Two cases of Mycobacterium shinjukuense pulmonary disease with a long-term response to treatment with clarithromycin, rifampicin, and ethambutol

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Abstract

Mycobacterium shinjukuense is a nontuberculous mycobacterium and its standard treatment has not been established. We herein report two cases of M. shinjukuense pulmonary disease. These two cases were treated with clarithromycin, rifampicin, and ethambutol, and the computed tomography findings improved. There have been a few reports of M. shinjukuense pulmonary disease, and many cases have been treated with the anti-tuberculosis drugs isoniazid, rifampicin, and ethambutol. Reports of multiple cases of M. shinjukuense pulmonary disease treated with clarithromycin, rifampicin, and ethambutol are valuable, and suggest that this regimen may be a new treatment option.

Introduction

Mycobacterium shinjukuense (M. shinjukuense) is a nontuberculous mycobacterium with 16S rRNA, rpo B, and hsp65 gene sequencing [1]. In the Runyon classification, it belongs to group III, similar to the Mycobacterium avium-intracellulare complex (MAC) [1]. However, while it is a nontuberculous mycobacterium, the TRC Rapid® M. TB assay (Tosoh, Tokyo, Japan) and the DNA probe “FR”-MTD® (FUJIREBIO Inc., Tokyo, Japan), which are rapid diagnostic methods for Mycobacterium tuberculosis (Tb), can show false-positive results [2-5]. This is because the nucleotide sequence of the 16S rRNA gene in M. shinjukuense exhibits high homology to its Tb complex counterpart (97.8% homology with the Tb ATCC27294 strain) [1].

M. shinjukuense was first isolated in Shinjuku Ward, a central location of Tokyo, Japan, in 2004 and it was first reported in 2011 by Saito et al. [1]. 23 cases of M. shinjukuense infection have been reported in Japan and Korea thus far [1-11]. However, the pathogenicity and prognosis are unknown, and there is no established treatment.

Case Presentation

Case 1: A 74-year-old woman with a history of osteoporosis visited her primary care doctor because of a cough and bloody sputum since the end of June 20XX. She was prescribed a cough suppressant, levofloxacin, and carbazocrom sodium sulfonate, and her symptoms improved after approximately two weeks. However, a chest radiograph taken after her symptoms improved showed an enhanced infiltrative shadow in the right lower lung field. For this reason, the patient was referred to our hospital in early July 20XX.

There were no abnormalities in her vital signs or physical findings at the time of the first visit. Blood tests showed no abnormalities in blood counts or biochemical tests. T-SPOT. Tb was positive, but anti-MAC antibody was negative (Table 1). Sputum smear microscopy for acid-fast bacilli was positive at the initial visit. Sputum polymerase chain reaction (PCR) for Tb (COBAS® TaqMan® MTB) and MAC (COBAS® TaqMan® 48) were both negative (Table 2). Chest radiography showed an infiltrating shadow with air bronchogram and bronchiectasis in the right middle and lower lung fields (Figure 1). Chest computed tomography (CT) showed bronchiectasis mainly in the right middle lobe and a cavity in the right S6 region (Figure 2).

Because nontuberculous mycobacterial lung disease was suspected by CT, bronchial lavage was performed in the right middle lobe in late July 20XX. Smear microscopy of bronchial lavage fluid for acid-fast bacilli was negative, PCR of bronchial lavage for Tb (COBAS® TaqMan® MTB) and MAC (COBAS® TaqMan® 48) were both negative. 

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negative, and *M. shinjukuense* was isolated in sputum collected at the initial examination and bronchial lavage fluid after six weeks’ incubation by administering mass spectrometry (MALDI-TOF MS) (Table 2), resulting in the diagnosis of *M. shinjukuense* pulmonary disease.

The patient was followed up without treatment after the diagnosis. However, because chest CT showed worsening of the shadows (Figure 3a, 3b), treatment with clarithromycin (CAM), rifampicin (RFP), and ethambutol (EB) was started in mid-January 20XX+1. After the initiation of treatment, the shadows on chest CT improved (Figure 3c, 3d), and respiratory symptoms also disappeared. Nevertheless, treatment was terminated in mid-January 20XX+2, as vision loss appeared with the administration of EB. The patient’s visual acuity improved after the end of treatment for *M. shinjukuense*. Although, after the start of treatment, the amount of sputum decreased and sputum examination could not be performed, sputum acid-fast bacilli culture in July 20XX+2 that she managed to submit was negative. The CT findings in March 20XX+4 remained stable with no recurrence or progression (Figure 3e, 3f).

