Short Communication

Nontuberculous Mycobacterial Osteomyelitis in Human Immunodeficiency Virus-Negative Patients: A Case Series

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SUMMARY: Nontuberculous mycobacterial bone infections among human immunodeficiency virus (HIV)-negative patients are rare, although a few studies have described such infections. We retrospectively reviewed the medical and microbiological data of HIV-negative osteomyelitis cases caused by nontuberculous mycobacteria treated in our tertiary-care hospital over 14 years from January 1, 2000, to December 31, 2013. Three HIV-negative patients had contracted bone infections due to nontuberculous mycobacteria. All of the patients had at least 1 predisposing condition that led to the infections: idiopathic CD4-positive lymphocytopenia and/or anti-interferon- γ autoantibody syndrome.

Nontuberculous mycobacteria (NTM) play a role in both pulmonary and extrapulmonary infections in human immunodeficiency virus (HIV)-positive patients. Although pulmonary infections due to NTM are still common among HIV-negative individuals, extrapulmonary infections, such as bone infections, are rare. Few cases of bone infections have been reported among HIV-negative patients (1,2).

We retrospectively reviewed the medical and microbiological data from our tertiary-care hospital over 14 years from January 1, 2000, to December 31, 2013, and extracted data from those who tested positive for NTM on bone aspiration cultures and those in whom, although bone aspiration was not performed, radiological evidence showed osteomyelitis with positive NTM culture from other samples, such as abscesses adjacent to the infected bones. From the data, we then selected those who tested negative for HIV and obtained consent from the eligible participants (except one deceased patient without relatives) after written and verbal explanations.

A total of 10,576 samples of all types, including sputum, in 3247 patients tested positive for NTM on culture. Of these, 8 patients had 1 or more positive cultures on bone aspiration or other samples with radiologically proven osteomyelitis. Of these 8 patients, 3 were HIV-negative (a 67-year-old woman, a 66-year-old man, and a 71-year-old man, numbered 1–3), as summarized in Table 1. *Mycobacterium avium* was cultured in multiple bones, sputum, lymph nodes, and blood of patient 1. The lymph node biopsy showed abscess formation with macrophage aggregation. Patient 2 had multiple bones and lymph nodes infected with *M. avium*. Patient 3 was not tested for bone tissue culture, but acid-fast bacilli,

which later turned out to be *M. kansasii*, was observed on the smear of the right psoas abscess adjacent to his L4 vertebrae, showing high signal intensity on the T2-weighted magnetic resonance imaging. No other pathogens were detected on the sample. None of the 3 patients had solid or hematological malignancies or had received immunosuppressive therapy. Patient 1 showed idiopathic CD4-positive lymphocytopenia (ICL). Patients 2 and 3 tested positive for anti-interferon- γ autoantibodies (anti-IFN γ Ab), for which patient 1 was not tested. Patient 2 had a medical history of tuberculosis 30 years earlier, whereas patient 3 had concurrent pneumoconiosis owing to his occupational exposure to small particles of clay and wood material as a craftsman.

Patient 1 was initially treated with ethambutol, rifabutin, and clarithromycin. Rifampin was not administered to avoid thrombocytopenia (as the patient's baseline platelet count was as low as 40,000/ μ L). Her lymphadenopathy shrank in size on the computed tomography performed during month 9 of antimicrobial chemotherapy. Ciprofloxacin was replaced with rifabutin during month 16, and ethambutol was carefully replaced with a lower dose of rifabutin during month 23 of the antimicrobial chemotherapy because of thrombocytopenia and neuropathy, respectively. The patient was diagnosed with myelodysplastic syndrome (MDS) during month 24 of therapy and was moved to another hospital for continuation of the therapy but subsequently died of MDS.

Patient 2 received clarithromycin, rifampin, and ethambutol. His lymphadenopathies had shrunk in size, and no deterioration in the bone lesions was observed on the follow-up computed tomography obtained during the first month of therapy. He is currently on month 16 of the 3-drug therapy, and no sign of deterioration has occurred.

