Original Article

EVALUATION OF CARE FOR ELDERLY PULMONARY TUBERCULOSIS PATIENTS

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Abstract [Purpose] To examine the clinical problem of elderly pulmonary tuberculosis patients.

[Methods] Clinical findings of pulmonary tuberculosis in elderly patients, who admitted to our hospital from 2001 to 2003, were analyzed in their status, complication, treatment, and prognosis.

[Results] There were 145 patients, and the early elders from 65 to 74 years old were 67, and the latter elders over 75 years old were 78. Most of the cases were treated by the standard tuberculosis treatment, but in the latter elders, less patients were treated by the short course treatment with PZA than the early elders. The rate of negative conversion of sputum culture was good in both the early and the latter elders who were able to continue treatment. But, the elderly pulmonary tuberculosis patients were severe status and their prognosis was in general not good. The elderly pulmonary tuberculosis patients needed frequent care continuously. Tuberculosis problem should be understood more correctly in the medical and the nursing facilities.

Key words: Pulmonary tuberculosis, Elders, Early elders, Latter elders

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Mycobacterium tuberculosis Complex Strains Cultured in Denmark. Journal of Clinical Microbiology. 1999 ; 37 : 2602−2606.

Original Article

COMPARISON OF USEFULNESS BETWEEN VARIABLE NUMBERS OF TANDEM REPEATS (VNTR) ANALYSIS AND RESTRICTION FRAGMENT LENGTH POLYMORPHISM (RFLP) IN THE GENOTYPING OF *MYCOBACTERIUM AVIUM*

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Abstract [Objectives] Comparison of usefulness of IS*1245* RFLP and VNTR in *M. avium* genotyping.

[Materials and methods] Thirty-six cases (55 strains) from sputum and BALF and twelve cases (29 strains) isolated from blood of HIV-infected patients were used. VNTR and RFLP using IS*1245* were performed.

[Result] Multiple samples were taken from 16 patients and 52 clinical isolates were used for VNTR and RFLP for comparison. (1) VNTR and RFLP results were identical in 12 out of 16 cases whose samples were collected several times. (2) Eight isolates were obtained from one patient. In this eight isolates, there were the cases of *M. avium* polyclonal infection and of mixed infection with *M. intracellulare*. VNTR patterns were two types and RFLP were 5 kinds of different in this case. (3) VNTR patterns of six isolates from one HIV-infected patient were identical, but there were three variations in RFLP patterns.

There were three cases of mixed infections with *M. tuberculosis* or *M. intracellulare*, and six strains polyclonal infection of *M. avium* (7.1%) in 84 isolates. These 6 clinical isolates were derived from sputum or BALF (5 strains) and HIV-infected blood (one strain).

VNTR patterns were similar in four pairs (9 strains) who did not contact closely, but they were distinguished clearly by RFLP. Seventeen strains had three or less IS*1245*-related bands in RFLP analyses of 89 strains.

[Discussion] As there is a possibility of polyclonal infection with *M. avium* and mixed infection with other species, the single clonal infection should be confirmed first by VNTR. When single colony was obtained, VNTR and RFLP were performed for genotyping of *M. avium*. Furthermore, strains with less bands by RFLP should be carefully judged in terms of both VNTR and RFLP. It is recommended that the specimens should be collected from each patient several times.

Key words: *Mycobacterium avium*, Variable Numbers of Tandem Repeats (VNTR), Restriction Fragment Length Polymorphism (RFLP), Polyclonal

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Original Article

OUTBREAKS OF TUBERCULOSIS IN FACILITIES USED BY AN UNSPECIFIED NUMBER OF PEOPLE NEAR A TRAIN STATION

— Problems Regarding Tuberculosis in Urban Areas —

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Abstract [Objectives] To report on the mass outbreak of tuberculosis (TB) in an urban area and to discuss current issues regarding the problem of TB in the metropolis.

[Materials and Methods] Case studies were mainly carried out. Discussions on the route of infection are based on the results of DNA fingerprinting analysis for *M. tuberculosis* and on information obtained by epidemiological research.

[Results] In an approximately 500-meter vicinity around Kawasaki Station in Kawasaki City, nine incidences of people contracting TB were reported during the period of one year and five months starting February 2005. Seven of the nine patients were resistant for streptomycin, and the tubercle bacilli of five patients showed identical patterns based on DNA fingerprinting analysis. These nine patients were relatively young, ranging from 16 years to 55 years in age, and three of the patients were homeless. The area for daily activities for all nine patients is a neighborhood of Kawasaki Station. Based on results from an epidemiologic survey, it is suspected that nine patients had come into contact with each other TB patient in places such as "Net cafes" before they developed TB.

[Discussion] Based on the epidemiological and bacteriological results, the route of infection related to this series of TB outbreak is considered to be facilities used by an unspecified number of people such as "Net cafes." Such "Net cafes" are open 24 hours a day and are used by an unspecified number of people, who go to such places to Internet or enjoy comic books. Recently, there are many "Net cafes" in the city, and has become to be used as temporary places to sleep, not only by young people but also by socially vulnerable people, such as the homeless. This study suggests that infection can happen easily once someone begins to discharge TB bacilli in such environments, due to young people, who for the most part are not infected with TB bacilli, and high-risk people, who have higher probability of developing the disease, sharing a closed space for a long period of time. Such social environments may also affect the distribution of TB to lean towards urban areas. The TB control program in the metropolis should be planned and carried out giving consideration to social aspects.

