

Original Article

MULTICENTER STUDY ON CLINICAL FEATURES AND GENETIC CHARACTERISTICS OF *MYCOBACTERIUM AVIUM* STRAINS FROM PATIENTS IN JAPAN WITH LUNG DISEASE CAUSED BY *M. AVIUM*

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Abstract [Background] The pulmonary disease caused by *Mycobacterium avium* shows diverse clinical manifestations. Little is known about the potential association between the genetic characteristics of *M. avium* strains and disease progression.

[Subjects and Methods] We enrolled 89 patients with disease caused by *M. avium*, from 12 hospitals in Japan and collected the corresponding *M. avium* isolates and clinical data. We divided the 89 patients into 2 groups: one group comprising 43 patients with progressive disease despite chemotherapy (“progressive”), and the other group comprising 46 patients with untreated disease (“untreated”). We compared clinical and bacteriological characteristics between these groups. The bacteriological characteristics that we examined were drug susceptibility, variable-number tandem-repeat (VNTR) typing, and presence of the insertion sequence *ISMav6*. Seventeen patients in the “untreated” group were started on chemotherapy because their condition had clinically deteriorated during follow-up.

[Results] The result of VNTR typing showed that there was no specific clustering according to geographical region or clinical group in the “untreated” or “progressive” groups. Six out of eight cases those of polyclonal infection, and 11 of 12 isolates that were highly resistant to clarithromycin were isolated from patients with progressive disease. The frequency of isolates with *ISMav6* inserted into upstream region of the *cfp29* gene, which is involved in the induction of interferon- γ

production, was significantly higher in patients with deteriorating disease than in stable patients in the “untreated” group ($p=0.002$).

[Conclusion] Polyclonal infection and clarithromycin resistance may be involved in disease progression. *ISMav6* inserted into the *cfp29* gene is also suggested to be a factor related to the deterioration of pulmonary *Mycobacterium avium* complex disease.

Key words : Nontuberculous mycobacteriosis, Polyclonal infection, Clarithromycin resistance, Variable-number of tandem-repeat (VNTR) typing, *ISMav6*, *cfp29*

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CAN AN INDIVIDUAL WITH A POSITIVE BASELINE QuantiFERON® TEST RESULT DEVELOP ACTIVE TUBERCULOSIS?

Lina YI, Takashi YOSHIYAMA, Masao OKUMURA, Hideo OGATA,
and Shoji KUDOH

Abstract [Objectives] QuantiFERON®-TB Gold (QFT-G) test has been recommended as a new tool for the diagnosis of latent tuberculosis (TB) infection. However, the risk of development of active TB in the future depends on the period after the infection. The aim of this study was to evaluate the risk of development of active TB in individuals who have been infected.

[Methods] Clinical development of TB in subjects with positive baseline QFT test results was retrospectively analyzed. The subjects included healthcare workers, since 2003, at the Fukujuji Hospital who were examined at employment.

[Results] In total, 667 subjects were examined using the QFT-2G test, and 62 subjects were QFT positive at the first examination. One was treated using isoniazid, and 61 subjects were followed up for an average of 4.7 years (286 person-years). None of the subjects developed active TB during the

observation period, and the probability of clinical breakdown (95% confidence interval) was 0–0.0104/person-year.

[Conclusion] The risk of development of active TB among subjects with positive QFT-G test results at baseline was low. Treatment of latent TB infection is not recommended, unless an individual has been recently infected.

Key words: Baseline QFT positive subjects, Incidence of TB, Treatment of latent tuberculosis infection

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A CASE OF THYMOMA AND *MYCOBACTERIUM INTRACELLULARE* INFECTION

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²Mio KAWAGUCHI, ²Koichi KURISHIMA, and ³Hiroichi ISHIKAWA

Abstract A 69-year-old man, who underwent total thymectomy 5 years previously, was referred to our division because the chest radiograph revealed abnormal shadows in both the lungs. The chest radiograph and CT scan showed pleural thickening in both apexes and tree-in-bud signs in both the lower lobes, which suggested bronchiolitis. We had retrospectively confirmed similar centrilobular small nodules and tree-in-bud signs on the chest CT scan when the thymoma was diagnosed. *Mycobacterium intracellulare* was detected in the sputum by acid-fast staining and polymerase chain reaction. The coincidence of thymoma and *Mycobacterium intracellulare* infection appeared to be incidental. Thus, in patients with thymoma, clinicians should carefully evaluate the lung parenchyma as well as the mediastinum on the chest radiograph to identify occult diseases, including *Mycobacte-*

rium intracellulare infections.

