Original Article

# ANALYSIS OF THE CLINICAL FEATURES OF PULMONARY DISEASE CAUSED BY *MYCOBACTERIUM SZULGAI*

## — A Review of 12 Cases over 10 Years and the Utility of Drug-Susceptibility Testing —

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**Abstract** [Subjects & Methods] We reviewed the patient characteristics, radiological findings, treatments, and clinical outcomes in 12 cases of pulmonary *Mycobacterium szulgai* disease diagnosed at our hospital from April 1998 to March 2008. In addition, drug susceptibility testing of the causative isolates was performed with several antibiotics, including clarithromycin (CAM) and rifampicin (RFP), using BrothMIC NTM®.

[Results] The patients included 10 men and 2 women, with a mean age of 57.2 years. Among them, 10 were smokers, 5 previously had pulmonary tuberculosis, 3 had a history of gastric ulcers, and 1 had a history of esophageal cancer surgery. All patients had been previously treated with various chemotherapeutic regimens. Six of them were treated with chemotherapy, including CAM, and they improved both radiologically and bacteriologically. The minimal inhibitory concentration of CAM for all the strains tested was less than 0.25 $\mu$g/mL, which is the likely critical concentration for clinical efficacy of CAM. The present study suggested that, in addition to smoking and a history of pulmonary tuberculosis, gastroesophageal disorders were relevant underlying conditions in patients with pulmonary *M.szulgai* disease.

[Conclusion] Chemotherapeutic drugs, including CAM, are clinically and bacteriologically effective for pulmonary *M. szulgai* disease.

**Key words** : Nontuberculous mycobacteria, *Mycobacterium szulgai*, BrothMIC NTM, Gastroesophageal disorders, Clarithromycin

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Original Article

# DISTRIBUTION OF PULMONARY *MYCOBACTERIUM AVIUM* COMPLEX (MAC) DISEASE CAVITIES AND THEIR COURSE UNDER CHEMOTHERAPY

[1]Atsuyuki KURASHIMA and [2]Mitsuko HORIBE

**Abstract** The presence of a cavitary lesion is important factor for pulmonary *Mycobacterium avium* complex (MAC) treatment.

[Purpose] Clarify the location of pulmonary MAC cavities and the changes of these cavities.

[Material & Methods] We observed the location of 56 cavities in 48 patients with pulmonary MAC on computed tomography (CT) images and evaluated the changes in the external diameter of these cavities before and after treatment with a regimen of rifampicin (RFP), ethambutol (EB), and clarithromycin (CAM).

[Results] These pulmonary MAC cavities were significantly frequently located in segments $S^2$, $S^3$, $S^9$, and $S^{10}$, and their distribution was different from that of pulmonary tuberculosis at the patients' initial visit. Examination of the external diameters of these cavities after chemotherapy showed that 42.1 % of cavities expanded, 0.2% were unchanged, and 56.1% shrank. The mean diameter of the cavities decreased significantly (by 3.1 mm) after chemotherapy.

The mean size of the cavities in the upper lobe did not differ from the mean size of the cavities in the lower lobe before chemotherapy; however, the reduction in cavity size was significantly higher in the lower lobe cavities. In 14 cases, the cavities disappeared under the standard chemotherapy regimen in an average of 971 days, and there was a tendency for lower lobe cavities to disappear more rapidly.

**Key words**: *Mycobacterium avium* complex (MAC), Chemotherapy, Cavity, Tuberculosis, Distribution

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Case Report

# HYPERSENSITIVITY PNEUMONITIS-LIKE DISEASE CAUSED BY EXPOSURE TO *MYCOBACTERIUM AVIUM* COMPLEX IN BATHTUB WATER AT HOME: A CASE REPORT

Kiyoshi KANNO, Masaya AKAI, Tomohiro KATO, Toshihiko TADA,
Kizuku WATANABE, Kouhei SHIOZAKI, and Mitsuo HASE

**Abstract** We report here a case of hypersensitivity pneumonitis-like disease in an adult, likely due to exposure to *Mycobacterium avium* complex (MAC) in his bathtub water at home. A 63-year-old man was referred to our hospital with exertional dyspnea. Chest computed tomography showed bilateral, diffuse, centrilobular ground-glass nodules. Bronchoalveolar lavage showed marked lymphocytosis. Transbronchial biopsy showed epithelioid cell granulomas and lymphocyte alveolitis. Cultures of the patient's sputum and bathtub water yielded MAC. Variable-number tandem repeat analysis of the MAC strains in the sputum and bathtub water samples showed that the strains were genetically identical. The clinical condition of the patient improved at home under chemotherapy by avoiding the use of the bathtub.

