Case Report

Clarithromycin-resistant *Mycobacterium Shinjukuense* Lung Disease: Case Report and Literature Review

Makoto Hayashi*1, Satoshi Matsukura1, Toshitaka Funaki1, Daisuke Inoue1, Yuko Kazumi2, Satoshi Mitarai2, Fumio Kokubu1 and Yusuke Shikama1

Abstract: *Mycobacterium shinjukuense* is a species of non-tuberculous mycobacteria newly reported in 2010. Herein, we report on an 85-year-old woman with *M. shinjukuense* lung disease. Radiographic examinations showed consolidation with bronchiectasis, which responded transiently to clarithromycin monotherapy. After 1 year of monotherapy, the diagnosis was established and drug susceptibility testing revealed elevated minimum inhibitory concentration for clarithromycin. The patient was then treated successfully with a combination of antituberculosis drugs. The transient response to clarithromycin suggested that the *M. shinjukuense* had acquired resistance to clarithromycin. Appropriate treatment for *M. shinjukuense* lung disease has not yet been established; therefore, it is important to accumulate information from case reports.

Key words: antituberculosis drugs, bronchiectasis, consolidation, macrolide resistance, non-tuberculous mycobacteria

Introduction

*Mycobacterium shinjukuense* is a slow-growing, non-chromogenic *Mycobacterium* species that was newly reported in 20101. To date, only a few cases of *M. shinjukuense* lung disease have been reported; therefore, the clinical features of this disease and its appropriate treatment remain to be determined1-6. Herein, we report on a patient with *M. shinjukuense* lung disease who was successfully treated with a combination of antituberculosis drugs, although susceptibility testing and the clinical course suggested acquired resistance to clarithromycin.

Case report

An 85-year-old Japanese woman with a history of pulmonary tuberculosis was referred to Showa University Fujigaoka Hospital for management of sustained fever, cough, and developing consolidation with bronchiectasis on chest X-ray. In the year prior to her referral, chest X-ray had shown consolidation with bronchiectasis in the middle right lung field, and sputum examinations for acid-fast bacilli (AFB) had been negative. The patient had declined a bronchoscopy...
Makoto Hayashi, et al

for diagnosis, and had been administered clarithromycin for a diagnosis of “bronchiectasis” with no specific etiology. During the first 6 months of clarithromycin monotherapy, the consolidation on chest X-ray decreased. However, over the next 6 months, consolidation started to recur. At the time of presentation to Showa University Fujigaoka Hospital, the patient’s height was 158 cm, her body weight was 30.0 kg, and her body temperature was 38.2°C; other vital signs were normal. The complete blood cell count and routine chemical laboratory data were all within the normal range, except for elevation of C-reactive protein to 4.31 mg/dl and a positive result on an interferon-γ release assay (QuantiFERON TB-3G, Japan BCG, Tokyo, Japan.) Repeated sputum examinations for AFB were negative on smear and culture. Chest X-ray and computed tomography (CT) revealed consolidation surrounding bronchiectasis in the right middle lung field, and old tuberculosis in the left lung and pleura (Fig. 1). To establish a diagnosis, bronchial lavage was performed from the right B3a via bronchoscopy. A smear for AFB of the specimen was positive for Ziehl–Neelsen staining, but no other bacteria were detected. Thus, we thought the patient’s tuberculosis had recurred, and the clarithromycin was replaced with a combination of antituberculosis drugs, namely isoniazid, ethambutol, and rifampicin. The patient’s symptoms were resolved, but real-time polymerase chain reaction of bronchial washings for M. tuberculosis, M. avium, and M. intracellulare, and DNA–DNA hybridization of the colonies cultured on egg-based solid media could not identify the mycobacterial species. However, analysis of the DNA-directed RNA polymerase subunit beta (rpoB) and 16S rRNA gene sequences detected M. shinjukuense. Drug susceptibility testing by the proportion method showed sensitivity to 0.2 µg/ml isoniazid, 2.5 µg/ml ethambutol, 40 µg/ml rifampicin, 10 µg/ml streptomycin, 20 µg/ml kanamycin, 20 µg/ml enviomyicin, 20 µg/ml ethionamide, 30 µg/ml cycloserine, and 1 µg/ml levofoxacin, and resistance towards 0.5 µg/ml para-aminosalicylic acid. The minimum inhibi-
Vitory concentrations (MICs) determined using the broth microdilution method were as follows: clarithromycin $\geq 32 \mu g/ml$, isoniazid $0.5 \mu g/ml$, ethambutol $1 \mu g/ml$, rifampicin $\leq 0.03 \mu g/ml$, kanamycin $2 \mu g/ml$, rifabutin $\leq 0.004 \mu g/ml$, and levofloxacin $\leq 0.25 \mu g/ml$. Given these findings, it was unlikely that the symptoms were being caused by some other pathogen, so the patient was finally diagnosed as having *M. shinjukuense* lung disease based on the diagnostic criteria for non-tuberculous mycobacteria (NTM) from the American Thoracic Society (ATS) / Infectious Diseases Society of America (IDSA)\(^8\). During the course of treatment, the consolidation shown on radiographic examinations improved, and no AFB were cultured from repeated sputum cultures. The same treatment with the combination of antituberculosis drugs was continued until the patient died of pneumonia 14 months after diagnosis.