Patient 3 started treatment with isoniazid, rifampin, ethambutol, and pyrazinamide for suspected tuberculosis (TB) infection, as his chest computed tomography showed bilateral multiple nodular opacities (which later turned out to be pneumosilicosis on bronchoscopy) and a blood test (QuantiFERON[®]-TB; manufactured by Cellestis Limited, Carnegie, Victoria, Australia) was

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Table 1. Clinical summary of nontuberculous mycobacterial osteomyelitis in human immunodeficiency virus-negative patients

Case #	Age, sex	BMI (kg/m ²)	Infected bone	Other sites of infection	Pathogen	Other underlying disease	Treatment	Outcome
1	67, F	15.1	Vertebrae, pelvic, sternum	Blood, lymph nodes, lung	<i>M. avium</i>	MDS, Idiopathic CD4+ lymphocytopenia (anti-IFN γ Ab not tested)	16 mo of CBE, 7 mo of CE + CPFX, 8 mo of CB + CPFX	Improved, but died of MDS
2	66, M	17.5	Pubic bone, L2-4 vertebrae, pelvic bone, costae, and scapulae	Lymph nodes	<i>M. avium</i>	Old TB, anti-IFN γ Ab syndrome	16 mo of CRE (continuing)	Improved, still on treatment
3	71, M	24.1	L4-vertebrae	Psoas muscle	<i>M. kansasii</i>	Pneumosisilicosis, anti-IFN γ Ab syndrome	1 mo of HREZ, 9 mo of CREL (continuing)	Improved, still on treatment

Anti-IFN γ Ab, anti-interferon-gamma autoantibodies; H, Isoniazid; R, Rifampin; B, Rifabutin; E, Ethambutol; Z, Pyrazinamide; C, Clarithromycin; L, Levofloxacin; CPFX, Ciprofloxacin; MDS, myelodysplastic syndrome.

positive for IFN γ . Neither *M. tuberculosis* nor NTM was detected from his sputum. As *M. kansasii* was detected from the right psoas abscess, we changed his drug therapy to clarithromycin, levofloxacin, rifampin, and ethambutol. He continues to receive the new 4-drug therapy. Isoniazid was avoided owing to its hepatotoxicity. His psoas abscess shrank within 8 months after initiation of the new 4-drug therapy with no deterioration of the bone lesions.

The epidemiology of NTM bone infection is not well reported in Japan. For pulmonary NTM infections, however, the most frequent pathogen in Japan is *M. avium* complex (MAC) (70%) followed by *M. kansasii* (24%) and others (2%) including rapid growers such as *M. fortuitum* and *M. abscessus* (3).

In a literature review, we found 31 case reports, mainly in the United States and Europe, of NTM vertebral osteomyelitis between 1965 and 2003 (4 of which were HIV-positive) (1). The most frequent pathogen was MAC, whereas *M. kansasii* was the fifth most common. In a single-institute retrospective review in Taiwan (2), there were 5 cases of HIV-negative bone infections due to NTM between 1997 and 2004: 3 caused by MAC and 1 each by *M. kansasii* and *M. abscessus*.

All 3 patients in our study had at least 1 immunodeficient condition that might have led to the NTM infections: idiopathic ICL, anti-IFN γ Ab syndrome, and pneumosisilicosis.

In a review of the literature between 1989 and 2012 (4), of 258 patients diagnosed with ICL, 44 (17%) had mycobacterial infections. Disseminated MAC was observed in 8 of those patients. In another cohort study between 1992 and 2006 (5), 37 patients had been diagnosed with ICL, and 2 of them had disseminated MAC infections. There was no reported case of disseminated *M. kansasii* (4,5). In case 1, ICL might have contributed to MAC dissemination leading to a bone infection.

Among disseminated NTM infections, 81–100% tested positive for anti-IFN γ Ab (6,7). Among NTM infections that were positive for anti-IFN γ Ab, the most common pathogen was *M. abscessus*, whereas *M. avium* and *M. kansasii* were both the second most common in 1 study (6). MAC and the rapid growers were the most common followed by *M. kansasii* in another study (7). Among NTM infections that were positive for anti-IFN γ Ab, 20–81% of the patients had bone/joint infections (6,8). Anti-IFN γ Ab contributes to both MAC and

M. kansasii bone infections.

Pneumosisilicosis is another predisposing factor of both pulmonary and extrapulmonary TB infections and pulmonary NTM infections (9). The odds ratios of TB and NTM lung infections in pneumosisilicosis are 5.0 and 4.9, respectively (10). However, the association between extrapulmonary NTM and pneumosisilicosis has not been asserted to the best of our knowledge. Pneumosisilicosis may have been a predisposing factor of NTM bone infection in our patient 3.

In conclusion, both ICL and anti-IFN γ Ab syndrome are major predisposing factors to non-HIV osteomyelitis. Pneumosisilicosis, on the other hand, may contribute to NTM pulmonary infections, but further studies should be conducted to prove or disprove the correlation with the extrapulmonary infections.

Conflict of interest None to declare.

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