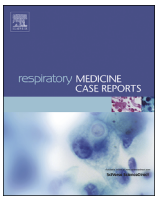
Respiratory Medicine Case Reports 45 (2023) 101894

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr



Case Report

Mycobacterium shinjukuense infection successfully treated with clarithromycin, rifampicin, and ethambutol

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ARTICLE INFO

Keywords:
Mycobacterium shinjukuense
Nontuberculous mycobacterium
Mycobacterium tuberculosis
Clarithromycin

ABSTRACT

We present the case of a 59-year-old woman diagnosed with *Mycobacterium shinjukuense* infection using mass spectrometry of bronchioalveolar lavage fluid. We initiated treatment with clarithromycin, rifampicin, and ethambutol based on the results of drug susceptibility testing, which improved lung opacities. Most previous cases were treated with the standard regimen for *Mycobacterium tuberculosis*. However, our regimen may provide a therapeutic option for this rare nontuberculous *Mycobacterium* infection.

1. Introduction

Nontuberculous mycobacteria (NTM) can cause several lung diseases. In 2011, Saito et al. [1] identified a new strain of NTM, called *Mycobacterium shinjukuense*, in Japan. To our knowledge, 16 cases of *M. shinjukuense* have been documented previously, with the majority reported being in Japan [1–10]. Clinical and pathological characteristics, as well as the optimal treatment, of *M. shinjukuense* are unclear. Most previous cases of *M. shinjukuense* were misdiagnosed as *M. tuberculosis* and primarily treated with the standard therapy therefor.

We report a case of *M. shinjukuense* that was effectively treated with drugs commonly used for treating *Mycobacterium avium complex,* including clarithromycin (CLA), rifampicin (RFP), and ethambutol (EB). The drug susceptibility testing indicated that the *M. shinjukuense* isolate was sensitive to these drugs.

2. Case presentation

A 59-year-old woman with right breast cancer presented to our department with suspicion of NTM infection based on abnormal lung opacities that had been detected 2 years ago. Because she had no respiratory symptoms and the opacities remained stable, she was initially monitored without medication. She underwent right breast resection, followed by treatment with paclitaxel and human epidermal growth factor receptor 2 monoclonal antibodies for 1 year, as well as radiation therapy (50 Gy) to the right chest. However,

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https://doi.org/10.1016/j.rmcr.2023.101894
Received 14 May 2023; Received in revised form 15 June 2023; Accepted 7 July 2023
Available online 8 July 2023

during chemotherapy for breast cancer, the lung opacities progressed and a cavitary mass was detected (Figs. 1 and 2). Therefore, she underwent further examinations.

Upon examination, she was asymptomatic and had normal vital signs. Staining and culture of three sputum samples, including for acid-fast bacteria, did not reveal evidence of bacterial infection. Additionally, interferon-gamma release assay (T-SPOTR; BML, Tokyo, Japan) yielded negative results. Bronchioalveolar lavage fluid via bronchoscopy and sputum samples were collected. Following a 6-week incubation period in a liquid medium, acid-fast staining and culture of the bronchioalveolar lavage fluid showed bacterial growth. However, polymerase chain reaction testing of the samples showed no growth of *M. tuberculosis*, *M. avium*, or *Mycobacterium intracellulae*. As a result, *M. shinjukuense* was diagnosed by mass spectrometry (MALDI-Biotyper, Bruker Daltonics, Bremen, Germany) [11,12].

Based on the worsening lung opacities, treatment was initiated for our patient based on 10 previous reports of 16 cases of *M. shinjukuense* (Table 1). Among these cases, eight were treated with anti-tuberculous drugs, one with erythromycin, one with CLA followed by anti-tuberculous drugs, one with RFP, levofloxacin, and CLA, and three with RFP, EB, and CLA.