**Key words**: *Mycobacterium avium* complex, Hypersensitivity pneumonitis, Hot tub lung

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# A CASE OF ENVIRONMENTAL INFECTION WITH PULMONARY *MYCOBACTERIUM AVIUM* COMPLEX DISEASE FROM A RESIDENTIAL BATHROOM OF A PATIENT SUGGESTED BY VARIABLE-NUMBER TANDEM-REPEAT TYPING OF *MYCOBACTERIUM AVIUM* TANDEM REPEAT LOCI

[1]Shu TAGA, [2,3]Masaki NIIMI, [2,3]Kazuhiro KUROKAWA, [3,4]Taku NAKAGAWA, and [3,4]Kenji OGAWA

**Abstract** A 63-year-old woman was referred to our hospital because of bilateral infiltrations and nodular opacities in her chest radiograph taken in the mass radiography screening in September 2010. The chest computed tomography showed patchy infiltrations with bronchiectasis in the lower lung fields on both sides. She was diagnosed with pulmonary *Mycobacterium avium* complex (MAC) disease based on the bacteria recovered from the sputum and the bronchoalveolar lavage fluid. To elucidate an environmental MAC source, we investigated her home, and isolated *M.avium* and *M.gordonae* from the bathtub and shower tap, respectively, in her residential bathroom. Analysis of the *hsp65*-PRA variants digested with *BamH*I and some insertion sequences showed that the clinical strains recovered from sputum and strains from the bathtub were *M.avium* subsp. *hominissuis*. A dendrogram of the *Mycobacterium avium* tandem repeat loci variable-number tandem-repeat (MATR-VNTR) analysis of the MAC strains showed that the bathtub strains formed a polyclonal colonization, and that 1 of the 5 MATR-VNTR patterns was identical to the corresponding pattern of the sputum strain from the patient. In conclusion, we believe that the residential bathroom of the patient was the environmental source of her pulmonary MAC disease, as has been previously reported.

**Key words**: *Mycobacterium avium* tandem repeat loci variable-number tandem-repeat (MATR-VNTR) typing method, *Mycobacterium avium* complex (MAC), Environmental infection, Residential bathroom, Bathtub

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Report and Information

# TUBERCULOSIS ANNUAL REPORT 2009
## —Series 10. Treatment Outcome and TB Deaths—

Tuberculosis Surveillance Center, RIT, JATA

**Abstract** Evaluation of the treatment outcome by the cohort analysis method is an important part of tuberculosis (TB) control. In the Japanese TB surveillance system, the treatment outcome is automatically classified by computer according to a pre-set algorithm, so the treatment outcome is evaluated very rigidly.

In the case of new sputum smear positive pulmonary TB cases (n＝8,999) newly notified in 2008, the patients' treatment outcomes based on the annual report 2009 database were as follows: "success," which combined "cured" and "completed," was 47.7%, "died" was 19.1%, "failed" was 1.1%, "defaulted" was 3.8%, "transferred out" was 2.8%, "on treatment after 12 months" was 11.8% and "not evaluated" was 13.6%.

In addition to evaluation of the treatment outcome by the cohort method, the proportion of deaths was observed among all forms of TB patients (n＝24,571) who were newly registered in 2008. In total, 17.3% of all forms of TB cases died within one year after the beginning of treatment. The proportion corresponding to this was 23.7% for new sputum smear positive pulmonary TB and 23.5% for re-treatment sputum smear positive pulmonary TB.

Among the new sputum smear positive pulmonary TB patients (n＝2,136) who died within one year after the beginning of treatment, 37.0% of them died within one month after the beginning of treatment, 51.6% died within two months and 61.9% died within three months.

