Clinical Case Reports

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CASE REPORT

A case of Manila type *Mycobacterium tuberculosis* infection in Japan

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Funding Information
This work was supported by the Japan Initiative for Global Research Network on Infectious Diseases (J-GRID) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (MEXT), by JSPS KAKENHI Grants Number 24406021 and 24580443, by a grant from MEXT for the Joint Research Program of the Research Center for Zoonosis Control, Hokkaido University, and by a grant from the US-Japan Cooperative Medical Science Programs.

Received: 9 December 2014; Revised: 10 March 2015; Accepted: 12 March 2015

***Clinical Case Reports* 2015; 3(7): 622–625**

doi: 10.1002/ccr3.277

Key Clinical Message

A 76-year-old Japanese woman contracted a *Mycobacterium tuberculosis* (TB, Manila type) infection in Japan, despite never having traveled. However, her son was treated for TB in the Philippines 3 years before he stayed at her house. Spoligotyping allows us to identify the TB genotype and identify the route of infection.

Keywords

Japan, Manila, *Mycobacterium tuberculosis*, Spoligo-International-Type, spoligotyping.

Introduction

Despite the great efforts of healthcare workers, *Mycobacterium tuberculosis* (TB) has remained a major public health threat for decades in many countries. In addition, due to globalization, the numbers of imported TB cases are also increasing. The molecular epidemiology of TB has been facilitated by the development of spoligotyping via

computer-assisted analysis, which can be used to identify the global transmission of TB. The deletion patterns of the direct repeat locus divides TB strains into several families, including the Beijing and non-Beijing types in Japan [1, 2]; 73% of all Japanese TB cases are reported as the Beijing type [3].

The Philippines is considered as a high TB-burden country, with a prevalence of 484 cases per 100,000 population and a higher drug-resistant rate than that found in Japan [4, 5]. To date, most cases of Philippines TB have been spoligotyped as the Manila type [6]. Although few cases of Manila type TB have been reported in Japan, one Japanese patient, who developed vertebral caries after visiting the Philippines, was found to be infected with the Manila type of TB [7]. Here, we describe a case of Manila type TB that was confirmed via spoligotyping, where the patient had never traveled abroad.

Clinical Report

A 76-year-old Japanese woman was hospitalized at the Miyagi Cardiovascular and Respiratory Center for active TB from June 18 to June 30, 2012. She had been taking prednisolone (5 mg) and inhaled fluticasone (400 mg) daily for prednisolone-dependent bronchial asthma from the age of 50 years. Her last asthma attack occurred in 2006, and she underwent laparoscopic colectomy in 2007 due to stage I colon cancer. At admission, she complained of a cough, purulent sputum, and fever that had lasted for 1 week. Blood tests revealed that her white blood cell count was 6600 cells/μL. A computed tomography (CT) scan revealed an infiltrative shadow and consolidation, and the infiltrative shadow in the left B1 + 2 regions was suspected to have spread throughout her respiratory tract (Fig. 1). A small amount of right pleural effusion was also observed, although no mediastinal or abdominal lymph node hyperplasia was found. Based on the results of a sputum smear and real-time polymerase chain reaction (COBAS TaqMan, Roche Diagnostics Japan, Tokyo Japan), she was subsequently diagnosed with pulmonary TB, despite not having a history of TB and being negative for HIV-1 antibodies. There were no findings to suggest she had cancer or other lung diseases.

However, her son had previously lived in the Philippines and was diagnosed with TB during that stay. He was treated in Manila until his smear tests results were negative, although the drug-resistance status of the TB isolate was unknown. After recovering from TB, he temporarily returned to Japan and spent several days at the patient's house in 2011. However, no other person in her family developed TB.

After isolation, she received a daily course of isoniazid (300 mg), rifampicin (450 mg), ethambutol (750 mg), and pyrazinamide (1.2 g) for 8 weeks, and the TB isolate exhibited no drug resistance. Her asthma treatment (3 mg oral prednisolone with inhaled steroid) was continued, and we started a course of ampicillin/sulbactam (6 g/day via infusion). However, 5 days later, her body temperature remained high and the chest infiltrative shadow had worsened. As we were unable to differentiate the concomitant bacterial infection from the initial TB aggravation, we changed her antibiotics to meropenem (1.5 g/day). However, she developed an itching sensation and a rash in her limbs immediately after starting the meropenem infusion. Therefore, we discontinued the infusion and introduced ceftriaxone (1.0 g/day), and the patient's body temperature and inflammation markers gradually decreased. In addition, chest radiography revealed improved permeability in her right middle lung.

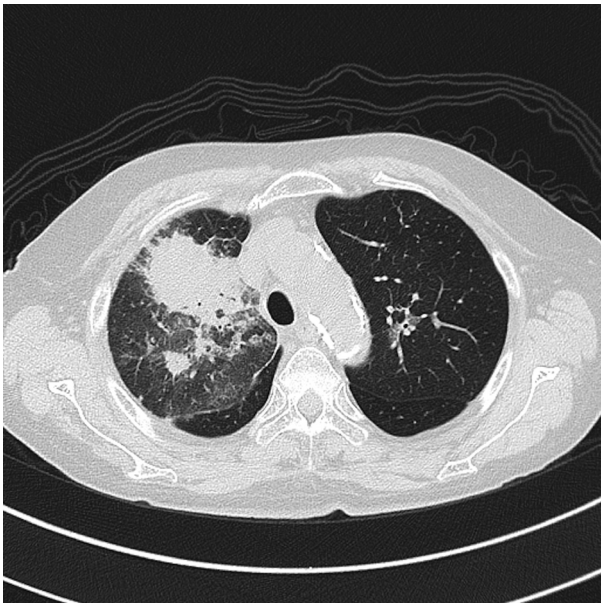

Figure 1. Chest computed tomography findings reveal consolidation in both lungs, without cavities, at admission.

