative report of distant bone metastases was conveyed, and subsequently CT-guided biopsies were performed to establish a definite diagnosis. Bone specimens taken from the ilium disclosed a picture of acute and chronic osteomyelitis. Acid-fast stain was positive and *Mycobacterium gordonae* was yielded later from bone specimens. CT-guided lung biopsy showed chronic granulomatous inflammation on histological examination. One of the repeat sputum smears was positive for acid-fast bacilli, and NTM were also retrieved from the sputum culture later.

A multidrug regimen of clarithromycin, rifabutin and ethambutol was commenced on the basis of susceptibility results. Adjunctive hyperbaric oxygen therapy was also performed for treating her osteomyelitis. Improvement in fever and symptoms was achieved four weeks afterwards, and remarkable resolution of skeletal lesions was documented on follow-up bone imaging (Figures 2 & 3, *arrows*).

Figure 1. Chest radiograph (A) and axial CT (B) revealing mediastinal lymphadenitis, interstitial infiltration in bilateral lower lung fields and subpleural consolidation over left lower lung (*arrow*).

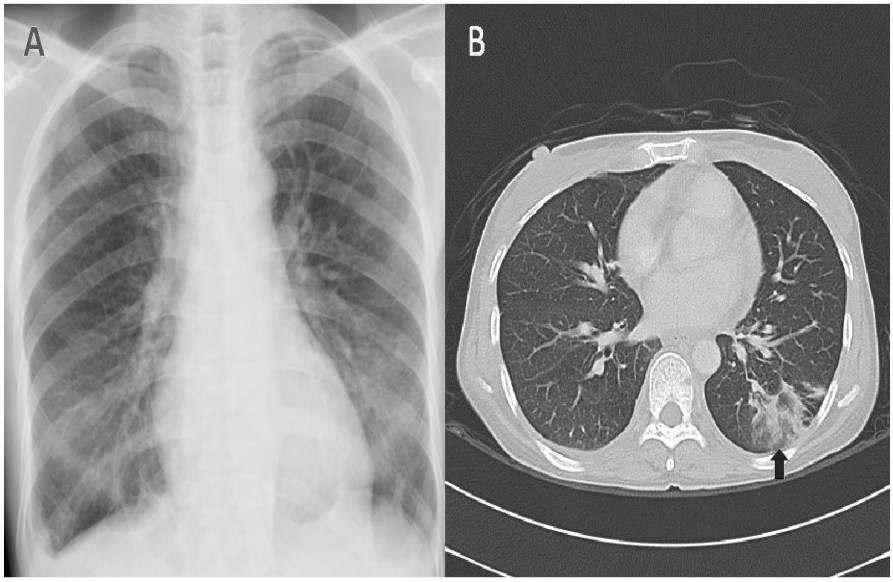


Figure 2. Tc-99m MDP bone scan revealed numerous lesions disseminated in the rib cage, spine, pelvis and long bones (A, *arrows*). Mixed osteoblastic and osteolytic lesions over the visible bony structure were also disclosed on her abdomen CT scan (B, *arrows*).

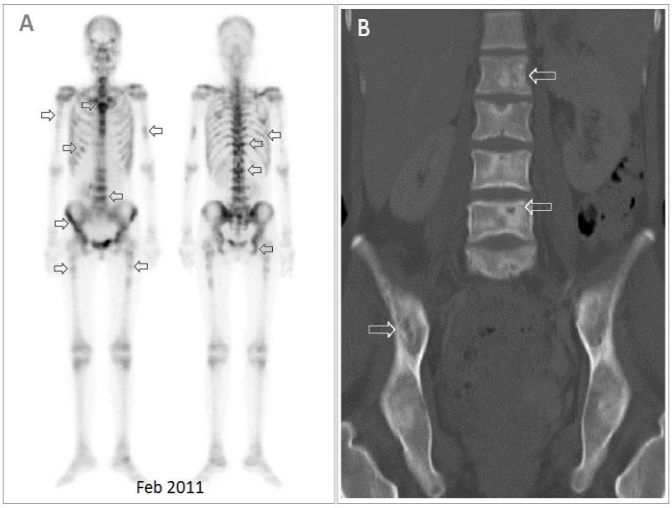
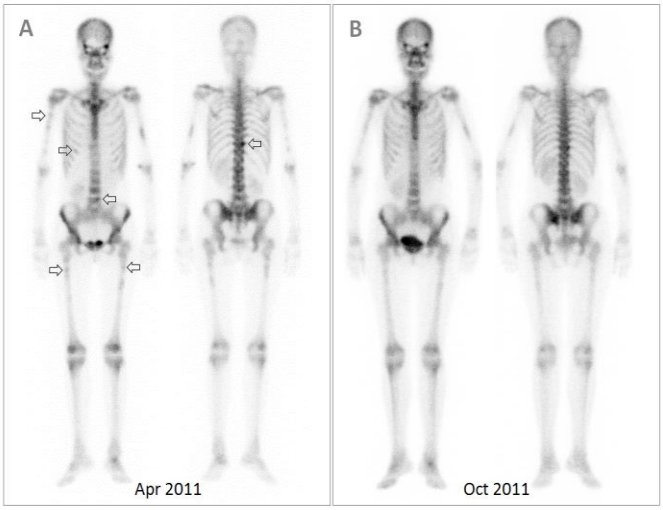


