INTERNAL MEDICINE

□ CASE REPORT □

The First Surgical Treatment Case of Pulmonary *Mycobacterium malmoense* Infection in Japan

Hideaki Ohno[1,4], Nobuko Matsuo[2], Naofumi Suyama[2], Yosuke Nagayoshi[1], Norihiro Kohara[3], Yuko Kazumi[5], Yoshitsugu Miyazaki[4] and Shigeru Kohno[1]

Abstract

Mycobacterium malmoense is a very rare pathogen of pulmonary infectious disease in Japan. We encountered a case of *M. malmoense* infectious lung disease which could be cured by surgical operation without chemotherapy. *M. malmoense* strains were isolated in both the bronchial washing lavage and the removed lung specimen, and it were identified using 16S rRNA gene and *rpoB* gene sequencing. This case might indicate that pulmonary infectious disease caused by a rare non-tuberculous mycobacteria pathogen should be positively considered to be treated surgically as an initial therapy when the patient's condition is admissive, and also indicated the importance of identification of the causative pathogen from surgical specimens. In addition, this was the second report of *M. malmoense* infectious disease, and the first case of surgical treatment case of *M. malmoense* lung disease in Japan, as far as we could determine.

Key words: *Mycobacterium malmoense*, segmentectomy, limited disease

(Inter Med 47: 2187-2190, 2008)
(DOI: 10.2169/internalmedicine.47.1520)

Introduction

In Japan the common pathogens of pulmonary infectious disease caused by non-tuberculosis mycobacteria (NTM) are *Mycobacterium avium* complex (MAC), *M. kansasii*, or rapid growth NTM such as *M. fortuitum* and *M. chelonae* (1). Regarding to treatment of such pulmonary NTM disease, chemotherapy is recommended for the initial treatment (2). However, consensus of treatment regimen against particular NTM infectious diseases (e.g., rapid growth NTM, or rare pathogen) has not been established yet, and moreover, indications of surgical treatment against NTM infectious disease are still controversial (2). Here, we report a case of pulmonary infectious disease caused by *M. malmoense* with underlying pathological pulmonary emphysema, which could be cured by operation without additional chemotherapy, this was the second case of *M. malmoense* infectious disease in Japan as far as we could determine.

Case Report

A 45-year-old man who worked in an office underwent a health check-up examination in August 2004. Chest X-ray examination revealed an abnormal shadow in his left upper lung area; however, he showed no symptoms or signs. Blood examinations including C-reactive protein were undertaken, however, significant findings could not be detected. His medical records included spontaneous pneumothorax of the right lung a year earlier at age 44 years, and having smoking behavior (about 40 pack years). One month later, he underwent a chest high resolution computed tomography (HRCT) examination. The images revealed nodular shadows and a cavity region beside the pleura in the left upper lung, and mild emphysema. He was transferred to Nagasaki municipal medical center, Nagasaki, Japan, in order to undergo further examination. Sputum samples were subjected to gram stain and acid-fast stain in triplicate and were also subjected to bacterial culture, including mycobacterial

[1]The Second Department of Internal Medicine, Nagasaki University School of Medicine and Dentistry, Nagasaki, [2]Department of Internal Medicine, Nagasaki Municipal Medical Center, Nagasaki, [3]Nagasaki Municipal Hospital, Nagasaki, [4]Department of Bioactive Molecules, National Institute of Infectious Diseases, Tokyo and [5]The Research Institute of Tuberculosis, Japanese Anti-Tuberculosis Association, Tokyo
Received for publication July 18, 2008; Accepted for publication September 10, 2008
Correspondence to Dr. Hideaki Ohno, h-ohno@nih.go.jp