Key words: Thymoma, *Mycobacterium intracellulare* infection

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Case Report

PET/CT FOR MONITORING THE THERAPEUTIC RESPONSE
IN A PATIENT WITH ABDOMINAL LYMPH NODE TUBERCULOSIS
AFTER COLON CANCER RESECTION

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Abstract In February 2007, a 76-year-old man underwent endoscopic mucosal resection (EMR) for sigmoid colon cancer. Histological examination of the EMR specimen revealed adenocarcinoma in adenoma that was confined to the mucosal layer, and pathological complete resection was achieved. Since then, the patient has been followed up every year with endoscopic examination of the colon, with normal results except for hemorrhoids. In June 2011, a positive result for occult blood was obtained on examination of a stool sample. In July 2011, enhanced computed tomography of the chest and abdomen was performed, and the left supraclavicular, paraaortic, and left common iliac artery lymph nodes were found to be enlarged. ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) identified accumulation of ^{18}F -FDG in the enlarged lymph nodes. Histopathological examination of a biopsy specimen from the left supraclavicular lymph node revealed tuberculous changes; therefore, the patient was administered anti-tuberculosis therapy. The culture isolate of the above lymphatic tissue specimen was identified as *Mycobacterium tuberculosis* by immunochromatographic assay with MPB64 protein (Capilia[®]TB). Laparoscopic examination of abdominal lymph nodes was not performed because the patient's consent could not be obtained. After the anti-tuberculosis therapy, the size of the

abdominal lymph nodes was reduced, and subsequently, ^{18}F -FDG accumulation decreased.

It is considered that mucosal colon cancer did not spread to the lymph nodes after it was removed completely. For the definitive diagnosis of abdominal lymph node swelling, it would have been necessary to perform laparoscopic examination, which was impossible in this case. When it is difficult to perform invasive examinations, such as laparoscopy in case of swelling of the abdominal lymph node, ^{18}F -FDG PET/CT can be useful for monitoring the therapeutic response of abdominal tuberculosis.

Key words: Abdominal lymph node tuberculosis, Supraclavicular lymph node tuberculosis, Colon cancer, Mucosal resection, ^{18}F -FDG PET/CT

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Case Report

**A CASE OF PULMONARY *MYCOBACTERIUM LENTIFLAVUM* INFECTION
DIAGNOSED BY MICROBIOLOGICAL ANALYSIS**²Yoko HIRAKI, ¹Yasumi OKOUCHI, and ¹Hitoshi TOKUDA

Abstract In 1998, a 51-year-old woman was diagnosed with *Mycobacterium avium* infection on the basis of chest radiographic findings, positive smear test results, and positive results of polymerase chain reaction (PCR) specific for *Mycobacterium avium* DNA in bronchial lavage fluid. Antimycobacterial therapy was administered for 11 months, and the chest radiographic findings improved. In 2001, re-treatment was performed because radiographic findings indicated exacerbation of disease and poor response. After 2005, the patient remained both smear and culture positive for mycobacterium. However, the precise species could not be identified using PCR and DNA-DNA hybridization, and her left lung lesions gradually worsened. The culture isolate was subjected to DNA analysis with PCR amplification and sequence analysis; this ultimately revealed the presence of *Mycobacterium lentiflavum*. Combination antimicrobial therapy was administered for 10

months. The patient's symptoms were alleviated, and the radiographic appearance remained stable.

