Original Article

SERODIAGNOSIS OF THE *MYCOBACTERIUM AVIUM* COMPLEX BY USING IgA ANTIBODIES FOR THE GLYCOPEPTIDOLIPID CORE ANTIGEN

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Abstract [Purpose] The diagnosis of *Mycobacterium avium* complex pulmonary disease (MAC-PD) can be challenging. A serodiagnosis enzyme immunoassay (EIA) kit, which detects the serum anti-glycopeptidolipid (GPL) core IgA antibody, has been commercialized recently; however, its clinical usefulness in the diagnosis of MAC-PD is still unclear. This study aimed to evaluate the availability of this kit and identify factors affecting testing accuracy.

[Methods] We performed a retrospective study of 195 patients who were evaluated with an EIA kit at Nagasaki University Hospital between November 2012 and March 2014.

[Results] 12 of 16 (75.0%) MAC patients have underlying diseases; 8 of 16 (50%) had complications associated with respiratory diseases. There were no significant differences between the seropositive and seronegative background of patients with confirmed MAC-PD. Regarding the accuracy of serodiagnosis EIA kit, its sensitivity and specificity were 81.3% and 88.3% (with a cut-off value of 0.7 U/m*l*), respectively. Of false-positive patients with bronchiectasis, 28.6% demonstrated a good response to anti-MAC treatment, indicating that the sensitivity of the EIA kit might be higher than that of culture-based diagnosis because patients with clinically diagnosed MAC-PD were included in the false-positive population.

[Conclusions] In the current study, the serodiagnosis EIA kit demonstrated good sensitivity and specificity for the diagnosis of MAC-PD. Further clinical investigations are necessary to clarify the role of this kit in definitively diagnosing MAC infections.

Key words: Nontuberculous mycobacteria, Pulmonary MAC disease, Capilia® MAC, Serodiagnosis, Bronchiectasis

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Original Article

THE CURRENT SITUATION OF FOREIGN TUBERCULOSIS PATIENTS AND THEIR CONCURRENT HIV INFECTION IN HOKKAIDO

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Abstract [Background and Purpose] According to recent news, patients with concurrent tuberculosis (TB) and human immunodeficiency virus (HIV) infection are increasingly common worldwide. This study aimed to investigate whether TB/HIV co-infected patients are visiting Hokkaido.

[Method] We conducted a questionnaire survey regarding foreign patients infected with TB or TB/HIV who visited Hokkaido between January 2001 and September 2014. We mailed questionnaires to health centers, AIDS treatment care hospitals, and TB hospitals in Hokkaido prefecture.

[Results] Seventy-one TB patients were of foreign nationality according to the answers obtained from health centers. Most of them were foreign students or occupational trainees between 20−30 years old. Approximately half these patients were from East Asia, and 7 patients were from Africa. As 21 % of the patients with TB who visited medical examination were over 1 month from disease onset, and the delay in visiting was recognized. The TB infection was mostly detected coincidentally during the physician visit. In the hospital survey, four TB patients with HIV were of foreign nationality. They were also of the age group from 20−30 years and hailed from sub-Saharan Africa.

[Discussion] During immigration, medical examination by performing a chest radiograph is important. If the immigrant hails from an area where TB and HIV co-infection is common, it is necessary to confirm whether HIV infection is present.

Key words: Hokkaido, Foreigners, Tuberculosis, HIV infection, AIDS, Internationalization

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CHANGES IN MAC ANTIBODY LEVELS BEFORE AND AFTER SURGERY AND AT THE TIME OF RELAPSE/RECURRENCE IN MAC LUNG DISEASE

— Can MAC Antibodies Be an Indicator of Postoperative Relapse/Recurrence? —

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Abstract [Background] Patients receiving surgical treatment for *Mycobacterium avium* complex (MAC), lung disease should be followed up with careful attention paid to relapse/recurrence, but there is some debate regarding the findings based on which relapse/recurrence should be diagnosed.

[Purpose and Methods] We hypothesized that we might be able to use anti-GPL core IgA antibodies (MAC antibodies), which have been attracting attention as a factor that may support diagnosis of MAC lung disease, to diagnose postoperative relapse/recurrence. Therefore, we compared the levels of these antibodies before and at the time of relapse/recurrence, and also compared antibody titers before and after surgery.

[Result] MAC antibody titers were elevated by an average of about 50% at the time of relapse/recurrence compared to those before relapse/recurrence for 6 patients. In contrast, MAC antibody titers were about 30% lower after surgery compared to those before surgery for 37 patients.