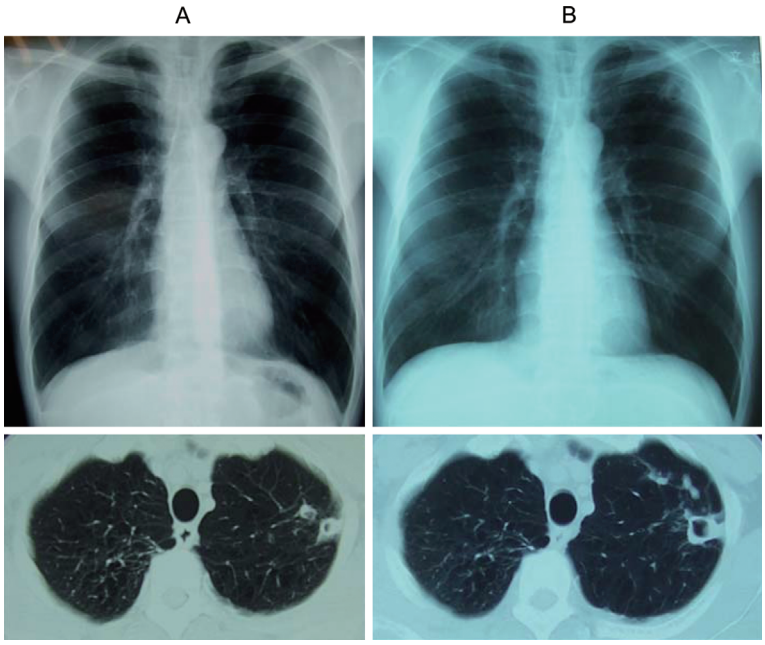

Figure 1. **Chest X-ray and HRCT images of the patient are shown. A: September 2004, B: April 2006. Nodular and cavitary region on the left upper lung showed increase of size and number of lesions.**

culture; however, significant pathogens could not be detected by microscopic evaluation. Several days later, transbronchial washing examination of his left upper bronchus (B^{1+2}) was carried out and bronchial washing lavage was cultured. Twenty-eight days after the bronchial washing examination, bacterial growth from the lavage specimen was confirmed on mycobacterial culture media (KRD liquid media, Nihon BCG supply, Tokyo, Japan). The culture was tested using DDH mycobacteria (Kyokuto Pharmaceutical Industrial Co. Ltd., Tokyo, Japan) and immunochromatographic assay (Capilia TB®; Becton Dickinson, Tokyo, Japan); however the isolate could not be identified. In addition, the culture was also compared with Amplicor®mycobacterium (Hoffmann-La Roche, Basel, Switzerland). It did not match for either *M. tuberculosis* or MAC. At this time, although he was suspected to have nontuberculous mycobacteriosis, the patient was observed without treatment as an outpatient. Five months later, the size and density of nodular shadow and cavity were confirmed to be growing by chest X-ray and chest HRCT (Fig. 1A). He then underwent a second transbronchial washing examination of the same upper bronchus. Although mycobacterial culture was positive after 17 days, the strain could not be identified using DDH and other assays. Therefore, the isolate was transferred to The Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Kiyose, Tokyo. It was identified as *M. malmoense* using 16S rRNA sequencing (identification rate comparing isolate to *M. malmoense* ATCC29571: 99.32%) and *rpoB* sequencing (99.7%) analysis. The patient was informed that his diagnosis was nontuberculous mycobacteriosis (pulmonary *M. malmoense* infection) and a recommendation of treatment by left upper segmentectomy rather than chemotherapy was made. However, the patient did not agree to surgery or to treatment with adequate chemotherapy because he had no symptoms so he was observed as an outpatient again.

In April 2006, his chest X-ray and chest CT revealed progression of the size of nodular shadows with small dissemination and an enlarged cavity (Fig. 1B); however, the lesions were still limited to the left upper segment of the lung. At this time, blood chemical examinations, and inflammatory response also showed unremarkable values. Finally, the patient agreed to have an operation, and left upper segmentectomy was performed on April 19 at Nagasaki Municipal Hospital. The diameter of the gross lesion was 2.5 cm (Fig. 2), and histopathology of the lesion showed caseous necrosis with epithelioid cell granuloma and Langhans giant cells (Fig. 3), and an emphysematous lung. Mycobacterial culture was performed using a resection specimen, and mycobacteria were recovered from the tissue. The isolate was subjected to 16S rRNA sequencing and *rpoB* sequencing analysis in order to identify it, and finally it was identified as *M. malmoense*.

After the operation, although he was under observation with no chemotherapy to date, chest examination has not shown any recurrence or new shadows.

Discussion

M. malmoense is one of the slow growing mycobacteria belonging to Runyon group III, and it was first described in northern Europe and the United Kingdom in 1977 (3). *M. malmoense* is also reported to be the second most common nontuberculous mycobacterium recovered from sputum and cervical lymph node specimens from children in northern Europe (2, 4), however, it has rarely been reported in the

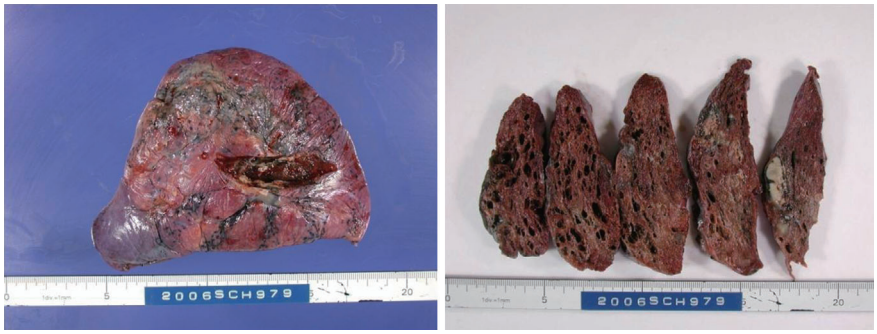

Figure 2. **Macroscopic histopathology of the removed left upper lung. Cavitary region and nodular regions were confirmed, and the diameter of the gross nodule lesion was around 2.5 cm. Finally, *M. malmoense* was recovered from this tissue specimen.**

