

Disseminated *Mycobacterium avium* Complex Infection in a Non-HIV-infected Patient Undergoing Continuous Ambulatory Peritoneal Dialysis

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Isolated bone marrow infection by nontuberculous mycobacteria (NTM) is extremely rare. Recently, we encountered a case of bone marrow *Mycobacterium avium* complex (MAC) infection, which presented as a fever of unknown origin shortly after starting continuous ambulatory peritoneal dialysis (CAPD). The patient was diagnosed with MAC infection on the basis of PCR-restriction fragment length polymorphism analysis and sequencing of DNA obtained from bone marrow specimens. Although this was a case of severe MAC infection, there was no evidence of infection of other organs. End-stage renal disease (ESRD) patients undergoing dialysis can be considered immunodeficient; therefore, when these patients present with fever of unknown origin, opportunistic infections such as NTM infection should be considered in the differential diagnosis. (*Korean J Lab Med* 2010;30:166-70)

Key Words : End-stage renal disease, *Mycobacterium avium* complex, Bone marrow

INTRODUCTION

Nontuberculous mycobacteria (NTM) are ubiquitous in the environment and have low virulence; however, they can be opportunistic and, at times, deadly. Approximately 30 of the more than 90 known species of NTM have been reported to be associated with human diseases. The NTM most commonly implicated in human diseases was *Mycobacterium avium* complex (MAC). Several studies have reported the occurrence of MAC-associated peritonitis, synovitis, spondylitis, and skin infections in dialysis patients [1-7]. Only 1 case of disseminated MAC infection in an AIDS patient undergoing continuous ambulatory peritoneal dialysis (CAPD) has been reported to date [2]. Here,

we report the case of a patient who presented with persistent fever shortly after starting CAPD; PCR analysis and sequencing of DNA extracted from bone marrow samples revealed that the patient had MAC infection.

CASE REPORT

In January 2008, a 69-yr-old woman with left renal agenesis and chronic renal failure caused by long-standing hypertension was admitted to the nephrology department for progressively worsening uremic symptoms such as general weakness and poor oral intake. She was scheduled for CAPD as part of the renal replacement treatment. Her blood pressure was 140/90 mmHg. The results of physical examination on admission were as follows: findings of the head and neck were unremarkable; chest auscultation did not reveal any crackles; the heart and abdomen were normal; pitting edema (1+) of the lower extremities was present; and skin lesions were absent. A plain chest radiograph showed no specific findings. The results of the ini-

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tial laboratory tests were as follows: hemoglobin level, 8.7 g/dL; white blood cell count (WBC), $5.6 \times 10^9/L$; and platelet count, $154 \times 10^9/L$. The results of a blood chemistry study of serum samples were as follows: blood urea nitrogen, 129 mg/dL; creatinine, 14.2 mg/dL; sodium, 136 mmol/L; potassium, 3.8 mmol/L; calcium, 8.1 mg/dL; glucose, 93 mg/dL; uric acid, 8.4 mg/dL; and albumin 2.5 g/dL. Arterial blood gas analysis yielded the following results: pH of 7.2, pCO_2 of 25 mmHg, HCO_3^- of 9.3 mEq/L, pO_2 of 85 mmHg, and an oxygen saturation of 98.8%. On the second day of admission, a Tenckhoff peritoneal catheter was inserted to start peritoneal dialysis. Then, CAPD was performed with 4 dwells per day (1.5 L/dwell) by using 1.5% glucose PD solution. On hospital day (HD) 3, the patient abruptly developed fever (body temperature 38.7°C), and abdominal examination showed diffuse mild tenderness with more severe tenderness in the left and middle lower abdominal quadrant, with the absence of bowel sounds. The PD catheter exit site was clean and showed no signs of erythema, purulent drainage, or tenderness of the subcutaneous tunnel. The dialysis fluid contained 170 WBCs/ μL with 88% neutrophils; gram staining revealed no microorganisms. A diagnosis of CAPD peritonitis was made, and empirical therapy was started with intraperitoneal ceftazidime and cefazolin. However, the fever did not subside and persisted even after intraperitoneal administration of vancomycin. Over the next 2 weeks, the patient had continuous fever with temperature being over 38°C and had persistent abdominal pain and cramping, but bacterial cultures of the blood, urine, and PD fluid tested negative. Because of the persistence of the fever, PD fluid staining and microbiological cultures for fungi and mycobacteria were performed simultaneously. We used only solid media for mycobacterial culture. However, the fungal and mycobacterial stains and cultures tested negative. Computed tomography (CT) of the abdomen showed multiple lymphadenopathies and multiple low-density masses in the splenic region, but did not show findings compatible with peritonitis; CT of the chest showed multiple non-specific small nodules in both lungs. On HD 17, we stopped peritoneal dialysis and decided to remove the PD catheter and started hemodialysis through