After 3 consecutive days of negative smear tests, the patient was discharged at 2 weeks after starting the TB therapy. In addition to the 8 weeks of isoniazid, rifampicin, ethambutol, and pyrazinamide, she completed another 16 weeks of isoniazid and rifampicin without any obvious adverse effects, and her chest radiography findings exhibited improvements. Drug-resistant testing indicated that the isolate was sensitive to all TB drugs. Her last visit to the outpatient department was 6 months after the start of treatment, and she showed no respiratory symptoms, including bronchial asthma attack; therefore, her TB treatment was considered successful. The prednisolone was decreased to 2 mg to prevent TB recurrence, and the inhaled steroid was continued.

Table 1. Comparison of the spoligotype pattern of the current sample with the Beijing type.

Sample (ID)	Spoligotype pattern[2]	SIT[3]	Label[3]
Current sample (kit-3)	■■□■■■■■■■■■■■■■■■■■■■■□□■■■■■■■■□□□□□■□■■■■■■■■■■	19	EAI2_Manilla
Typical Beijing type[1]	□□□■■■■■■■■■	1	Beijing

[1]The majority of Japanese *M. tuberculosis* isolates belong to the Beijing genotype (Spoligo International Type [SIT] number 1).
[2]Squares indicate spacers 1 to 43 in the spoligotyping. A closed square indicates a positive spacer, while an open square indicates a negative spacer.
[3]SIT number and label were determined using the SpolDB4 database (Reference 8).

Spoligotyping of her TB isolates was performed and revealed a Manila type isolate (Table 1, Spoligo-International-Type number 19), which is labeled as EAI2_Manilla in the SpolDB4 international spoligotype database [8].

Discussion

To the best of our knowledge, this is the first case of a Japanese patient developing a domestic infection with Manila type TB. In Miyagi, Japan, the Miyagi Cardiovascular and Respiratory Center is designated as the local TB hospital, and provides care for approximately 100 inpatient cases of TB per year. We have performed spoligotyping for more than 200 TB samples, which were stored in the center for 2 years, and have only identified 2 Manila type cases (including the present case). The only other case was in a young Filipino woman, who came to Japan from the Philippines more than 10 years ago and was suspected of having reemergent latent Manila type TB. Most of the other TB cases have been classified as the Beijing type. As the present patient had no history of traveling abroad before the TB onset, it is possible that she was infected with Manila type TB during her son's visit 3 years before the onset. Unfortunately, we were unable to spoligotype the son's bacteria to confirm this connection between the two cases. However, her respiratory TB symptoms developed 1–2 months before the admission, and her previous annual chest radiography check-up (before the son's visit) did not reveal any active TB or pneumonia. Therefore, we believe intra-familial infection is highly likely in this case.

This case report demonstrates the spread of Manila type TB to Japan and highlights the possibility of high infectivity and rapid progression of Manila type TB. Inhaled *Mycobacterium tuberculosis* typically induces pneumonia over a course of several years, and most Japanese patients with active TB are thought to be experiencing recurrence of a decades-old infection, as many of them have a history of TB infection. In contrast, the Manila type TB in this case was likely transmitted from the smear-negative son to the patient, who subsequently developed pneumonia within 3 years. However, the possibility of infection via another route cannot be excluded. For example, smear-negative TB is not considered clinically infective, despite the fact that patients' TB sputum cultures can occasionally test positive later. Alternatively, the recurrence of the son's partially treated TB (in Manila) may also explain the transmission in Japan. Finally, the patient developed TB only 3 years after the exposure, likely due to her steroid therapy for her asthma, as patients who are receiving 10 mg prednisolone for more than 1 month are at high-risk of developing TB [9].

The present study provides new insights into the increase in drug-resistant TB in Japan, because the resistance can be induced by both insufficient directly observed therapy and the domestic spread of imported drug-resistant TB. Fortunately, the present case was not drug resistant and the World Health Organization's standard regimen was successful [10]. The TB isolates are different among each country, however, most of the Philippines TB isolates are EAI2_Manilla, and this strain has high drug-resistance and mortality rates [11, 12]. Therefore, it is possible that the drug-resistant Manila type TB has already been imported and spread domestically elsewhere in Japan, which may result in a higher drug-resistance rate in the future. To distinguish imported TB from domestic TB, variable number tandem repeat (VNTR) testing must be combined with spoligotyping, as spoligotyping is considered insufficient to track the local outbreak. Therefore, further clinical isolates must be collected to evaluate the correlation between the epidemiology, spoligotype, and VNTR of the isolates. In this context, spoligotyping and VNTR of the isolates would be important tools to evaluate how imported TB is transmitted as a domestic infectious disease [13].

Acknowledgments

This work was supported by the Japan Initiative for Global Research Network on Infectious Diseases (J-GRID) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (MEXT), by JSPS KAKENHI Grants Number 24406021 and 24580443, by a grant from MEXT for the Joint Research Program of the Research Center for Zoonosis Control, Hokkaido University, and by a grant from the US-Japan Cooperative Medical Science Programs.

Conflict of Interest

None declared.

Consent

Written informed consent was obtained from the patient regarding publication of this case report and the accompanying images. A copy of the written consent is available for review upon request.

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