Case 2: An 82-year-old woman with no prior medical history visited her primary care doctor in early August 20XX for a fever. She was diagnosed with COVID-19 infection by COVID-19 antigen test and was referred to our department for close examination and treatment because of hypoxemia.

The patient had a fever of 38°C and SpO2 was 86% in room air and there were no abnormalities in her physical findings at the time of the first visit. Blood tests showed no abnormalities in blood counts, but biochemical tests showed mild elevation of CRP. T-SPOT. Tb and anti-MAC antibody was negative (Table 3). Sputum smear microscopy for acid-fast bacilli performed at the initial visit was negative. Sputum polymerase chain reaction (PCR) for Tb (COBAS® TaqMan® MTB) and MAC (COBAS® TaqMan® 48) were both negative (Table 4). Chest radiography showed an infiltrating shadow in the right upper and lower lung fields (Figure 4). Chest computed tomography (CT) showed an infiltrative shadow and bronchiectasis in the right upper and middle lobes, and lobular central granular shadows in both lower lobes (Figure 5).

As nontuberculous mycobacterial lung disease was suspected by CT findings, bronchial lavage was performed in the right middle lobe in late November 20XX. Smear microscopy of bronchial lavage fluid for acid-fast bacilli was negative, PCR of bronchial lavage for Tb (COBAS® TaqMan® MTB) and MAC (COBAS® TaqMan® 48) were both negative, and *M. shinjukuense* was isolated in bronchial lavage fluid after eight weeks’ incubation by administering mass spectrometry (MALDI-TOF MS) (Table 4), resulting in the diagnosis of *M. shinjukuense* pulmonary disease.

For about six months after diagnosis, the patient was followed up without treatment. However, because the structural destruction of the lungs had already progressed and CT showed no improvement in the shadows (Figure 6a), treatment with CMA, RFP, and EB was initiated in early February 20XX+1. The lobular central granular shadows in both lower lobes have been improving since the start of treatment (Figure 6b), and at the time of writing this paper, treatment has been ongoing for 10 months and will continue in the future.

Discussion

As *M. shinjukuense* is a relatively recently identified species, evidence of its biology, etiology, and clinical behavior has not accumulated sufficiently. Only 25 cases of *M. shinjukuense* pulmonary disease, including these cases at the time of writing, had been reported by December 2023 (Table 5) [1-11]. Among them, 24 cases were reported from Japan and 1 from Korea. The median age of the patients was 73 years old, with 5 males and 20 females encountered. Among the 18 cases for which CT images were available, 10 cases showed nodules and bronchiectasis patterns, 1 case showed a fibrocavitary pattern, and 7 cases showed fibrocavitary plus nodules and bronchiectasis patterns. Compared to MAC pulmonary disease, there are no significant differences with respect to the age, sex ratio, or imaging findings [12].

*M. shinjukuense* has been reported to have good susceptibility to isoniazid (INH), RFP, EB, and CAM *in vitro* [2-4, 6]. However, in the case of nontuberculous mycobacterium, the results of the drug susceptibility test should be interpreted carefully, as the susceptibility *in vitro* and *in vivo* may not be consistent [13]. Although no standard chemotherapy for *M. shinjukuense* has been established, as considering past treated cases without our cases, 9 of 15 cases were treated with INH, RFP, and EB (including 1 case in which the initial
Regimen was INH + RFP + EB + pyrazinamide [PZA] and changed to CAM + RFP + EB during the course of treatment, 1 case that changed to EM during the course of treatment, 1 case that switched from INH + RFP + EB + PZA, and 1 case that switched from CAM, 5 cases were treated with CAM + RFP + EB (including 1 case that switched from INH + RFP + EB + PZA treatment, and 2 cases that switched from CAM + RFP + EB + kanamycin), 2 cases were treated with ethionamide (EM) (including 1 case that switched from INH + RFP + EB to EM), and 1 case in which the initial regimen was INH + RFP + CAM and changed to RFP + CAM + levofloxacin (Table 3) [2-11]. Many patients were treated with the anti-Tb regimen, suggesting that they might have been diagnosed with pulmonary Tb and initiated treatment due to a false-positive rapid tuberculosis diagnosis [3, 4]. Based on previous reports, both treatment regimens were considered effective against *M. shinjukuense* (Table 5).