Key words : Pulmonary non-tuberculous mycobacteriosis, *Mycobacterium lentiflavum*, *Mycobacterium avium*, Microbiological analysis

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A CASE OF AGRANULOCYTOSIS CAUSED BY RIFAMPICIN DURING
TREATMENT OF TUBERCULOUS LYMPHADENITIS
IN A CHRONIC RENAL FAILURE PATIENT

Masafumi SUGIYAMA

Abstract A 52-year-old woman was admitted to our hospital because of intermittent high fever and chronic renal failure. Computed tomography of the thorax showed swelling of the paratracheal lymph nodes that was confirmed by gallium scintigraphy. Biopsy of the supraclavicular lymph node on the right side showed necrotizing lymphadenitis with Langhans' giant cells surrounded by epithelioid cells. Anti-tuberculosis treatment, including isoniazid, rifampicin, ethambutol, and pyrazinamide was initiated. One month after treatment, the patient developed agranulocytosis (white blood cell [WBC], 2100 cells/ μ l; neutrophils, 5%) accompanied by severe diarrhea. Bone marrow histology showed poor development of granulocytes, but no atypical cells were observed. Therefore, rifampicin was discontinued, and treatment with granulocyte colony-stimulating factor (G-CSF) was initiated. Subsequently, the white blood cell count and the proportion of neutrophils

increased to 12500 cells/ μ L and 80%, respectively. Rifampicin in the anti-tuberculosis chemotherapy regimen was replaced with levofloxacin. This is a rare case of agranulocytosis caused by rifampicin administered during anti-tuberculosis treatment in a chronic renal failure patient.

Key words: Agranulocytosis, Rifampicin, Tuberculous lymphadenitis, Chronic renal failure

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————— Case Report —————

A CASE OF PULMONARY *MYCOBACTERIUM GORDONAE* INFECTION
DIAGNOSED BY GASTRIC JUICE CULTURE AND
SUCCESSFULLY TREATED WITH MULTIDRUG CHEMOTHERAPY

Atsuhito NAKAZAWA, Eri HAGIWARA, Satoshi IKEDA, Tsuneyuki ODA,
Shigeru KOMATSU, and Takashi OGURA

Abstract In September 2008, a 60-year-old woman presented to our hospital with a complaint of bloody sputum; she was healthy until this event. Chest computed tomography scan revealed a cavity, nodular shadows, and bronchiectasis in the left upper lobe and in the left and right middle lobes. Acid-fast bacilli were detected 2 times on gastric juice culture and *Mycobacterium gordonae* was identified on biochemical study. No active chemotherapy was administered because the discharge of this strain was considered casual and clinically nonsignificant. However, her radiological findings worsened in the following 1 year and 3 months, and *M. gordonae* was detected 2 more times on gastric juice culture. Subsequently, she was diagnosed with pulmonary mycobacteriosis caused by *M. gordonae* and was treated with clarithromycin, rifampicin, and levofloxacin. After 1 month, her gastric juice culture yielded negative results for *M. gordonae*, and after a year and a half, her radiological findings improved.

In this case, gastric juice culture was as useful as sputum examination for diagnosis and evaluation of the disease. Although *M. gordonae* is usually considered nonpathogenic, our study shows that it can be pathogenic, and *M. gordonae* infection may require treatment with chemotherapy.

Key words: Nontuberculous mycobacterial disease, Pulmonary *Mycobacterium gordonae* infection, Gastric juice culture

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MYCOBACTERIUM XENOPI LUNG INFECTION IN A PATIENT WITH
MULTIPLE LUNG CYSTS THAT RESPONDED WELL TO
CHEMOTHERAPY: A CASE REPORT

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¹Tsugumi SAMEJIMA, ¹Yoshitaka SEKI, ¹Hiroshi TAKEDA, ¹Akira KINOSHITA,
and ²Kazuyoshi KUWANO

Abstract An abnormal shadow was observed on the chest radiograph of a 39-year-old man during health examination. The chest CT scan showed a consolidation around the cysts in the left upper lobe. The patient was diagnosed with *Mycobacterium xenopi* lung infection based on the presence of acid-fast bacilli in the sputum culture several times, which were identified as *Mycobacterium xenopi* by DNA-DNA hybridization. Two weeks after the initiation of chemotherapy with 4 drugs (isoniazid, rifampicin, ethambutol, and clarithromycin), the patient's sputum smear and culture test results were negative; additionally, the consolidation on the chest CT scan improved after 10 months of treatment. There have been several case reports on *Mycobacterium xenopi* lung infection in Japan. However, few have studied *Mycobacterium xenopi*

lung infections associated with multiple lung cysts that responded well to chemotherapy are rare.

