CASE REPORTS

Refractory Bacteremia and Osteomyelitis Resulting in Fatal Bacteremic Pneumonia with Multiorgan Failure Caused by Mycobacterium simiae in a Non-Human Immunodeficiency Virus-Infected Adult

Kuei-Pin Chung,¹ Tzu-Hsiu Tsai,¹ Yu-Tsung Huang,¹,² and Po-Ren Hsueh¹,²*

Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan,¹ and Department of Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan²

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Bacteremic pneumonia caused by Mycobacterium simiae in non-human immunodeficiency virus (HIV)-infected patients has rarely been 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 16S rRNA gene analysis.

CASE REPORT

A 73-year-old human immunodeficiency virus (HIV)-seronegative man was admitted to the hospital in July 2007 with fever and bone pain at the pelvis for 3 months. Upon admission to the hospital, magnetic resonance imaging (MRI) showed multiple lesions at the lower thoracolumbar spine, pelvis, and bilateral proximal femurs. Microbiological studies of the biopsy specimen from the pelvic lesion revealed acid-fast bacilli, which were subsequently identified as Mycobacterium avium complex (MAC) (isolate A) by 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 1 year prior to this admission.

Rifampin (rifampicin) (600 mg daily), ethambutol (1,200 mg daily), and clarithromycin (500 mg every 12 h) were administered. The 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 2 months after treatment. Antimycobacterial agents were temporarily discontinued due to suspicion of drug eruptions. Rechallenge with clarithromycin or rifampin aggravated the skin eruptions. Ciprofloxacin was given with ethambutol, but angioedema and severe cutaneous rash occurred. Antimycobacterial treatment was then discontinued 6 months after the initiation of treatment.

However, intermittent fever developed 3 months later. Amikacin (500 mg three times per week), clarithromycin (500 mg 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 conventional methods. Chest X-ray showed no abnormality (Fig. 1A). Abdominal MRI suggested osteomyelitis of the thoracolumbar spines (Fig. 1B). Repeated HIV screening also gave negative results, and the CD4 lymphocyte count was 859/µl. Cutaneous eruptions recurred after the initiation of treatment. Imipenem (500 mg every 8 h) and amikacin (500 mg daily) were given instead of amikacin, clarithromycin, and ethambutol, and the fever gradually subsided. After 3 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 8 months of treatment, all antimycobacterial agents were discontinued. Sputum cultures were not done after completion of antimycobacterial treatment due to lack of any respiratory secretion from this patient.

Intermittent fever recurred 1 month later, with progressive dyspnea. Hemogram showed leukocytosis (white cell count of 31,730/µl with 8% bandemia). Serum biochemical analysis showed the following values: blood urea nitrogen, 24.3 mg/dl; creatinine, 1.2 mg/dl; aspartate aminotransferase, 29 U/liter; and alanine aminotransferase, 22 U/liter. Hypoxic respiratory failure developed 3 weeks after the onset of fever. Chest radiograph revealed multilobar pneumonia in the right middle and lower lobes (Fig. 1C). Imipenem (500 mg every 8 h) and amikacin (300 mg every 12 h) 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 1 week after admission. Three samples of sputum (isolate D)
and two sets of blood culture (isolate E) later also yielded MAC identified by conventional methods.

**Microbiology.** All 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 the identity 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* (GenBank accession number EF362378.1; 99% identity). Randomly amplified polymorphic DNA analysis of the five isolates (isolates A to E) using three random primers, INS-2 (3'-CGAGGAAGAC-5'), B1245 (3'-AGGTGGCGT CGAGGAAGAC-5'), and IS986FR (3'-AGGCTCAACGCC AGAGACCA-5'), revealed the identical patterns of the five isolates from the patient, indicating the persistence of *M. simiae* infection of the patient during the 18-month period. Randomly amplified polymorphic DNA patterns of three *M. simiae* isolates (control isolates) recovered from sputum specimens from three different patients admitted in the hospital were different. The MICs of the isolates to clarithromycin, rifampin, ciprofloxacin, imipenem, and amikacin using the Etest (AB Biodisk, Solna, Sweden) were 2 µg/ml, 8 µg/ml, 4 µg/ml, 4 µg/ml, and 16 µg/ml, respectively.

**Discussion.** *M. simiae*, a slow-growing nontuberculous mycobacterium, 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 non-HIV-infected patients (2). This 83-year-old man had a fatal *M. simiae* infection with isolates from cerebrospinal fluid and bronchoalveolar lavage samples (2). Most of the previous reports of *M. simiae* infection have been from the southwestern United States, Cuba, and Israel (1–5, 7–9, 11). Our patient is the first case of disseminated *M. simiae* infection in a non-HIV-infected Asian 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* was 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 that 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 have 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 (50%) 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 nontuberculous mycobacterium and nontyphoid *Salmonella* species tends to develop in patients with primary immunodeficiency, HIV infection, and defects in type 1 cytokines (especially interleukin 12, interleukin 23, and gamma interferon) or receptors (12). Our patient did not 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 who presented with refractory bacteremia, osteomyelitis, and fatal bactereemic pneumonia. *M. simiae* should be listed in the etiologies causing disseminated infection and pneumonia in non-HIV-infected patients.
REFERENCES