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Mycobacterium Shinjukuense Pulmonary Disease Progressed to Pleuritis after Iatrogenic Pneumothorax: A Case Report

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ABSTRACT

Mycobacterium shinjukuense is a newly identified nontuberculous mycobacteria (NTM) and its gene sequence of 16S rRNA shows high homology to that of *Mycobacterium tuberculosis*. We present a case of *M. shinjukuense* pulmonary disease progressed to pleuritis after iatrogenic pneumothorax. The patient was initially diagnosed as tuberculosis based on a positive result for the 16S rRNA of an *M. tuberculosis* identification kit using scrapings from the cavitary nodule. We need to bear in mind that pneumothorax following bronchoscopy may induce NTM pleuritis and *M. shinjukuense* infection should be considered in the differential diagnosis of mycobacterial pulmonary disease with effusion.

1. Introduction

Mycobacterium shinjukuense is a newly identified nontuberculous mycobacteria (NTM) that belongs to group III of Runyon's classification the same as *M. avium-intracellulare* complex (MAC) [1]. The biochemical and immunological properties of *M. shinjukuense* differ from those of the *Mycobacterium tuberculosis* group, but the gene sequence of 16S rRNA of *M. shinjukuense* shows high homology (98.6%) to that of the *M. tuberculosis* type strain H37Rv^T [1]. This similarity results in a false-positive reaction in the 16S rRNA of an *M. tuberculosis* identification kit (TRCRapid M. TB: Tosoh Bioscience, Tokyo, Japan) that utilizes a transcription-reverse transcription concerted reaction (TRC) [1-5]. Because *M. shinjukuense* has been isolated from sputum and bronchial lavage fluid samples of only 16 patients in Japan and one patient in Korea in the English literature, information on the disease phenotype of *M. shinjukuense* pulmonary disease and its prognosis has not been sufficiently accumulated [1, 3, 4, 6-8].

NTM, especially MAC pulmonary disease, is occasionally accompanied by pleuritis or empyema, probably due to direct spread of pulmonary lesions [9, 10]. However, pleural involvement of *M. shinjukuense* has not been reported. We herein report a very rare case of *M. shinjukuense* pulmonary disease, which rapidly progressed to pleuritis after iatrogenic pneumothorax, that was successfully treated with antituberculous therapy.

2. Case Report

A 66-year-old female complained of chronic productive cough. Seven years earlier, a chest radiographic abnormality on a chest X-ray was found during a health examination. At that time, chest X-ray and CT revealed bilateral multiple micro-nodules and infiltration mainly in the right middle lobe and right lower lobe. Bronchiectasis was observed in the right middle lobe and lingula (Fig. 1A, B). The patient had been followed up with suspicion of NTM pulmonary disease, but a sputum examination had failed to detect the acid-fast bacillus. A nodular shadow with a cavity appeared at segment 6 of the right lung six years later (Fig. 1C, D) and enlarged (Fig. 1E, F). The number of micro-nodules in both lungs also increased gradually during the observation