Key words: Tuberculosis, Urban area, Homeless, Young people, Facility used by an unspecified number of people, Net cafe

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Case Report

A CASE OF PULMONARY INFECTION WITH *MYCOBACTERIUM CHELONAE* IN HEALTHY BREAST-FEEDING WOMAN

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Abstract We report a case of pulmonary infection caused by *Mycobacterium chelonae*. The patient was a healthy breast-feeding 29 year-old female. An abnormal shadow had been pointed out by the chest X-ray in the regular checkup of the office workers. The chest X-ray film showed consolidation at right lower lung field, which initially suggested pulmonary tuberculosis. The chest CT scan showed scattered consolidation. Smears and cultures of the sputum were repeatedly positive for mycobacteria, which was identified as *M. chelonae*. By chemotherapy with isoniazid, rifampicin, and clarithromycin on the basis of susceptibility test, sputum converted to negative within 2 months, abnormal shadows on the roentgenogram and laboratory data showed improvement. There are no signs of recurrence after completion of the treatment for 12 months.

Key words: *Mycobacterium chelonae*, Drug susceptibility test, Breast-feeding woman, Medical checkup, Chest abnormal shadow

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The 82nd Annual Meeting Special Lecture

ANTI-TUBERCULOSIS CHEMOTHERAPY

Masako WADA

Abstract The era of the modern chemotherapy in the treatment of tuberculosis has started by the discovery of streptomycin in 1943. Soon after the introduction of SM, it became evident that drug-resistance against streptomycin (SM) quickly emerged when used singly, and the combination therapy with para-aminosalicylate (PAS) and isoniazid (INH), both of which were developed a little later, had been the standard regimens for the treatment of tuberculosis. But, long-term therapy, more than a year, sometimes of two or three years, was required to get recovered from tuberculosis by three-drug combination therapy of SM-PAS-INH. Introduction of rifampicin (RFP) in 1966 and re-evaluation of pyrazinamide (PZA) in early 1970's have brought a revolutionary change in the concept of tuberculosis chemotherapy, and very potent six-month regimen, consisting of two-month initial intensive phase (INH-RFP-PZA and EB or SM) and four-month maintenance phase (INH-RFP) has been established as the global standard regimen.

Tuberculosis chemotherapy has liberated tuberculosis patients from lengthy stay in sanatoria or hospitals. Now, tuberculosis patients could be and should be treated by the intensive short-course chemotherapy under ambulatory settings. One of the most serious obstacles of ambulatory treatment is the incompliance of the patients to the prescribed regimen. Obvious outcome of such incompliance is the treatment failure at the level of individual patients and also the prevalence of multidrug-resistant- (MDR-) and extensively drug-resistant- (XDR-) tuberculosis all over the world. MDR- and XDR-tuberculosis are already threatening tuberculosis control policy in some countries and districts in the world.

Early diagnosis of infectious patients and successful treatment of newly diagnosed patients under DOTS are the most recommendable strategies to prevent the emergency of MDR- and XDR-tuberculosis worldwide.

In Japan, the policy of tuberculosis treatment has been more or less diverged from the global standards, namely, higher rate of hospitalization, longer hospitalization periods, and longer treatment. One of the most important reasons for such cost-effectively inefficient practices is the lack of reliable and practical DOT system for ambulatory treatment. Recently, we successfully completed a trial to implement a DOT system in which the city-pharmacists served as the observer. We believe that this system is well acceptable for both city-pharmacies and tuberculosis patients, and expect to be adapted through the whole country.

New anti-tuberculosis drugs which enable the intermittent therapy of much shorter duration are eagerly expected.

Key words: Anti-tuberculosis chemotherapy, Short-course chemotherapy, Resistant tuberculosis, Directly observed chemotherapy, Intermittent chemotherapy

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The 82nd Annual Meeting Symposium

RECENT PROGRESS IN MYCOBACTERIOLOGY

Chairpersons: [1]Masaji OKADA and [2]Kazuo KOBAYASHI

Abstract *Mycobacterium tuberculosis* is one of the most successful bacterial parasites of humans, infecting over one-third of the population of the world as latent infection without clinical manifestations. Over 8.8 million new cases and nearly 2 million deaths by tuberculosis (TB) occur annually. TB poses a significant health threat to the world population. The goal of this symposium is to open new avenues for combating tuberculosis. The speakers have presented their data and provided control strategies against tuberculosis and pulmonary disease due to *M. avium* complex (MAC) from aspects of molecular epidemiology, pathogenesis, serodiagnosis, new anti-TB drugs, and vaccine development.

Drs. Maeda and Murase have reported that the 12-locus VNTR analysis is very useful for molecular epidemiology of *M. tuberculosis* strains isolated in Japan better than IS*6110*-RFLP and suggested that the analysis is powerful tool for the molecular epidemiology.