Figure 3. A comparison of two (A) and six (B) months after antimycobacterial therapy, a progressive resolution of the bone lesions was evident, as documented on the subsequent bone scan (*arrows*).



DISCUSSION

Nontuberculous mycobacteria (NTM) are a vast group of organisms, commonly found in drinking water and soil, and has only been recently appreciated [1]. People who develop NTM infections are likely to harbor immune deficiency disorders, such as those on long-term steroids or those infected with HIV [3]. The usual portal of entry for disseminated disease is thought to be the respiratory and gastrointestinal tracts [4]. Healthy hosts are also susceptible following direct inoculation through wounds, surgical incisions or medical procedures [3]. A broad spectrum of manifestations has been described in NTM infection, including lung disease, lymphadenitis, skin, soft-tissue and bone infections, catheter-related infections, and dissemination in immunocompromised hosts [5].

However, NTM primarily affects the lungs, in rare instances, causing osteomyelitis or disseminated disease [6,7]. Disseminated disease is most commonly seen in association with profound immunosuppression [3,5]. In general, mycobacteria are initially scavenged by macrophages, which respond for production of interleukin-12 (IL-12), in turn up-regulates interferon-gamma **(**IFN-γ). IFN-γ activates neutrophils and macrophages to kill intracellular pathogens, including mycobacteria [8]. IL-12 and IFN-γ are crucial elements of the host defense response to mycobacteria and other pathogens. Defects in these pathways increase susceptibility to mycobacterial and certain infections [8,9]. Disseminated NTM disease is regarded as a manifestation of immunologic defect, either acquired, such as HIV and iatrogenic factors, or genetic, caused by defects in the above IFN-γ /IL-12 pathway [2]. We have no convincing data for the immunological disruption in our case**,** since the IFN-γ autoantibody is typically not included in routine testing. Admittedly, one year earlier she had had Legionnaires' disease, which occurs predominantly in immunosuppressed hosts [10]. We speculate that our patient might be susceptible to opportunistic infections.

The clinical manifestations, radiographic and histological features of NTM diseases are usually indistinguishable from those of an atypical infection or malignancy [11]. The constitutional symptoms of weight loss, fever and night sweats are present in only 30 to 50% of patients, and often indicate advanced disease [2]. To diagnose NTM infection, clinical, radiological and microbiological evidence of disease should be gathered [2]. A prompt screening for occult diseases is required; this may include computed tomography. Whole body bone scan is a well established tool for detecting malignancy or metabolic changed due to infection and trauma, and plays an important role in making a wider range of assessment: early acknowledge before the onset of x-ray findings, disclosure of remote foci, and monitoring of therapy response. Culture is essential to differentiate among the possible etiologies, specify species of pathogens, and execute drug-susceptibility testing. However, a firm diagnosis of NTM disease is based on a tissue biopsy with positive cultures and staining for mycobacteria, not depending on a single positive result [2].

Treating NTM disease is recommended with at least three drugs, to which the isolate is susceptible or likely susceptible, if susceptibility testing is pending. The regimen is continued for the initial one to two months or until therapeutic response is noted [2]. In NTM osteomyelitis the affected bone is poorly perfused, a combination of sequestrectomy and anti-mycobacterial regimen is often required for a complete eradication of the infection [3]. No guidelines exist regarding which patients should undergo surgery in addition to medical therapy. Nevertheless, our patient was treated successfully with combined drug regimen only. The optimal duration of anti-mycobacterial therapy is unknown but probably should be for at least 6 months [12].

CONCLUSION

This case calls attention to a rare group of pathogens which may cause disseminated infection. It demonstrates that a high index of suspicion, an adequate knowledge of diagnostic procedures, and an appropriate management are crucial to eradicate such infections.

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CONFLICTS OF INTEREST

On behalf of all authors, the corresponding author states that there is no conflict of interest.

STATEMENT OF HUMAN AND ANIMAL RIGHTS:

All procedures performed in human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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