**Key words**: Tuberculosis, Sputum smear positive, Cohort, Treatment outcome, Success rate, Death

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—— The 86th Annual Meeting Symposium ——

# RESTRUCTURING THE MEDICAL SERVICE SYSTEM

Chairpersons: [1]Tomokazu INAGAKI and [2]Seiya KATO

**Abstract** The incidence of tuberculosis in Japan was a little below 20/100,000 population in 2010. A review of the history of tuberculosis control in western countries suggests that the medical service system in Japan is now at a turning point toward lower incidence.

The symposium titled "Medical Service System under the Infectious Diseases Law" at the 84th annual meeting of the Japanese Society for Tuberculosis in 2009 discussed five issues of the medical service system for tuberculosis: (1) eliminating tuberculosis beds which resulted in poor accessibility and a shortage of TB beds, (2) extremely poor profitability in tuberculosis medical care, (3) medical service systems in low incidence countries, (4) clinical issues such as the increase in patients with serious underlying diseases due to aging, and (5) challenges for restructuring the system at the prefectural level.

This symposium was organized based on discussions in the above symposium and on a series of discussions in the meetings of the Infectious Disease Subcommittee of the Health Science Council on the National Guideline for Tuberculosis Control, which was revised and addressed in May 2011 so that the contents would be useful to consider medical systems for tuberculosis in the future.

The first speaker, Dr. Tomoo Ito of the Infectious Disease and Tuberculosis Department, Ministry of Health, Labour and Welfare, presented discussions at the meetings of the Infectious Disease Subcommittee of the Health Science Council and directions for restructuring the medical service system mentioned in the revised National Guideline.

Dr. Akifumi Mita from the Headquarter of the National Hospital Organization (NHO) pointed out three major roles of NHO: treatment of tuberculosis patients, human resource development, and research. He also reported issues and challenges among NHO hospitals such as the increased number of patients with complications, reorganization of the medical system in response to the decreased number of tuberculosis patients, and poor profitability at their hospitals.

Dr. Kunihiko Ito from the Research Institute of Tuberculosis presented the results of a nationwide survey of tuberculosis hospitals conducted to set up facility standards for tuberculosis hospitals. The survey demonstrated that the current situation of tuberculosis beds varies widely and in general is far from ideal.

Dr. Eriko Shigeto from the NHO Higashihiroshima Medical Center reported issues of patients with complications and poor access to tuberculosis hospital care. She also reported on local coordination mechanisms for tuberculosis using varieties of clinical passes with members of the medical association.

Dr. Atsushi Ajisawa from the Tokyo Metropolitan Cancer and Infectious Diseases Center of Komagome Hospital reported on the current situation of treating tuberculosis patients in infectious disease wards. He pointed out that careful consideration is important for accepting tuberculosis patients in infectious disease wards.

Dr. Hideo Maeda from the Tokyo Metropolitan Government stated the need for promoting Community DOTS by coordination among hospitals and out-patient treatment in order to deal with groups at high risk for default, particularly in major cities. He also mentioned reducing the hospitalization period and establishing medical service systems for tuberculosis with collaboration mechanisms in communities for patients of productive age.

Dr. Tadayuki Ahiko from Yamagata Prefectural Government mentioned that the quality of medical service at core hospitals should be maintained. He insisted that legislation should be revised to allow infectious disease wards or general hospitals to treat tuberculosis patients.

We also actively participated in discussions from the floor. This symposium clearly demonstrated that various issues and challenges remain unsolved and that multilateral, comprehensive discussions are necessary for restructuring the medical system.