**Discussion**

*M. shinjukuense*, a slow-growing NTM first isolated from respiratory specimens of seven Japanese patients in 2004, was identified in 2010 by Saito *et al*\(^1\) on the basis of *16S* rRNA gene, *16S–23S* internal transcribed spacer (ITS), heat shock protein 65 (*hsp65*), and *rpoB* sequencing. Because the species has base sequences of *16S* rRNA with high homology for *M. tuberculosis*, the TRCRapid M.TB assay (Tosoh Bioscience, Tokyo, Japan) and Amplified MTD Test (Hologic, Bedford, MA, USA) falsely identify this NTM as *M. tuberculosis* complex\(^9\). Although *M. shinjukuense* causes pulmonary infectious disease, the clinical features, including patient characteristics, radiographic features, drug sensitivities, and treatment responses, are not well known. Saito *et al*. also reported that two of their seven patients fulfilled the ATS / IDSA diagnostic criteria for NTM\(^1\). In addition, to date another 11 cases of *M. shinjukuense* lung disease have been reported in the literature\(^2-7\). These patients, who fulfilled the diagnostic criteria of NTM lung disease, consisted of nine middle-aged or elderly women (aged 56–83 years) and four men (aged 58–93 years) who had no history of immunosuppressive diseases. However, in some cases, the patients had predisposing respiratory diseases: old tuberculosis in four patients, pulmonary *M. avium* complex lung disease in one patient, and pulmonary emphysema in one patient. Radiographic examinations showed bronchiectasis and nodules in nine patients, cavitary lesions in five patients, and consolidation in two patients\(^1-7\). In summary, *M. shinjukuense* lung disease primarily occurs in elderly women, with or without a predisposing pulmonary condition, and the radiographic feature is that of bronchiectasis with nodules, often accompanied by cavities or consolidation. The findings in the present patient were consistent with these clinical and radiographic features. Drug susceptibility testing has been described for the nine reported patients. The MICs for antituberculosis drugs and clarithromycin were determined for eight patients, and were generally low for antituberculosis drugs and clarithromycin\(^2, 3, 7\). The proportion method was used to determine susceptibility in one case, revealing susceptibility for $0.2 \mu g/ml$ isoniazid, $2.5 \mu g/ml$ ethambutol, and $40 \mu g/ml$ rifampicin\(^5\). Ten patients received antibiotic treatment, and nine were successfully treated with combinations containing rifampicin, ethambutol, and isoniazid or clarithromycin\(^2-5, 7\). One patient was treated with erythromycin monotherapy, and although this patient’s lung disease was temporarily improved, it did recur. According to these reports and the present case, *M.*
shinjukuense shows sensitivity for antituberculosis drugs and clarithromycin, and the lung disease responds to treatment regimens consisting of combinations of these drugs. The treatment effect of macrolide monotherapy seems to be transient. However, unlike previous reports\textsuperscript{2,3}, the MIC for clarithromycin was $\geq 32 \mu g/ ml$ when the diagnosis was established in our patient. Unfortunately, we could not detect \textit{M. shinjukuense} before clarithromycin monotherapy. It is possible that another bacterial infection was present before clarithromycin monotherapy and that after clarithromycin monotherapy persistent, clarithromycin-resistant \textit{M. shinjukuense} was detected by bronchoscopy. However, the series of radiographs and the patient’s clinical background showed features of \textit{M. shinjukuense} lung disease that have been reported previously. Therefore, we believe our patient had \textit{M. shinjukuense} lung disease before starting on clarithromycin monotherapy. In addition, we are not able to verify whether the resistance to clarithromycin was natural or acquired. However, the patient’s chest X-ray showed a transient improvement and then worsening after starting clarithromycin, so we presume this monotherapy resulted in acquired resistance to clarithromycin, similar to that occurring in other NTM species\textsuperscript{8}). To our knowledge, this case report is the first of clarithromycin-resistant \textit{M. shinjukuense}, and there is presently no information on macrolide monotherapy for \textit{M. shinjukuense} lung disease. However, clarithromycin monotherapy should be avoided, similar to that for other species of NTM, because of the likelihood of acquired resistance and an insufficient clinical response.

In summary, we report herein on our experience with an elderly woman with \textit{M. shinjukuense} lung disease. Radiographic examinations showed consolidation and bronchiectasis in the middle lung field, and the disease responded to combination therapy with antituberculosis drugs including isoniazid, ethambutol, and rifampicin. Clarithromycin monotherapy before diagnosis had an unsatisfactory treatment effect and resulted in apparent acquired resistance. Appropriate treatment for \textit{M. shinjukuense} lung disease is not yet established; therefore, it is important to accumulate more information from more cases.

**Acknowledgement**

The authors are grateful to their colleagues in the Department of Respiratory Medicine and Clinical Laboratory, Showa University Fujigaoka Hospital, for their valuable support.

**Conflict of interest disclosure**

None of the authors has any conflicts of interest to declare.

**References**


[Received September 12, 2016 : Accepted October 6, 2016]