[Conclusion] It may be possible to use MAC antibodies as an indicator of postoperative relapse/recurrence for MAC lung disease.

Key words: Anti-GPL core IgA antibody, MAC antibody, *Mycobacterium avium* complex (MAC), Surgical treatment, Relapse, Recurrence

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Short Report

USE OF QuantiFERON® TB-GOLD IN-TUBE IN A CONTACT INVESTIGATION TO DETERMINE THE ONSET OF TUBERCULOSIS WITH OR WITHOUT LATENT TUBERCULOSIS INFECTION TREATMENT

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Abstract [Purpose] QuantiFERON® TB-Gold In-Tube (3G) testing was performed on tuberculosis-positive index cases and their contacts. The purpose of this study was to evaluate the relationship between 3G test results and the subsequent development of tuberculosis, and to identify effective strategies to prevent the onset of tuberculosis.

[Methods] Index cases and their contacts were subjected to 3G testing in a contact investigation in Osaka City in 2011−2012. For index cases, sputum smears were tested, and the infecting organism was identified. For the contacts, the following information was collected: age, results of 3G testing, presence or absence of latent tuberculosis infection (LTBI) treatment, and onset of tuberculosis disease within 2 years of follow-up from the last contact with the index cases.

[Results] (1) There were 830 index cases, including 774 subjects with pulmonary tuberculosis (93.3%) and 3 with laryngeal tuberculosis (0.4%). From sputum smear tests, 726 patients (87.5%) were determined to be 3G positive, and 83 (10.0%) were determined to be 3G negative. (2) In total, 2,644 contacts were subjected to 3G testing. Of these, 2,072 patients (78.4%) tested negative, 196 (7.4%) showed an equivocal result, and 375 (14.2%) tested positive. Their mean ages were 33.7, 38.0, and 38.8 years, respectively, showing significant differences in tuberculosis status according to age ($P < 0.001$). (3) Among the 2,072 3G-negative contacts, tuberculosis developed in 2 (0.1%) of 2063. None of these contacts was treated for LTBI. Among the 375 3G-positive contacts, tuberculosis developed in 36 (36.0%) of 100 subjects that were not LTBI treated, while tuberculosis developed in 3 (1.1%) of 275 subjects that were LTBI treated. A significant difference in the incidence of tuberculosis between treated and untreated 3G-positive contacts was observed ($P < 0.001$).

[Discussion] Tuberculosis developed in a high proportion of 3G-positive contacts that were not LTBI treated, suggesting the need for preventive management of 3G-positive contacts.

Key words: Pulmonary tuberculosis, Contact investigation, QFT-GIT, LTBI, Onset

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Short Report

COMPARISON OF QuantiFERON® TB GOLD TEST RESULTS BEFORE AND AFTER ENDOTOXIN CONTAMINATION

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Abstract [Purpose] In response to a case of endotoxin contamination of tubes used in QuantiFERON® TB Gold (QFT-3G) testing in Japan in 2013, the effect of this contamination on QFT-3G test results was investigated.

[Methods] We analyzed QFT-3G results from 4,258 participants in a tuberculosis contact investigation in Yamagata, Japan from September 2010 to April 2015. Of these, 2,488 samples were collected before the endotoxin contamination, while 1,770 samples were collected after the contamination.

[Results] Negative control values in the group tested after the contamination were significantly lower than those in the group tested before the contamination ($P < 0.0005$). The proportion of positive controls that exceeded the calculated limit (10 IU/m*l*) in the group tested after the contamination (87.8%) was lower than that in the group tested before the contamination (96.8%; $P < 0.0005$). The proportion of intermediate results in the group tested after the contamination (3.2%) was markedly lower than that in the group tested before the contamination (6.6%).

[Discussion] Differences in QFT-3G test results were found to be related to a difference in blood collection before or after endotoxin contamination of blood collection tubes. Values resulting from QFT-3G testing were lower in blood samples that were collected after the contamination relative to those collected before the contamination.