## 1. New strategy of medical delivery system for tuberculosis in Japan: Tomoo ITO (Infectious Disease and Tuberculosis Department, Ministry of Health. Labour and Welfare)

Circumstances of tuberculosis in Japan are changing. First, the number of patients is decreasing year by year. So the occupation rate of tuberculosis isolation beds is also decreasing. In the point of businesses, treatment of tuberculosis is bad. So many hospitals want to close tuberculosis department. In some rural area, there are a few tuberculosis hospitals and patients cannot get treatment easily. Second, the number of aged tuberculosis patients are increasing, therefore a lot of patients have not only tuberculosis infection but also some other diseases. Usually tuberculosis department focuses on isolation not treatments like intensive care. So to treat these patients with serious complication needs cooperation with other department and sometimes other hospitals. To solve these problems, we made a new prevention guideline. In the guideline we mentioned about importance of building cooperation networks for tuberculosis treatments. In country level, we prepare specialized hospital for very difficult cases like XDR in Tokyo and Osaka. In prefecture level, we locate some hospitals which can be main hospitals for tuberculosis treatment in those areas. Around those hospitals, we prepare local hospitals which can treat normal tuberculosis patients

and patients with complications. We also focus on strengthen DOTS. It is also a very important factor to provide patients good treatment care. With these strategies, we want to achieve low prevalence of tuberculosis.

3. Current situation of tuberculosis wards: Kunihiko ITO (Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association)

We surveyed the situations of tuberculosis wards, focused on the aspects of equipments, by sending question sheets to all tuberculosis wards in Japan. Response rate was around 69.3%. Situation of equipments and other related items in tuberculosis wards were highly variable, for example, in the points of patient management policy, amenities for long hospital stay, and floor space of patient rooms for one patient. But in general, situations of tuberculosis ward were far from ideal one. When we make equipment standards for tuberculosis ward in Japan, we must take those highly variable, but generally poor, situations into consideration.

4. Clinical Practice Issues: Eriko SHIGETO (National Hospital Organization Higashihiroshima Medical Center)

The major issues are the treatment of various complications and the worsening access for tuberculosis care. The Model Beds are available for the patients with complications, but not sufficient in some areas. An attempt to enhance the liaison between tuberculosis experts and general hospital and practitioners involved in a health center was successful in terms of the spread of the Standard Care for Tuberculosis and better access for patients. The difficulties in the management of tuberculosis wards and the Model Beds are also the issue, which requires government involvement.

5. Alternative use for infectious pulmonary tuberculosis in medical facilities designated for Category I or II infectious diseases treatment: Atsushi AJISAWA (Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital)

Our medical facilities designated for Category I or II infectious diseases treatment were completely renovated at Jan. 2010. We conducted this renovation for isolation of many patients with SARS or pandemic influenza in wards. We had two private compartments for airborne infection like tuberculosis, measles, and chickenpox. If we use the two private rooms for only infectious pulmonary tuberculosis, our nosocomial pulmonary tuberculosis patients occupied year-round. We suppose a careful case-by-case analysis of the medical facilities is important to accept the pulmonary tuberculosis.

7. Current Issues and perspectives on tuberculosis medical care service system in low-incidence regions in Japan: Tadayuki AHIKO (Yamagata Prefectural Institute of Public Health)

The incidence rate of TB in 2010 in Yamagata Prefecture is 11.2 per 100,000 population, which is close to the level of low-incidence countries. Current TB epidemiology in Yamagata shows increasing the proportion of elderly patients, especially those over 80 years of age. TB patients with various complications or concurrent diseases are increasing, as elderly TB patients increasing. However, there is only one hospital having a 50-bed isolation ward for inpatients with smear-positive TB. Therefore, some patients have to travel to the hospital far away from their homes, which is particularly inconvenient for elderly. To allow TB patients hospitalized in other hospitals, which has been designated for inpatients with infections other than TB, the central government should amend the relevant laws.

**Key words**: Tuberculosis, Medical service system, Complication, National Guideline for Tuberculosis Control, Facility standards

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**The 86th Annual Meeting Symposium**

# FOREFRONT OF THE CLINIC AND RESEARCH OF PULMONARY MAC DISEASE

Chairpersons: [1]Atsuyuki KURASHIMA and [2]Kenji OGAWA

**Abstract** The estimated prevalence of nontuberculous mycobacterial lung disease in Japan was a high level identified 5.6 in 2007 and that continued to increase thereafter.

We focused on pulmonary MAC disease with this symposium and five reports were presented from the facilities vigorously conducted on MAC treatment and research.

Each subject was the genetic host factor, the genetic bacterial factor, a development of new serodiagnostic test, the cohort study of trends in pulmonary MAC HRCT images and the validation of the appropriate chemotherapy period. The all presentations were an epoch-making high level contents.