In our patient, the minimum inhibitory concentrations (MICs) of CLA, RFP, EB (BrothMIC NTM, Kyokuto Pharmaceutical Industrial Co., Ltd., Tokyo, Japan), and INH (Vit spectrum-SR, Kyokuto Pharmaceutical Industrial Co., Ltd.) using the broth microdilution method were <0.03, <0.03, <1, and <0.02 μg/mL, respectively. In our study, the MIC of CLA was similar to that of the cases 5 and 14previously reported (Table 1) (3, 9). We treated our patient with RFP, EB, and CLA instead of RFP, EB, and INH because of the more common side effects with INH than CLA. The initial treatment included 600 mg/day of CLA, 500 mg/day of EB, and 300 mg/day of RFP. The patient weighed 48 kg, and no side effects were observed during the first month of treatment. Therefore, we increased the

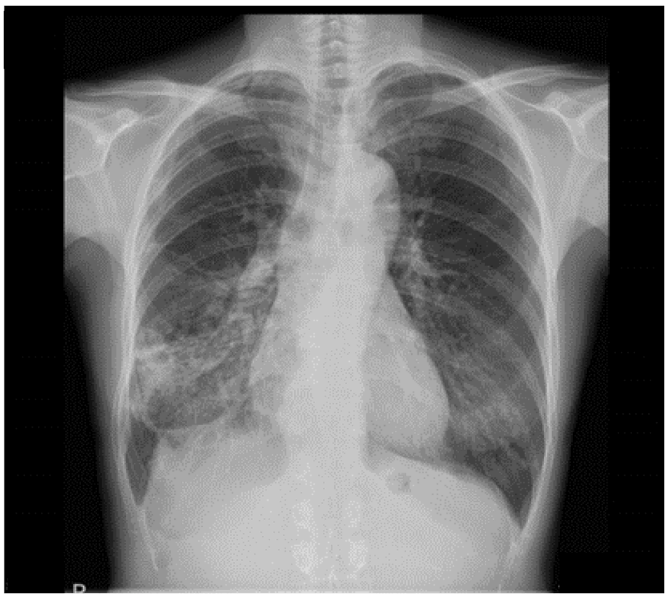

Fig. 1. The pre-treatment chest radiograph shows infiltrations in both lower lung fields.

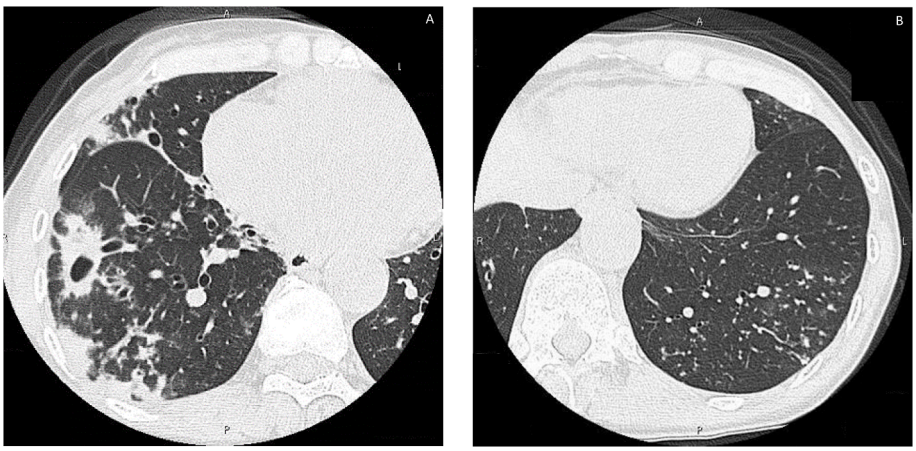

Fig. 2. Chest CT shows fibrocavitary disease in the right lower lobe (A) and nodules in the left lower lobe (B).

