Refractory Bacteremia and Osteomyelitis Resulting in Fatal Bacteremic Pneumonia with Multiorgan Failure Caused by *Mycobacterium simiae* in a Non-HIV-infected Adult

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Bacteremic pneumonia caused by *Mycobacterium simiae* in non-HIV-infected patients was rarely reported. We describe a non-HIV infected adult with refractory bacteremia, osteomyelitis, and colonization of *M. simiae* in the respiratory tract who subsequently developed fatal bacteremic pneumonia. The isolate was confirmed as *M. simiae* by the 16S rRNA gene analysis.
CASE REPORT

A 73 year-old HIV-seronegative man was admitted to the hospital in July 2007 with fever and bone pain at the pelvis for three months. During the admission, magnetic resonance imaging (MRI) showed multiple lesions at the lower thoracolumbar spine, pelvis and bilateral proximal femurs. Microbiological studies of the biopsied specimen from the pelvic lesion revealed acid-fast bacilli, which was subsequently identified as *M. avium* complex (MAC) (Isolate A) by the conventional biochemical methods. Multifocal osteomyelitis due to MAC was diagnosed. He had no history of cirrhosis, diabetes mellitus, or immunosuppressant use. The patient had been treated for *Salmonella* bacteremia one year prior to this admission.

Rifampin (600 mg daily), ethambutol (1200 mg daily), and clarithromycin (500 mg every 12 hours) were administered. Fever and bone pain subsided after treatment. However, maculopapular rash with pruritus developed on the lower legs and evolved to the thighs, hips, trunk, and arms two months after treatment. Anti-mycobacterial agents were temporarily discontinued due to suspicion of drug eruptions. Re-challenge with clarithromycin or rifampin aggravated the skin eruptions. Ciprofloxacin was given with ethambutol, but angioedema and severe cutaneous rash
occurred. Anti-mycobacterial treatment was then discontinued six months after the initiation of treatment.

However, intermittent fever developed three months later. Amikacin (500 mg three times per week), clarithromycin (500mg three times per week) and ethambutol (800 mg three times per week) were empirically administered. Three sputum samples (Isolate B) and two sets of blood cultures (Isolate C) all yielded MAC by the conventional methods. Chest X-ray showed no abnormality (Fig. 1A). Abdominal magnetic resonance image (MRI) suggested osteomyelitis of the thoracolumbar spines (Fig. 1B). Repeated HIV screening was also negative and the CD4 lymphocyte count was 859/µl. Cutaneous eruptions recurred after the initiation of treatment. Imipenem (500 mg every 8 hours) and amikacin (500 mg daily) were given in substitution and fever subsided gradually. After three weeks of combination treatment with imipenem and amikacin, rifabutin (300 mg daily), moxifloxacin (400 mg daily), and minocycline (100 mg daily) were given as maintenance treatment. Follow-up blood cultures 7 months after the initiation of therapy were negative for MAC. After eight months of treatment, all anti-mycobacterial agents were discontinued. Sputum cultures were not done after completion of anti-mycobacterial treatment due to lack of any respiratory secretion from this patient.
Intermittent fever recurred one month later, with progressive dyspnea. Hemogram showed leukocytosis (white cell count 31730/µl with bandemia 8%). Serum biochemistry showed blood urea nitrogen 24.3 mg/dl, creatinine 1.2 mg/dl, aspartate aminotransferase 29 U/l, and alanine aminotransferase 22 U/l. Hypoxic respiratory failure developed three weeks after the onset of fever. Chest radiograph revealed multi-lobar pneumonia in the right middle and lower lobes (Fig. 1C). Imipenem (500 mg every 8 hours) and amikacin (300 mg every 12 hours) were administered but acute respiratory distress syndrome and septic shock ensued. Renal function deteriorated (blood urea nitrogen and creatinine levels, 59.8 mg/dl and 2.3 mg/dl, respectively) and anuria developed. The patient died one week after admission. Three samples of sputum (Isolate D) and two sets of blood culture (Isolate E) later also yielded MAC identified by the conventional methods.