1. Human susceptibility genes for pulmonary MAC disease: Naoto KEICHO, Ikumi MATSUSHITA, Minako HIJIKATA (Department of Respiratory Diseases, National Center for Global Health and Medicine, Research Institute)

Pulmonary MAC infection is a disease in which genetic predisposition is deeply involved. Candidate gene association studies and animal models have been used to determine disease susceptibility genes for mycobacterial infection. Although many associated genes involved in mucosal immunity and systemic immunity such as *MUC5B*, HLA-related genes, *CFTR* and *SLC11A1* have been reported thus far, no major susceptibility genes have been found, partly because non-genetic host factors, environmental factors and virulence of pathogens also confer a risk and partly because insufficient systematic approaches have been adopted. Genome wide association studies and other high-throughput technology may also be a breakthrough in this field.

2. Genetic research of *Mycobacterium avium* complex: Taku NAKAGAWA, Kenji OGAWA (Department of Pulmonary Medicine, National Hospital Organization Higashinagoya National Hospital)

We conducted genetic research of *Mycobacterium avium* complex (MAC) to elucidate the bacterial factors contributing to an increase in the prevalence of MAC infection in Japan and diversity of disease progression. MATR-VNTR typing is inexpensive and easy to perform and has an excellent discriminatory power compared with IS*1245*-RFLP typing. MATR-VNTR typing revealed that *M.avium* isolates from HIV-positive patients are analogous to the isolates from pig enterically-transmitted rather than those from HIV-negative patients with pulmonary diseases. Clinical strain of *M.avium* from a HIV-negative patient with severe pulmonary disease was subjected to genome sequencing. It is considerably different from the published sequence of *M.avium* 104, which is recovered from a HIV-positive patient.

We showed that *M.avium* strains in Japan are distinct from strains in Western countries in terms of the prevalence of IS*Mav6*. Genetic analysis for *M.avium* isolates collected from 12 hospitals all over Japan failed to show that distinct clusters correlate with disease progression or region with the use of VNTR typing. We identified 16 VNTR loci in the genome of *M.intracellulare* ATCC1395 and applied them as a molecular epidemiological tool to clinical isolates.

3. Serodiagnosis of *Mycobacterium avium* complex pulmonary disease: Seigo KITADA, Ryoji MAEKURA (Respiratory Medicine, National Hospital Organization Toneyama National Hospital)

Diagnosis of *Mycobacterium avium* complex pulmonary disease (MAC-PD) can be difficult because isolation of the organism does not necessarily mean that the patient has disease. New diagnostic tests are needed to help clinicians differentiate patients with MAC-PD from those without disease. The serodiagnostic test that detect serum IgA antibody to glycopeptido lipid core could be used in clinical settings for the rapid diagnosis for MAC-PD.

4. Charasteristics of changes over time of computed tomographic findings in the pulmonary non-tuberculous mycobacteriosis: Yoshifumi KIMIZUKA, Naoki HASEGAWA (Division of Pulmonary Medicine, Keio University School of Medicine)

We reviewed records of patients who met the ATS criteria for the diagnosis of non-tuberculous mycobacteriosis. The data of patient demographics were collected. Including them, we extracted the patients who were examined regularly computed tomography. The results were analyzed to examine the correlation with other clinical parameters.

5. Evaluating the treatment period in patients with pulmonary *Mycobacterium avium* complex disease: Kozo MORIMOTO (Respiratory Center, Fukujuji Hospital, Japan Anti-Tuberculosis Association)

The optimal treatment period for pulmonary *Mycobacterium avium* complex (MAC) disease is unclear. We retrospectively studied 100 patients evaluable for post-treatment 2 years. The primary endpoint was 2 consecutive positive cultures. 12 months of culture-negative were not significantly different from＞12 months of culture-negative with non-cavitary lesions. However, in patients with cavitary lesions, ＞12 months treatment showed significantly better prognosis than treatment for standard periods.

**Key words**: *Mycobacterium avium*, Disease susceptibility genes, IS*Mav 6*, GPL-core IgA antigen, Cavitiy

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