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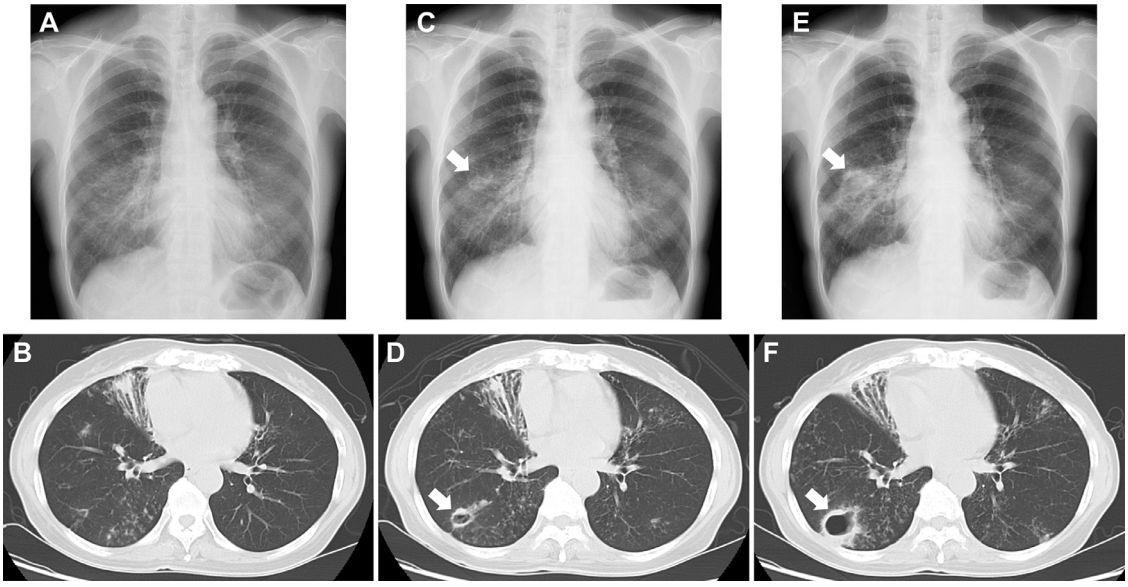

Figure 1. Time course of chest X-ray (A, C, E) and CT (B, D, F) images before treatment [(A, B): seven years ago; (C, D): one year ago; (E, F): before bronchoscopic examination]. (A, B) multiple micro-nodules and infiltration mainly in the right middle lobe and right lower lobe, and bronchiectasis in the right middle lobe and lingula (C, D) a newly-appeared nodular shadow with a cavity at segment 6 of the right lung (arrow) and increased number of micro-nodules in both lungs (E, F) enlargement of the cavitary lesion (arrow) and worsening of pulmonary lesions.

period (Fig. 1B, D, F). Next, bronchoscopic examination was performed and it revealed that scrapings from the cavitary lesion were positive with an acid-fast bacillus smear and TRCRapid M. TB. The bronchoscopy was complicated by a right-sided pneumothorax and fever appeared from that night. The next day, the patient was transferred to our hospital.

On admission, she still had the pneumothorax (Fig. 2A). Laboratory data were as follows: white blood cell count, 8670/μL (neutrophils, 77.67%; lymphocytes, 12.9%; eosinophils, 0.1%; monocytes, 9.2%; basophils, 0.2%); hemoglobin, 11.3 g/dL; platelet count, 20.1 × 104/μL; C-reactive protein, 7.73 mg/dL; serum albumin, 3.7 g/dL. Although a sputum acid-fast bacillus smear was positive (Gaffky 5), polymerase chain reaction (PCR) tests for *M. tuberculosis, M. avium* and *M. intracellulare* of the sputum were all negative. Based on the positive TRCRapid M. TB result, a diagnosis of pulmonary tuberculosis was plausible and quadruple therapy (isoniazid (INH); 300 mg/day, rifampin (RFP); 450 mg/day, ethambutol (EB); 750 mg/day, pyrazinamide; 1000 mg/day) was started. Just after the start of treatment,