a perm catheter inserted via the right internal jugular vein. All bacteriologic studies, including cultures of body fluids, sputum, blood, and catheter tips, were negative. The fever persisted even after the treatment regimen was modified to comprise several classes of antibacterial drugs, such as intravenous fluoroquinolone, imipenem, vancomycin, metronidazole, and aminoglycoside, and antifungal agents, such as fluconazole. On HD 40, we performed an aspiration biopsy of the bone marrow because her complete blood cell count showed the gradual occurrence of pancytopenia. Histological analysis of the bone marrow specimens showed normocellular, reactive marrow with histiocytic hemophagocytosis and atypical, non-caseous necrotic regions (Fig. 1).

We suspected that the multiple atypical necrotic regions represented foci of mycobacterial infection of the bone marrow, but AFB staining and PCR analysis of the bone marrow specimens tested negative. However, we started empirical anti-mycobacterial treatment by using the HREZ regimen (isoniazid, 200 mg qd; rifampicin, 450 mg qd; pyrazinamide, 750 mg qd; and ethambutol, 800 mg qd). After 2 weeks of antimycobacterial treatment, the patient's fever decreased gradually and significantly, and her general status improved slightly. However, the patient's body temperature was not completely normalized. Therefore, we performed a PCR analysis of the *rpoB* segment followed by DNA sequencing to confirm atypical mycobacterial infection. DNA sequencing of the PCR products revealed that

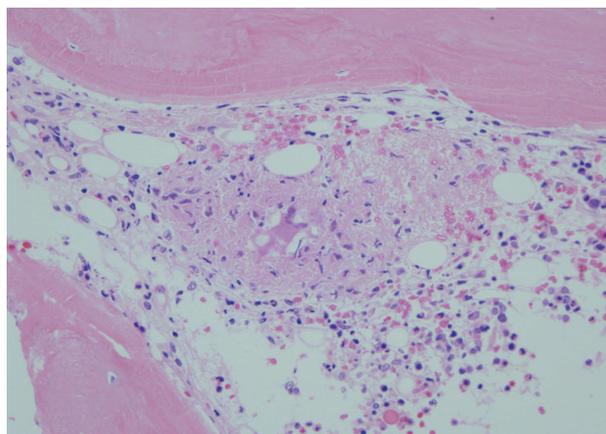


Fig. 1. Bone marrow was normocellular and reactive, with histiocytic hemophagocytosis and atypical, non-caseous necrotic regions (hematoxylin and eosin stain, $\times 400$).

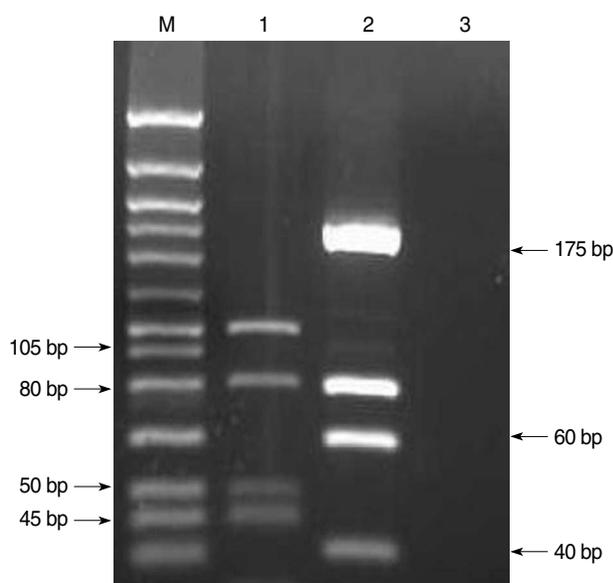


Fig. 2. Metaphor agarose gel (4%) electrophoresis of the *Msp* I-digested PCR product. Lane M, molecular size marker. Lane 1, bone marrow specimen of the patient, showing a protein profile similar to that of *Mycobacterium avium* (105 bp, 80 bp, 50 bp, and 45 bp). Lane 2, positive control (*Mycobacterium tuberculosis*; 175 bp, 80 bp, 60 bp, and 40 bp). Lane 3, negative control.

the patient had MAC infection (Fig. 2, 3).