Key words: QFT-3G, Endotoxin

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Case Report

A CASE OF PULMONARY *MYCOBACTERIUM ABSCESSUS* INFECTION THAT DEVELOPED DURING IMMUNOSUPPRESSIVE THERAPY FOR MYASTHENIA GRAVIS WITH RECURRENT THYMOMA

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Abstract A 58-year-old man developed cough, sputum, and low-grade fever during immunosuppressive treatment with corticosteroids and cyclosporine for myasthenia gravis with recurrent thymoma. Since chest CT revealed diffuse nodular opacities in both lung fields, he was referred to our department. *Mycobacterium abscessus* was repeatedly cultured from his sputum, and he was diagnosed with pulmonary *M.abscessus* infection. Although both chest radiological findings and clinical symptoms were mild, he required treatment with immunosuppressive agents and systemic anesthesia for resection of the recurrent thymoma. Based on complications and according to the patient's preference, oral treatment with clarithromycin 600 mg/day, levofloxacin 500 mg/day, and faropenem 600 mg/day was initiated on an outpatient basis. Following these treatments, his chest CT findings and clinical symptoms subsided, and the thymoma was successfully resected. Our experience with the present case suggests a possible treatment strategy for *M.abscessus* infection in immunocompromised and complicated cases.

Key words: Nontuberculous mycobacteriosis, *Mycobacterium abscessus*, Myasthenia gravis

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A CASE OF MILIARY TUBERCULOSIS ORIGINATED FROM CUTANEOUS INFECTION

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Abstract An 86-year-old woman with severe dementia had been treated with oral prednisolone at 2 mg/day for autoimmune bullous dermatosis for several years. One year ago, she referred to our hospital due to an ulcerative skin lesion over the right tibial tuberosity. The lesion was treated by an iodine-containing ointment, but did not heal. Subsequently, a new skin lesion appeared in the right popliteal fossa. One month ago, the patient had increased sputum production that was accompanied by fever, anorexia, and dyspnea; consequently, she visited our department. Chest computed tomography revealed diffuse micronodules with ground-glass attenuation. Acid-fast bacteria staining of the sputum was positive and the polymerase chain reaction detected *Mycobacterium tuberculosis*. In addition, the bacilli were also found in the skin lesions of the right limb. Therefore, a diagnosis of cutaneous, and miliary tuberculosis was made. Although the anti-tuberculous combination chemotherapy consisting of isoniazid, rifampicin, and ethambutol was immediately initiated, her condition did not improve. She died on day19 of hospitalization. Drug susceptibility testing revealed no resistance to all the three drugs; hence, it was concluded that the time-delay in diagnosis of cutaneous tuberculosis lead to the progression to miliary tuberculosis and subsequent death.

Key words: Cutaneous tuberculosis, Miliary tuberculosis, Acute respiratory distress syndrome

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TUBERCULOUS CONSTRICTIVE PERICARDITIS DETECTED ON POSITRON EMISSION TOMOGRAPHY

Hiroki TAKAKURA, Kouichi SUNADA, and Kunihiko SHIMIZU

Abstract A 72-year-old man presented with fever, dyspnea, and weight loss. He was referred to our hospital for further examination of the cause of the pleural effusions. Chest computed tomography showed pleural effusions, a pericardial effusion, and enlarged lymph nodes in the carina tracheae. We administered treatment for heart failure and conducted analyses for a malignant tumor. The pericardial effusion improved, but the pericardium was thickened. Positron emission tomography–computed tomography (PET-CT) showed fluorine-18 deoxyglucose accumulation at the superior fovea of the right clavicle, carina tracheae, superior mediastinum lymph nodes, and a thickened pericardium. Because these findings did not suggest malignancy, we assumed this was a tuberculous lesion. Echocardiography confirmed this finding as constrictive pericarditis; therefore, pericardiolysis was performed. Pathological examination showed features of caseous necrosis and granulomatous changes. Hence, the patient was diagnosed with tuberculous constrictive pericarditis. PET-CT serves as a useful tool for the diagnosis of tuberculous pericarditis.

Key words: Tuberculous pericarditis, Constrictive pericarditis, FDG-PET

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Review Article

PECULIARITY OF NATIONAL TUBERCULOSIS PROGRAM, JAPAN

— Public-Private Mix from the Very Beginning, and Provision of X-ray Apparatus in Most General Practitioner's Clinics —

Tadao SHIMAO

Abstract Modern National Tuberculosis Program (NTP) of Japan started in 1951 when Tuberculosis (TB) Control Law was legislated, and 3 major components were health examination by tuberculin skin test (TST) and miniature X-ray, BCG vaccination and extensive use of modern TB treatment. As to the treatment program, Japan introduced Public-Private Mix (PPM) from the very beginning, and major reasons why PPM was adopted are ①TB was then highly prevalent (Table 1), ②TB sanatoria where many specialists are working are located in remote inconvenient places due to stigma against TB, ③health centers (HCs) in Japan are working exclusively on prophylactic activities, and minor exceptions are treatment of sexually transmitted diseases and artificial pneumothorax for TB cases, however, as it covers on the average 100,000 population, access is not so easy in rural area, ④Out-patients clinics mainly operated by general practitioners (GPs) are located throughout Japan, and the access is easy.