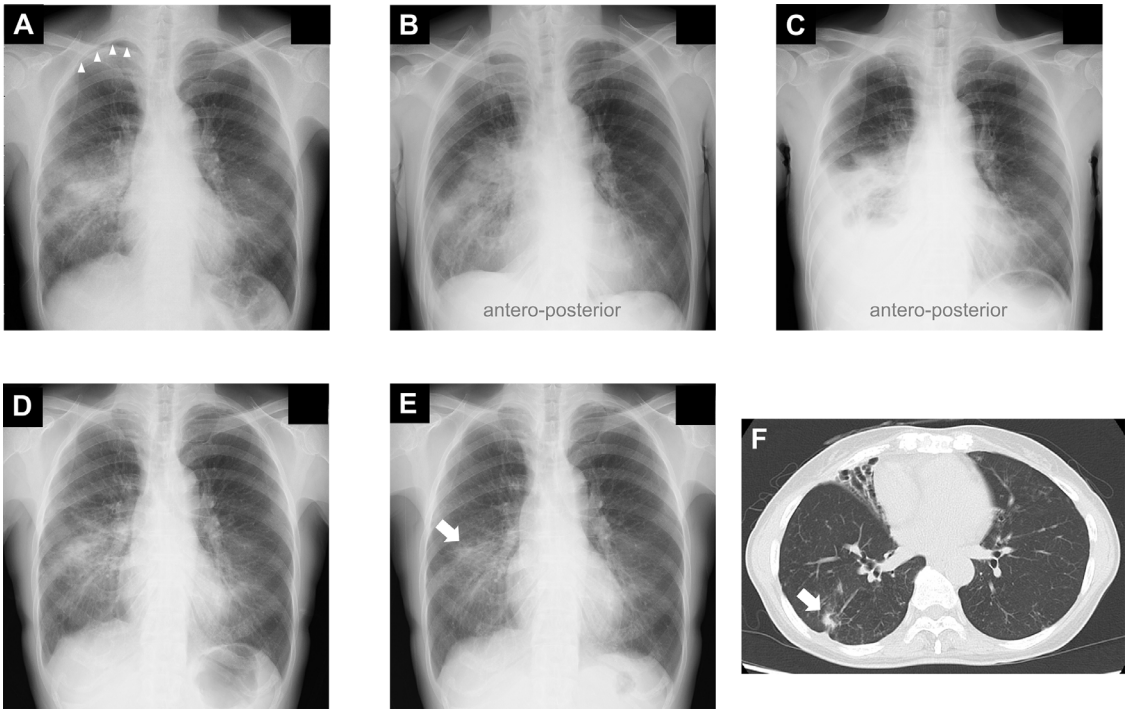

Figure 2. Time course of chest X-ray (A-E) and CT (F) images after treatment [(A): on addmision; (B): at 4 days; (C): at 2 weeks; (D): at 2 months; (E) and (F): after one year of treatment]. (A) right-sided pneumothorax (arrowhead) (B) appearance of right-sided pleural effusion (C) massive pleural effusion at the right side (D) decreased pleural effusion (E, F) reduction in the size of the cavitary lesion (arrow) and number of micro-nodules.

pleural effusion on the same side as the pneumothorax appeared (Fig. 2B) and rapidly increased (Fig. 2C). Diagnostic puncture yielded a clear yellow fluid that was consistent with lymphocytic pleurisy: total cell count, 1720/μL (lymphocytes, 85%; neutrophils, 10%; macrophages, 5%); total protein, 4.9 g/dL; LDH, 139 U/L. Adenosine deaminase (ADA) in the pleural effusion was 18.8 U/L (5.0-20.0). An acid-fast bacillus smear and PCR tests for *M. tuberculosis, M. avium* and *M. intracellulare* of the effusion were negative. Over three weeks of the treatment, the fever gradually improved and the sputum acid-fast bacillus smear became negative. Eight weeks after chemotherapy was started, pleural effusion markedly decreased (Fig. 2D). Since this strain was sensitive to all principal antituberculous drugs except pyrazinamide, we changed the quadruple therapy to treatment with INH, RFP and EB. Sputum obtained on admission proved to be positive with an acid-fast bacterial culture, but the isolate was negative on PCR tests for *M. tuberculosis, M. avium and M. intracellulare.* Moreover, the isolate could not be identified by DNA-DNA hybridization (DDH). A variable number tandem repeat (VNTR) profile did not match any strain of *M. tuberculosis,* suggesting that the TRCRapid M. TB result was false-positive. Finally, sequence analysis of 16S rRNA, *hsp*65, and the *rpoB* gene of the isolate showed high homology (100%, 100% and 99.7%, respectively) to those of *M. shinjukuense*. Chemotherapy was continued for a total period of 12 months without side effects. Sputum cultures yielded no mycobacteria during the treatment. After the chemotherapy, chest X-ray and CT showed a reduction in the size of the cavitary lesion and the number of micro-nodules (Fig. 2E, F).