**Microbiology.** All the five MAC isolates were negative for niacin accumulation, catalase at 68 °C, hydrolysis of Tween 80, or arylsulfatase at 14 days. The colonies of the isolates were buff initially and turned yellowish after 14 days of incubation. Confirmation of these isolates to the species level was performed by partial 16S rRNA gene (1,464 bp) analysis (10). The sequences were compared to known 16S rRNA gene sequences in the GenBank database of the National Center for Biotechnology Information using the BLAST algorithm. The species of all the isolates with the best
match was *M. simiae* (accession number EF362378.1, 99% identity). Randomly amplified polymorphic DNA (RAPD) analysis of the five isolates (Isolates A-E) using three random primers: INS-2 (3’-GCGTAGGCGTCGTTGAAA-5’), B1245 (3’-AGGTGGCGTCGAGGAAGAC-5’), and IS986FR (3’-ACGCTCAACGCGCAGAC5’) revealed the identical patterns of the five isolates from the patient indicating the persistence of *M. simiae* infection of the patient during 18 months of period. RAPD patterns of three *M. simiae* isolates (control isolates) recovered from sputum specimens from three different patients admitted in the hospital were different. Minimum inhibitory concentration (MIC) of the isolates to clarithromycin, rifampin, ciprofloxacin, imipenem, and amikacin using the Etest (AB Biodisk, Solna, Sweden) was 2 µg/ml, 8 µg/ml, 4 µg/ml, 4 µg/ml, and 16 µg/ml, respectively.

**Discussion.** *M. simiae*, a slow-growing non-tuberculous mycobacterium (NTM), was first isolated in 1965 from rhesus monkeys (6). Disseminated *M. simiae* infection is rare and almost all reported cases were in AIDS patients (1). Only one case of disseminated *M. simiae* infection has been reported in HIV-non-infected patients (2). This 83-year-old man had a fatal *M. simiae* infection with isolates from cerebrospinal fluid and bronchoaveolar lavage (2). Most of the previous reports of *M. simiae* infection have been from the southwestern US, Cuba, and Israel (1-5, 7-9, 11). Our
patient is the first Asian case of disseminated *M. simiae* infection in a non-HIV infected adult.

*M. simiae* was found in the environment including the hospital water supply (3). Clinical *M. simiae* isolation is usually from respiratory specimens and most of them are from patients with AIDS, cancer, or chronic obstructive pulmonary disease (1). The clinical relevance of *M. simiae* isolation from respiratory specimens either as a colonizer of the respiratory tract or as a true pathogen causing pneumonia ranged from 9% to 24% (9, 11). In our patient, *M. simiae* were recovered from multiple respiratory secretion specimens during hospitalization. Surveillance for the presence of the organism in the patient’s environment (e.g. tap water at home or hospital water supplies) to elucidate the possibility of environmental contamination is necessary. Unfortunately, environmental surveillance was not performed in this study.

The commonly reported symptoms are productive cough, dyspnea, malaise, fever, sweat, and body weight loss (9). The lack of respiratory symptoms and the negative findings of chest radiographs suggest our patient may have had long-term *M. simiae* colonization which subsequently developed into multilobar pneumonia.

The optimal regimen and treatment duration for *M. simiae* infection has yet to be determined. *In vitro, M. simiae* was frequently less susceptible to most
antimycobacterial drugs and high rates of resistance to rifampin (100%), amikacin (92%), clarithromycin (75%), and ciprofloxacin (30%) among *M. simiae* isolates were reported, although there were no recommended interpretive criteria for defining susceptibility for *M. simiae* isolates (1, 5). Clarithromycin and fluoroquinolones are recommended in the American Thoracic Society (ATS) guidelines (4), the use of which is associated with most reported favorable outcomes. Disseminated infection caused by NTM and non-typhoid *Salmonella* species tends to develop in patients with primary immunodeficiency, HIV infection, and defects in type 1 cytokines (especially interleukin 12, interleukin 23, and interferon γ) or receptors (12). Our patient didn’t have HIV infection, and the age of onset excluded the possibility of primary immunodeficiency in this patient. The possibly unrecognized impaired immunity, intolerance to clarithromycin, and inadequate duration of antimycobacterial therapy might all have partly contributed to the refractory course and fatal outcome of our patient.

In conclusion, we report a case of disseminated *M. simiae* infection in a non-HIV infected adult, presented with refractory bacteremia, osteomyelitis, and fatal bacteremic pneumonia. *M. simiae* should be listed in the etiologies causing disseminated infection and pneumonia in non-HIV infected patients.
References


FIG. 1. Chest radiographs showing (A) the absence of lung lesions of the patient eight months prior to the development of pneumonia, (B) abdominal MRI revealing a lesion with rim enhancement in the thoracolumbar spine suggesting osteomyelitis (T1-weighted image with fat suppression and contrast enhancement), and (C) multilobar pneumonia over the right middle, lower lobe, and left lower lobes in a patient with *M. simiae* bacteremia and positive cultures of *M. simiae* from three sputum samples.