There have been 5 cases of *M. shinjukuense* treated with CAM + RFP + EB [2, 4, 10, 11], and including the 2 cases in this report, there have been 7 cases. Although there have been many reports of *M. shinjukuense* treated with anti-tuberculosis drugs as mentioned above, recently, some cases of *M. shinjukuense* that responded to treatment with CAM, RFP, and EB has also been reported [2, 4, 10, 11]. Case 1 in this report has completed 12 months of treatment and has remained stable without treatment for 26 months. This case has the longest known treatment course of *M. shinjukuense* lung disease cases reported to date. In most of the reports to date, *M. shinjukuense* cases treated with CAM, RFP, and EB have been reported in more detail. And in many cases, as in Case 1 of the present case, the treatment course of the case is known for a relatively long time compared to cases treated with anti-Tb drugs (Table 5).

There are two limitations in our case report. One is that we were unable to submit drug susceptibility tests for *M. shinjukuense* in both cases. Although *in vitro* drug sensitivity of nontuberculous mycobacterium is not necessarily reflective of *in vivo* conditions, we believe it provides important information for determining treatment strategies. Another is that nontuberculous mycobacterium may heal spontaneously without treatment, so it may not be possible to conclude that drug treatment has been successful.

**Conclusions**

Although there are no data directly comparing the efficacy of anti-Tb drugs with CAM, RFP, and EB against *M. shinjukuense*, considering previous case reports, CAM + RFP + EB may be a valid option for treatment of *M. shinjukuense*. The standard treatment for *M. shinjukuense* has not yet been established, and the accumulation of further cases is desired.

**Appendices**

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<th>TABLE 1: The serum test results at the initial visit to our department in Case 1</th>
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<th>TABLE 3: The serum test results at the initial visit to our department in Case 2</th>
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### TABLE 4: Acid-fast bacteriology test in Case 2

Acid-fast bacteriology test in Case 2.

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### TABLE 5: Case List and Clinical Features of M. shinjukuense pulmonary infection

Case List and Clinical Features of *M. shinjukuense* pulmonary infection.

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Chest radiography at the initial visit to our hospital showed an infiltrative shadow with air bronchogram and bronchiectasis in the right middle and lower lung fields.
FIGURE 2: Chest computed tomography (CT) at initial visit in Case 1

CT in early July 20XX (at the initial visit) to our hospital showed a cavity in the right S6 region (a) and bronchiectasis mainly in the right middle lobe (b).
FIGURE 3: Progress of CT in Case 1
(a, b) CT in mid-January 20XX+1 showed an enlarged cavity and worsening infiltrative shadow. (c, d) CT in mid-January 20XX+2 showed reduction in the cavity and improvement in the infiltrative shadow. (e, f) CT in mid-March 20XX+4 did not show re-expansion of the cavity or reaggravation of the infiltrative shadow.
FIGURE 4: Chest radiography at the initial visit in Case 2

Chest radiography at the initial visit to our hospital showed an infiltrating shadow in the right upper and lower lung fields.
FIGURE 5: CT at initial visit in Case 2

CT showed an infiltrative shadow and bronchiectasis in the right upper (a) and middle lobes, and lobular central granular shadows in both lower lobes (b).
FIGURE 6: Progress of CT in Case 2

(a) CT in mid-February 20XX+1 showed no improvement of lobular central granular shadows in both lower lobes.
(b) CT in early October 20XX+1 showed improvement of lobular central granular shadows in both lower lobes.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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1. Saito H, Iwamoto T, Ohkusu K, et al.: Mycobacterium shinjukuense sp. nov., a slowly growing, non-