After treatment, mycobacterial culture of the bone marrow aspirate tested negative. However, the patient died of intracranial hemorrhage (ICH) due to inadequate control of blood pressure and thrombocytopenia.

DISCUSSION

We report a case of disseminated MAC infection, which occurred shortly after starting CAPD. To the best of our knowledge, this is the first report of disseminated MAC infection in an HIV-negative patient who had end-stage renal disease (ESRD) or CAPD. All reported cases of MAC-associated infections, including crescentic glomerulonephritis, kidney mycobacteriosis, peritonitis, synovitis and spondylitis, and multiple skin lesions in hemodialysis patients, were localized to specific organs, except 1 case in which disseminated MAC was reported in an AIDS patient undergoing CAPD [1-9]. MAC infection causes premature death in most patients: this is evidence of the severity of the disease and reflects the comorbidity burden of the patient pop-

ulation.

Nonmycobacterial peritonitis can develop in CAPD patients even in the absence of disseminated infection or HIV infection. Because CAPD patients have to undergo numerous sterile exchanges per day, there is a high probability of peritoneal infection by environmental pathogens such as MAC. Moreover, these patients are frequently malnourished, which, in turn, decreases cell-mediated immunity, the principal host defense against mycobacteria. In addition, CAPD effluent itself lowers the cytokine levels in the peritoneum and decreases the absolute T-cell and macrophage counts. Finally, phagocytosis and respiratory oxidative burst are inhibited in the peritoneal macrophages, thereby further contributing to an increased susceptibility to mycobacterial infection [6]. The incidence of peritonitis with MAC in HIV-negative patients is uncommon, and the incidence of disseminated MAC infection in an ESRD or CAPD patient is extremely rare.

With the implementation of effective tuberculosis control measures and the development of advanced microbiological diagnostic methods, NTM have been recognized as an important causative agent of human diseases. Among the NTM, the species most commonly associated with infections were MAC (61%), *Mycobacterium fortuitum* complex (19%), and *Mycobacterium kansasii* (10%) [10]. Disseminated MAC infection primarily occurs in severely immunocompromised patients, such as progressive AIDS patients generally with low CD4 cell count [11]. Disseminated MAC is thought to arise from an infection of mucosal surfaces, such as those of the gut or lung, followed by local multiplication and entry into the blood stream and seeding of other organs and tissues. In general, the AIDS epidemic has been accompanied by an epidemic of disseminated MAC infection because severely immunocompromised patients are exposed to these ubiquitous but relatively less virulent environmental organisms.

ESRD patients have an impairment of several aspects of lymphocyte and granulocyte function, irrespective of whether they undergo dialysis or not. Unidentified uremic toxins are thought to be responsible for this condition, and malnutrition can sometimes be a contributory factor. Despite