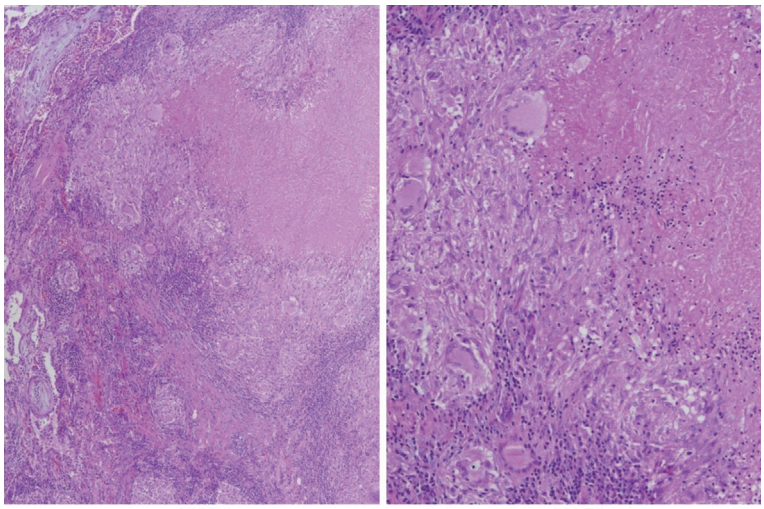

Figure 3. **Microscopic histopathology of nodular region is shown. Severe granulomas with caseous necrosis, and Langhans giant cells, similar to tuberculosis histopathology, were seen in the emphysematous lung.**

United States (5). In Japan, the most frequent NTM disease is caused by MAC, followed by *M. kansasii*, and the frequency of those 2 strains accounts for more than 90% of all NTM diseases (1). Therefore, the first case of *M. malmoense* infectious disease was reported in 2005 (6), and this report is the second case report, to our knowledge, from Japan.

Sometimes it is difficult to diagnose NTM infectious disease because NTM contamination from the environment should be considered. A novel set of diagnostic criteria was published by the American Thoracic Society/ the Infectious Diseases Society of America in 2007 (2), and our case also met these criteria. In addition, some reports stated that pulmonary *M. malmoense* infection was mainly complicated by chronic obstructive lung disease, such as pneumoconiosis, chronic airway infection, or pulmonary emphysema (7, 8, 9). Moreover, it was reported that *M. malmoense* infection was usually observed among HIV-negative people (2, 10). The reason for this is still unclear, however, *M. malmoense* infectious disease might be more strongly correlated with airway clearance than host immune status. In the present case, in addition to being HIV-negative, the patient had pathological pulmonary emphysema. On the other hand, one of the reasons why *M. malmoense* infection was not reported before 2005 in Japan might be the technical issue of identification of mycobacteria (5, 11). Nowadays, we have genetic mycobacterium identification techniques, such as PCR, DNA-DNA or DNA-RNA hybridization assays from over 10 years before; however they did not cover *M. malmoense* because it was not a significant pathogen in Japan. In the past, patients with NTM disease in which the strain had not been identified were treated using protocols for MAC disease. After introducing 16S rRNA or *rpoB* sequencing analysis, we could clearly distinguish *M. malmoense* from other NTM species (12). Therefore, we should make an effort to identify the species in order to provide adequate treatment and follow-up procedure. In this case, *M. malmoense* strain was also recovered from the surgically removed lung specimen fortunately, and it was helpful for us to make a clinical decision on treatment.

The first choice of treatment for NTM disease is chemotherapy. However, standard chemotherapy against *M. malmoense* has not been established yet, compared to MAC or *M. kansasii* (2). An official statement and other reports rec-