Table 1
Clinical features of 14 cases of *M. shinjukuense* disease.

case	age	sex	underlying lung disease	underlying general disease	imaging findings	drug regimen	term of therapy	outcome	reference
1	59	F	none	brest cancer	fibrocavity, nodules, bronchiectasis	RFP,EB,CLA	24 months ND	improved	our case
2	73	F	ND	ND	infiltrates, nodules, broncieCtasis	INH, RFP,EB	ND	improved	5
3	75	M	old pulmonary tuberculisus	diabetes mellitus	fibrocavitary	INH, RFP,EB, PZA→INH, RFP,EB	12 months	improved	2
4	93	M	old pulmonary tuberculisus	chronic heart failure	fibrocavitary, nodules, bronchiectasis	INH, RFP,EB→EM	ND	no cahnge	2
5	82	M	old pulmonary tuberculisus	prostate cancer	fibrocavitary, nodules, bronchiectasis	INH, RFP,EB	ND	improved	2
6	83	F	pulmonary emphysema	hypertension	nodules, bronchiectasis	INH, RFP,EB,PZA→RFP, EB, CLA	ND	improved	2
7	72	F	pulmonary M.Avium complex disease suspected	hypertension, dyslipidemia	nodules, bronchiectasis	INH, RFP,EB	ND	improved	2
8	57	F	none	goiter	nodules, bronchiectasis	EM	ND	improved, but recurred	2
9	64	F	none	none	nodules, bronchiectasis	RFP,EB,CLA	six months	improved	3
10	80	F	none	none	nodules, bronchiectasis	INH, RFP,EB	ND	improved	4
11	73	F	ND	ND	cavity lesion	ND	ND	ND	1
12	56	F	history of TB	none	nodules, bronchiectasis, atelectasis	ND	ND	ND	6
13	62	M	none	hypertension	nodules, bronchiectasis	RFP, EB, CLA	30 months	improved	9
14	68	F	none	hypertension hyperlipidemia	infiltrates, bronchiectasis	RFP, EB, CLA	ND	improved	9
15	72	F	none	PMR	fibrocavitary, nodules, bronchiectasis	RFP, LVFX, CLA	18 months	improved	10
16	85	F	history of TB	ND	consolidation surrounding bronchisctasis	CLA	six months	improved, but recurred	7
						→INH, RFP, EB	14 months	improved	
17	66	F	ND	ND	micro nodules, infiltration, bronchiectasis	INH, RFP, EB, PZA	12 months	improved	8

ND, not described; RFP, rifampicin; EB, ethambutol; CLA, clarithromycin; INH, isoniazid; PZA, pyrazinamide; EM, erythromycin, levofloxacin; LVFX, PMR; polymyalgia rheumatoid arthritis.

dose of CLA to 800 mg/day and continued EB and RFP at the same doses. After 6 months of treatment initiation, the sputum culture was negative for acid-fast bacilli. Due to the presence of a cavitary lesion and the absence of an established treatment duration for this regimen, we continued treatment for 2 years, similar to previous cases of *M. avium* complex, to ensure mycobacterial elimination. After 2 years of treatment, the nodules and fibrocavitary disease significantly improved (Fig. 3).