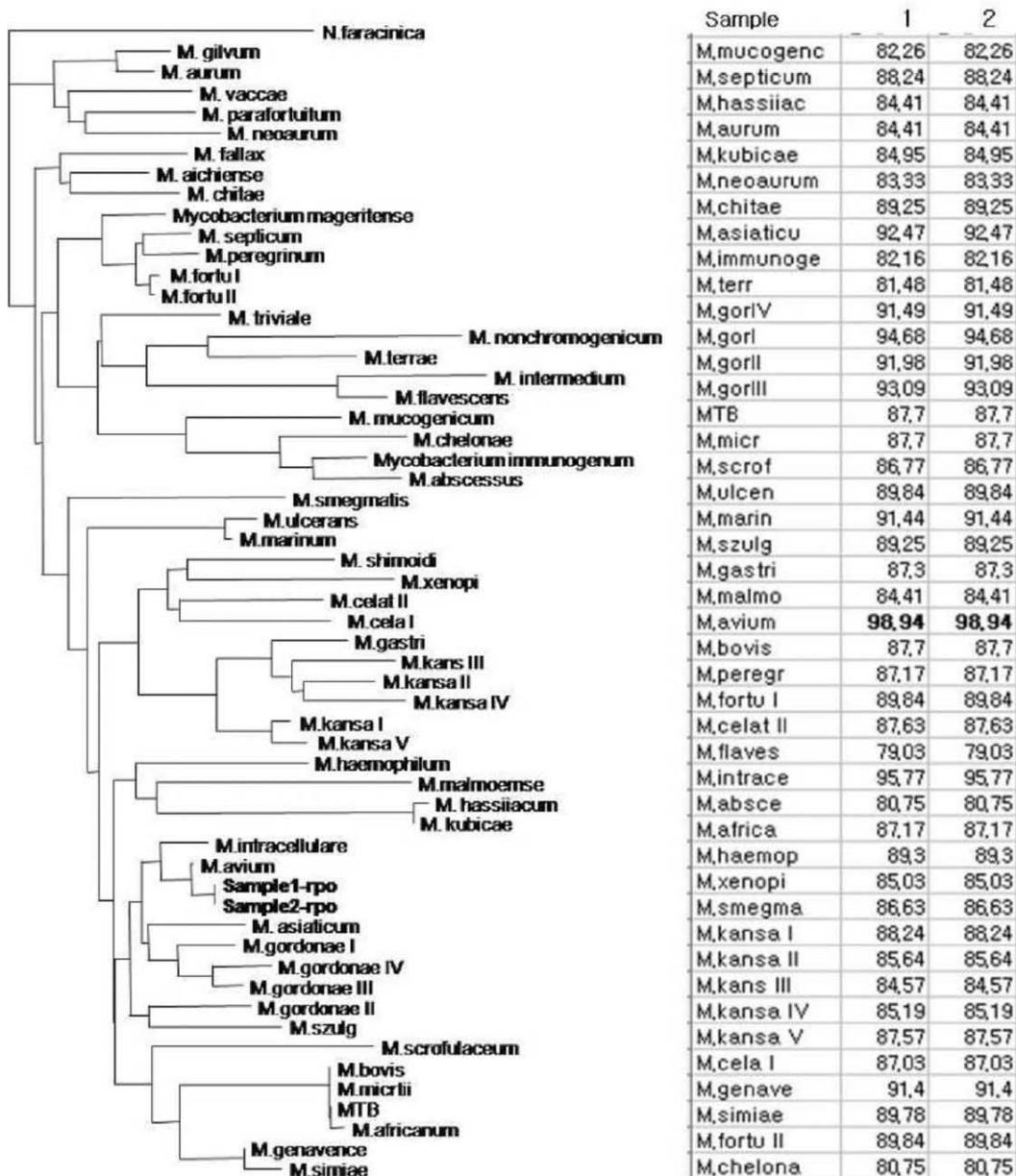


Fig. 3. Phylogenetic tree constructed using the *rpoB* gene sequences. Samples 1 and 2 are bone marrow specimens from the patient.

the knowledge of the above mentioned risk factors in ESRD patients, the mechanism of development of disseminated infection in HIV-negative patients with ESRD is yet unknown. Therefore, future research should focus on elucidating the possible mechanisms of development of this infection.

Several multidrug regimens have been used to treat disseminated MAC. Current treatment guidelines for disseminated MAC infection recommend the administration of clar-

ithromycin (1,000 mg/day) or azithromycin (500 mg/day) and ethambutol (15 mg kg⁻¹ day⁻¹) with or without rifabutin (150–300 mg/day) [6]. This treatment regimen has achieved sufficient suppression of infection, thereby resulting in symptomatic improvement and clearing of bacteremia in some cases; however, the regimen has proven futile in most cases. Although disseminated MAC infection in our case was eventually diagnosed, successful treatment could not be administered because the diagnosis was established too

late and because the patient suddenly developed ICH, which proved to be fatal. We believe that ESRD patients have qualitative and quantitative immune deficiencies, and this should be recognized even when treating patients without HIV infection. Therefore, opportunistic infection by pathogens such as NTM should be considered as a possible cause of fever of unknown origin in immunocompromised patients, particularly when usual microbiological cultures test negative.

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