ommended using isoniazid, rifampin, or ethambutol with and without quinolones and macrolides (2, 10, 11, 13-15). However, the effect of chemotherapy is still controversial. In the case of NTM, in vitro drug susceptibility does not always correlate with treatment effect in vivo (2). Moreover, the effective regimen of chemotherapy is varied (13-16), and it is species or strain dependent. Therefore, in the case of limited NTM disease, resection is a more effective cure than chemotherapy, even when adequate drug susceptibility tests have been performed. In this case, we did not perform a drug susceptibility test for the isolate because the significance of such a test was considered to be of little value for actual chemotherapy. In addition, *M. malmoense* infectious disease is associated with high morbidity and mortality (15). Surgical treatment should be always considered as part of the treatment course in cases where the lesion is of limited area and unilateral, otherwise the chance to cure the disease is lost. Regarding the treatment, although the patient had been suspected to have underlying chronic obstructive lung disease due to smoking behavior, tests showed an almost normal lung function (%VC=118%, FEV1.0%=74.3%, DLco/VA=5.12 mL/min/mmHg/L). Thus, he could be treated by surgical treatment due to the disease area being limited, and this has produced a successful clinical course to date. On the other hand, regarding combination chemotherapy with surgical treatment, the evidence in *M. malmoense* infectious cases still remains limited. We should perform careful observation on this patient.

Finally, due to the advancement of molecular biology and clinical microbiological techniques, the frequency of infectious disease caused by a rare NTM pathogen in Japan might increase in the future. Therefore, making an effort to determine an accurate diagnosis or detection of such pathogens should be required for clinicians.

Acknowledgement

The authors thank Mr. Akihiro Hamamoto and all other members of the clinical laboratory of Nagasaki Municipal Medical Center for their helpful and devoted work on mycobacterial culture, and also thank Dr. Jyunji Irie and Dr. Isamu Sugawara for their contributions to diagnosis and treatment.

References

1. Sakatani M. The non-tuberculous mycobacteriosis. Kekkaku **80**: 25-30, 2005 (in Japanese).

2. American Thoracic Society/Infectious Disease Society of America. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous Mycobacterial diseases. Am J Respir Crit Care Med **175**: 367-416, 2007.

3. Schröder KH, Juhlin I. *Mycobacterium malmoense* sp. nov. Int J Syst Bacteriol **27**: 241-246, 1977.

4. Lopez-Calleja AI, Lezcano MA, Samper S, de Juan F, Revillo MJ. *Mycobacterium malmoense* lymphadenitis in Spain: first two case in immunocompetent patients. Eur J Clin Microbiol Infect Dis **23**: 567-569, 2004.

5. Buchholz UT, Mcneil MM, Keyes LE, Good RC. *Mycobacterium malmoense* infections in the United States, January 1993 through June 1995. Clin Infect Dis **27**: 551-558, 1998.

6. Kumamoto M, Nishiyama H, Kazumi Y, Ogata H. A case of pulmonary infection caused by *Mycobacterium malmoense*. The Journal of the Japanese respiratory society **43**: 454-458, 2005 (in Japanese).

7. Banks J, Jenkins PA, Smith AP. Pulmonary infection with *Mycobactrium malmoense*—a review of treatment and response. Tubercle **66**: 211-217, 1985.

8. Evans AJ, Crisp AJ, Colville A, Evans SA, Johnston ID. Pulmonary infections caused by *Mycobacterium malmoense* and *Mycobacterium tuberculosis*: comparison of radiographic features. AJR **161**: 733-737, 1993.

9. Job V, Lacaze O, Carricajo A, Fournel P, Vergnon JM. Medical-surgical treatment of pulmonary infection with *Mycobacterium malmoense*. Rev Mal Respir **21**: 993-996, 2004.

10. Subcommittee of the Joint Tuberculosis Committee of British Thoracic Society. Management of opportunist mycobacterial infecttions: Joint Tuberculosis Committee guidelines 1999. Thorax **55**: 210-218, 2000.

11. Al-Moamary MA, Black W, Elwood K. Pulmonary disease due to *Mycobacterium malmoense* in British Columbia. Can Respir J **5**: 135-138, 1998.

12. Kazumi Y, Maeda S, Sugawara I. Identification of mycobacteria by sequencing of *rpoB* gene and 16S rRNA. Kekkaku **81**: 551-558, 2006 (in Japanese).

13. Enzensberger R, Hunfeld KP, Krause M, Rusch-Gerdes S, Brade V, Boddinghaus B. *Mycobacterium malmoense* infections in immunocompetent patients. Eur J Clin Microbiol Infect Dis **18**: 579-581, 1999.

14. Handrick W, Schwede I, Ebeling O Wogawa B, Berthhold F. Pulmonary infection due to *Mycobacterium malmoense*. Pneumologie **59**: 244-247, 2005 (in German).

15. The Research Committee of the British Thoracic Society. Pulmonary disease caused by *M. malmoense* in HIV negative patients: 5-yr follow-up of patients receiving standardised treatment. Eur Respir J **21**: 478-482, 2003.

16. Hoffner SE, Hjelm U, Kallenius G. Susceptibility of *Mycobacterium malmoense* to antibacterial drugs and drug combinations. Antimicrob. Agents Chemother **37**: 1285-1288, 1993.