Methods of TB treatment was developing rapidly in early 1950s, however, in 1952, as shown in Table 2, artificial pneumothorax and peritoneum were still used in many cases, and to fix the dosage of refill air, fluoroscopy was needed. Hence, GPs treating TB under TB Control Law had to be equipped with X-ray apparatus.

To maintain the quality of TB treatment, "Criteria for TB treatment" was provided and revised taking into consideration the progress in TB treatment. If applied methods of treatment fit with the above criteria, public support is made for the cost of TB treatment. To discuss the applied treatment, TB Advisory Committee was set in each HC, composing of 5 members, director of HC, 2 TB specialists and 2 doctors recommended by the local medical association.

In 1953, the first TB prevalence survey using stratified random sampling method was carried out, and the prevalence of TB requiring treatment was estimated at 3.4%, and only 21% of found cases knew their own disease, and more than half of all TB were found above 30 years of age. Based on these results, mass screening was expanded to cover whole population in 1955, and since 1957, cost of mass screening and BCG vaccination was covered 100% by public fund.

Unified TB registration system covering whole Japan was introduced in 1961, and in the same year, national government subsidy for the hospitalization of infectious TB cases was raised from 50% to 80%.

Hence, Japan succeeded to organize PPM system in TB care, and with 10% annual decline of TB, in 1975, Japan moved into the TB middle prevalence country.

Key words: TB Control Law, PPM (Public-Private Mix), Medical institutions designated to treat TB cases under TB Control Law, Artificial pneumothorax

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Review Article

M1 AND M2 MACROPHAGE POPULATIONS: THOSE INDUCED AND ACTIVATED BY MYCOBACTERIAL INFECTIONS

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Abstract In the advanced stages of mycobacterial infections, host immune systems tend to change from a Th1-type to Th2-type immune response, resulting in the abrogation of Th1 cell- and macrophage-mediated antimicrobial host protective immunity. Notably, this type of immune conversion is occasionally associated with the generation of certain types of suppressor macrophage populations. During the course of infections due to pathogenic mycobacteria, the generation of macrophages which possess strong suppressor activity against host T- and B-cell functions is frequently encountered. This review describes the immunological properties of M1- and M2-type macrophages generated in hosts with certain microbial infections including mycobacteriosis and those generated in tumor-bearing animals. Particularly, this paper highlights the immunological and molecular biological characteristics of M1 and M2 macrophage populations, which are induced by mycobacterial infections.

Key words: M1 macrophage, M2 macrophage, Immunosuppressive macrophage, Th17 cell, Mycobacterial infection

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TUBERCULOSIS ANNUAL REPORT 2014

— (1) Summary of Statistics on Tuberculosis Notification and Foreign-born Tuberculosis Patients —

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Abstract This brief is the first of a series of documents based on the *Tuberculosis Annual Report 2014*. It includes a summary of tuberculosis (TB) statistics, including data on foreign-born TB patients notified and registered in Japan in 2014.

For the first time, the number of newly notified cases (all forms of TB) fell below 20,000. In 2014, a total of 19,615 patients were notified, a rate of 15.4 per 100,000 population. The number of sputum-smear positive pulmonary TB patients notified was 7,651, a rate of 6.0 per 100,000 population.

The number of patients with latent TB infections increased slightly from 7,147 in 2013 to 7,562 in 2014. The proportion of miliary TB cases has constantly increased over the past 10 years, especially among women aged 80 years and older.

The number of foreign-born TB patients continued to increase from 1,064 in 2013 to 1,101 in 2014. In 2014, new foreign-born TB patients aged 20−29 years accounted for 44.1 % of all new TB patients in that age group. Among foreign-born TB patients, half were from the Philippines (26.5%) and China (23.5%). However, the number of patients from Vietnam and Nepal is increasing. Among foreign-born TB patients, 28% were regular employees, 26% were students, and 20% were unemployed. The changing trend in the nationality of foreign students entering Japan may at least partially explain the differences in TB burden among foreign-born patients, by country of birth. As we expect to see the proportion of foreign-born TB patients continue to rise, more tailored case identification and treatment support activities are needed.

Key words: Tuberculosis, Notification rate, Latent tuberculosis infection, Country of origin, Occupation

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