3. Discussion

In our case, pleuritis probably occurred due to direct spread of pulmonary lesions through the hole(s) in the visceral pleura which appeared during the bronchoscopic examination (lung scraping). A similar case of NTM pleuritis following pneumothorax due to bronchoalveolar lavage to diagnose NTM infection was reported [11]. Some cases of pleuritis with spontaneous pneumothorax following NTM pulmonary disease were also reported [9, 10, 12]. In general, pleural involvement of NTM is considered to be less than in tuberculosis infections. The pathogenesis of tuberculous pleurisy is mainly a delayed-type hypersensitivity immunogenic reaction to a few mycobacterial antigens entering the pleural space rather than direct tissue destruction by mycobacterial proliferation [13]. On the other hand, in the case of NTM infection, it seems that desensitization works naturally and an allergic reaction is unlikely to occur because NTM habitually residues in the soil and aqueous environments [14]. However, the rapid increase in pleural effusion, no detection of *M. shinjukuense* in the effusion and low probability of desensitization due to an extremely rare disease suggest the involvement of a hypersensitivity reaction in our patient.

No standard treatment regimen for *M. shinjukuense* infection has been established, but previous reports suggested that about one year of chemotherapy with drugs such as INH, RFP and EB or clarithromycin, RFP and EB is effective [3, 4]. Generally, NTM pleuritis associated with pneumothorax is often intractable [9, 10], but fortunately antituberculous therapy was successful in this case. The good treatment response may have reflected the low amount of *M. shinjukuense* in the pleural cavity of our patient in addition to its susceptibility to antituberculous drugs.

The positive TRCRapid M. TB result initially seemed to be reliable, since the newly appeared cavitary lesion at segment 6 of the right lung in our patient was not inconsistent with pulmonary tuberculosis secondary to preceding NTM pulmonary disease. Moreover, progression to pleuritis also supported the diagnosis. However, the subsequent examinations revealed that the TRCRapid M. TB result was false-positive. TRC is an isothermal mRNA amplification technique, that enables rapid detection of the target RNA [5]. In the detection of mycobacterium tuberculosis, the TRCRapid M. TB test has been reported to be more sensitive than the PCR method [15], but false positives have been reported for some mycobacterial species [2]. Even for TRCRapid M. TB-positive cases, identification of the strain by sequence analysis is necessary when subsequent examinations are not suggestive of tuberculosis infection.

One limitation of this case report is the lack of confirmatory assessment of lymphocytic pleurisy. Mycobacteria were not detected in the pleural effusion and the pleural effusion ADA level was found to be in the normal range. However, pleural biopsy could not be performed as the patient refused. Furthermore, the T lymphocyte subpopulation and cytokine levels in the pleural effusion were not evaluated. Detailed analysis of pleural effusions and pleural tissues in patients with NTM pleuritis represents a good opportunity to compare the human immune response to NTM infection at sites of disease activity with tuberculosis infection.

4. Conclusions

Although bronchoscopic examination is widely used for the definitive diagnosis of NTM pulmonary disease, we need to bear in mind that pneumothorax following bronchoscopy may induce NTM pleuritis. Our case indicated that *M. shinjukuense* could also be a pathogenic bacterium for pleurisy and *M. shinjukuense* infection should be considered in the differential diagnosis of mycobacterial pulmonary disease with effusion. The accumulation of *M. shinjukuense* cases, including those outside Japan, is necessary to improve the management of this rare disease.

Availability of data and materials

All data supporting our findings is contained within the manuscript.

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Authors' contributions

T.T. drafted the initial manuscript. T.S. edited and submitted the manuscript. N.H. and S.I. were involved in diagnosing and treating the patient. Y.M. and S.M. performed molecular genetic studies. F.O. was the attending physician throughout the disease. All authors read and approved the final manuscript.

Ethics approval

Approval from the ethical committee was not required due to the nature of this case report.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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Not applicable.

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