Key words: *Mycobacterium xenopi*, Nontuberculous mycobacteriosis, *Mycobacterium heckeshornense*

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Field Activities

**EVALUATION OF THE EFFECT OF DOTS ON TREATMENT OUTCOMES
IN PATIENTS WITH SMEAR-POSITIVE PULMONARY TUBERCULOSIS
IN OSAKA CITY**

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¹Shinichi KODA, ¹Kazuhiko TERAOKA, and ²Akira SHIMOUCI

Abstract [Purpose] To investigate the possibility of improving the results of therapy, we analyzed the association between the performance of directly observed treatment short course (DOTS) and treatment outcomes in patients with tuberculosis.

[Methods] Patients with sputum smear-positive pulmonary tuberculosis who were newly registered in Osaka City between 2007 and 2010 were included in the study. The patients' drug-taking was confirmed at least once a week during DOTS.

[Results] (1) In total, 2,423 patients were enrolled in the study (676, 563, 631, and 553 in 2007, 2008, 2009, and 2010, respectively). Of these, patients who died, those who were transferred during treatment, and those who remained under treatment at the time of analysis, were excluded. In 2007, 2008, 2009, and 2010, 84.1%, 82.3%, 86.2%, and 92.0% of patients, respectively, underwent DOTS and 91.6%, 91.7%, 92.6%, and 95.1%, respectively, were considered to be cured or to have completed treatment, demonstrating increases in both the parameters. On the other hand, 8.4%, 8.3%, 7.4%, and 4.9% of patients, respectively, were considered to have failed to respond to treatment or defaulted, showing a decreasing trend. (2) We examined the results of treatment of the 2010 cohort of patients with respect to whether a patient was supported by the DOTS service. Four percent of the 377 patients who underwent DOTS failed or defaulted compared with 15.2% of the 33 patients who did not undergo DOTS, which was a significant difference ($P < 0.01$). (3) In total, 131 patients failed to respond to treatment or defaulted between 2007 and 2010, with reasons for such including abandonment of treatment, departure from

the hospital, or refusal of treatment in 61 patients (46.6%); premature discontinuation of treatment due to physicians' instructions in 33 (25.2%); and side effects in 22 (16.8%). The absence of a DOTS partner was considered a risk factor for discontinuation of treatment in 31 (56.4%) of the 55 patients who failed to respond to treatment or defaulted in 2009 and 2010.

[Conclusion] An increase in the coverage of DOTS may be important for improving treatment outcomes. The most common reasons for patients failing to respond to treatment or defaulting were abandonment of treatment, earlier departure from hospital, or refusal of treatment. The absence of a DOTS partner accounted for more than 50% of cases of premature discontinuation of treatment. Thus, it may be mandatory to adequately evaluate the risk of treatment discontinuation in individual patients and to take appropriate action against it.

Key words: Pulmonary tuberculosis, DOTS, Treatment outcome, Failure defaulter, Risk of defaulter, Medication support

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Report and Information

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— (6) Tuberculosis Characteristics upon Diagnosis—1 —

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Abstract This article focuses on the bacteriological status and chest radiography findings of tuberculosis (TB) patients registered at diagnosis in 2010.

Among newly identified pulmonary TB (PTB) patients, the proportion of bacteriologically positive cases increased greatly from 25.7% in 1979 to 83.5% in 2010. During this period, the proportion of PTB patients with far-advanced cavities in the lungs remained stable at approximately 2%. This finding may indicate that the patients are diagnosed with TB on the basis of bacteriological test results rather than radiological findings.

The proportion of cases that were confirmed by bacteriological tests increased with age for both male and female TB patients. Among male TB patients, the proportion of cavitory cases increased with age up to 50–59 years, and then decreased.

In the 30–59 years age group, the proportion of sputum smear-positive PTB cases with cavitory lesions was 30.7% among male patients and 16.5% among female patients.

Among the male patients, this proportion was the highest for “Temporary workers” (40.4%), and the lowest for “Teachers/Nursery nurses” (12.5%). Among the female patients, the proportion was the highest for “Other self-employed” (28.1%), and the lowest for “Medical workers” (11.4%).

Key words: Tuberculosis, Bacteriologically positive, Sputum smear-positive, Chest radiography, Cavity, Sex, Age, Occupation

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