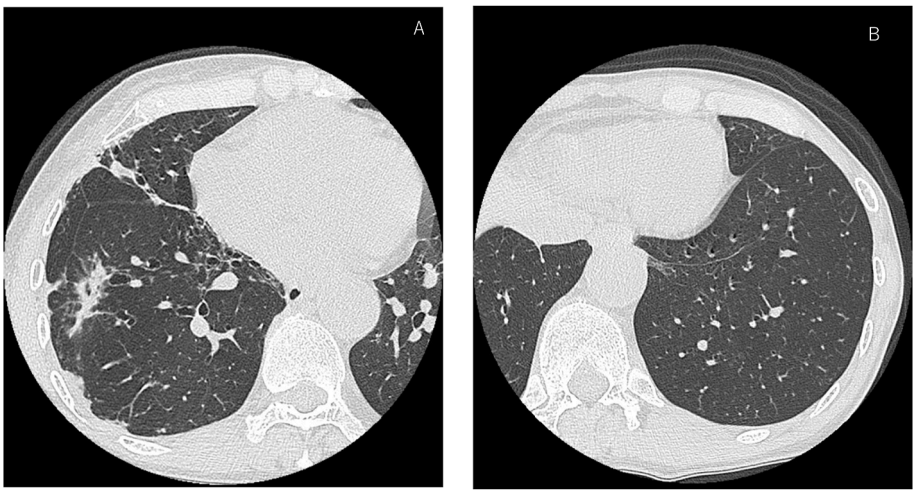

Fig. 3. Chest CT after 24 months of treatment shows that the fibrocavitary disease and nodules had improved following treatment with clarithromycin, rifampicin, and ethambutol.

3. Discussion

M. shinjukuense is a rare type of NTM that was first reported in Japan in 2011 [1]. It is a slow-growing organism that takes approximately 2–3 weeks to grow. To our knowledge, 17 cases of *M. shinjukuense* have been reported, including our patient (Table 1). Most cases were reported from Japan and a single case was reported from Korea in 2015 [6].

M. shinjukuense may be misdiagnosed as *M. tuberculosis*, as the TRCRapid M.TB rRNA identification kit (Tosoh Bioscience, Tokyo, Japan) is often unable to differentiate between *M. tuberculosis* and other pathogens, including *M. shinjukuense* and *M. marium* [2,4]. Consequently, several cases of *M. shinjukuense* were misdiagnosed as *M. tuberculosis* and treated with RFP, INH, EB, and pyrazinamide. In our case, we conducted a tuberculosis-specific IFNγ assay and polymerase chain reaction of the bronchioalveolar lavage fluid and sputum samples to exclude a diagnosis of *M. tuberculosis.* Therefore, awareness of the characteristics of TRC rapid M.TB is important for differentiating *M. shinjukuense* from *M. tuberculosis*; a definitive diagnosis can be made using mass spectrometry and gene sequencing. We used matrix-assisted laser desorption ionization-time of flight mass spectrometry to diagnose our patient, which is the preferred modality for identifying NTM species due to its accuracy, speed, cost-effectiveness, and simplicity (11, 12).

The optimal treatment of *M. shinjukuense* is unclear. However, eight cases showed improvement following treatment with INH, RFP, and EB [2,4]. In one case, improvement was observed following treatment with CLA, RFP, and EB; the MIC of CLA for *M. shinjukuense* in our case, and the cases 4 and 14 were 0.03 μg/mL, and that in the case 13 was 0.06 μg/mL (Table 1) [3,9]. Two cases received macrolide monotherapy: one received erythromycin [2] and the other received CLA [7]. Although both cases initially showed improvement, recurrence was subsequently observed. Therefore, macrolide monotherapy may induce drug resistance in *M. shinjukuense*. Based on the effectiveness of CLA, EB, and RFP against *M. shinjukuense*, a low MIC for CLA [3,9], and side effects of INH [13,14], we treated our patient with CLA, EB, and RFP. After 24 months of treatment, our patient improved significantly. The present and previous cases have demonstrated that *M. shinjukuense is* sensitive to CLA, RFP, and EB, suggesting that drug susceptibility testing may be important for initiating this regimen. Although only four cases of *M. shinjukuense*, including ours, have been treated with CLA, EB, and RFP, this regimen may be an effective treatment option. However, it is uncertain whether the MIC of CLA reflects its clinical effectiveness for treating NTM, including *M. shinjukuense*. Therefore, evaluating more cases treated with CLA is necessary to establish its efficacy. Additionally, the optimal treatment regimen (CLA, EB, and RFP or RFP, INH, and EB), and duration for *M. shinjukuense* remain unclear.

4. Conclusion

We report a case of *M. shinjukuense* infection successfully treated with the standard *M. avium* complex regimen, which included CLA, EB, and RFP, based on the drug susceptibility testing results. This regimen may be effective for treating *M. shinjukuense*. However, further cases are needed to clarify the clinical features and establish a standard treatment for this rare NTM.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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