Drs. Matsumoto and Kobayashi have discovered a protein, mycobacterial DNA-binding protein 1 (MDP1), overproduced in dormant *M. tuberculosis* that plays key roles in latent/persistent infection, disease progression, and host protection. They have concluded that MDP1 may be a possible target for anti-tuberculosis drugs and vaccines.

Drs. Kitada and Maekura have developed serodiagnosis of MAC disease based on enzyme immunoassay (EIA) by detecting anti-glycopeptidolipid (GPL) antibody in sera of human patients. GPL is specific for MAC. The EIA is a simple, rapid and accurate measure with high sensitivity and specificity. The levels of antibody also reflect disease activity. A large-scale clinical multicenter study is currently in progress.

Dr. Makoto Matsumoto has discovered an innovative new anti-TB drug, OPC-67683 that is a derivative of nitroimidazole compounds. OPC-67683 inhibited mycolic acid synthesis and exerted potent antimycobacterial activity, including multidrug-resistant *M. tuberculosis*. Multidrug therapy using OPC-67683 could also shorten the course of chemotherapy. The drug is clearly the most promising new anti-TB agent that has been identified in many years.

Dr. Okada has presented the vaccine candidates for TB, such as HVJ-liposome/HSP65 DNA＋IL-12 DNA and HVJ-envelope/HSP65 DNA＋IL-12 DNA. The candidates exhibited an excellent protective efficacy in mice compared to current BCG vaccine, and improved histopathologic lesions induced by *M. tuberculosis* infection. The candidates also exerted the therapeutic effect in mice against both drugsusceptible TB and extensively drug-resistant TB. Using the cynomolgus monkey model (similar to human TB), HVJ-liposome/HSP65 DNA＋IL-12 DNA provided higher protective efficacy than BCG assessed by mortality. The combination of BCG and HVJ-liposome/HSP65 DNA＋IL-12 DNA by the prime-booster procedure could lead to a synergistic effect of 100% survival in infected monkeys. These data suggest that the novel DNA vaccine is a possible candidate for human clinical trials.

This symposium has highlighted new advances in our understanding of molecular epidemiology and pathogenesis of "Mycobacteriology" and development of new serodiagnostics, anti-TB drugs, and vaccines.

1. The establishment of the quick genotyping method for TB in Japan using the variable numbers of tandem repeats (VNTR): Shinji MAEDA, Yoshiro MURASE (Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association)

The 12-locus VNTR analysis that we have established optimally for *Mycobacteriun tuberculosis* in Japan was superior to the proposed 15-locus VNTR method in European countries. The discriminatory power of our system was also higher than that of IS*6110*-based restriction fragment length polymorphism analysis. In future, we will investigate the stability of copy number in each locus by using the strains that suspected epidemiological links in contact investigations.

2. A virulence factor of *Mycobacterium tuberculosis*, which contributes to persistent infection, reactivation, and host protection: Sohkichi MATSUMOTO (Department of Host Defense, Osaka City University Graduate School of Medicine), Kazuo KOBAYASHI (Department of Immunology, National Institute of Infectious Diseases)

Majority of adult tuberculosis is caused by reactivation of previously implanted *Mycobacterium tuberculosis*. During latent infection, some bacilli are in dormant state, which confers some survival advantage to not only bacteria but also the host. We presented that a protein overproduced in dormant *M. tuberculosis* plays key roles in persistent infection, disease progression, and host protection. We also presented utility of this protein, such as development of anti-tuberculosis drug and vaccine.

3. Serodiagnosis of *Mycobacterium avium* complex pulmonary disease by enzyme immunoassay using glycopeptidolipid antigen: Seigo KITADA, Ryoji MAEKURA (Department of Internal Medicine, National Hospital Organization National Toneyama Hospital)

The diagnosis of *Mycobacterium avium* complex pulmonary disease (MAC-PD) and/or its discrimination from pulmonary tuberculosis is sometimes complicated and time consuming.

We have developed serological test by enzyme immunoassay that detect serum antibody to glycopeptidolipid antigen. The serodiagnosis is useful for the rapid diagnosis of MAC-PD and differential diagnosis from pulmonary TB. The antibody levels reflected the disease activity including radiographic severity.

4. A novel antituberculous agent, OPC-67683: Research and development: Makoto MATSUMOTO (Microbiological Research Institute, Otsuka Pharmaceutical Co., Ltd.)

We initiated a program to screen new antituberculous agents that have potential to shorten the total duration of treatment, provide improved efficacy against MDR-TB, be useful in treating HIV co-infected patients, and target latent TB infections. Our efforts led to the discovery of OPC-67683, a novel oxazo-imidazole derivative with a distinctive characteristic as a subclass mycolic acid inhibitor. Our evaluation studies confirmed OPC-67683 to possess potent *in vitro* and *in vivo* antituberculous activity, suggesting potential usefulness in alleviating the current TB problems.

5. The development of novel vaccines against *M. tuberculosis*: Masaji OKADA (Clinical Research Center, National Hospital Organization Kinki-Chuo Chest Medical Center)

We have developed a novel tuberculosis (TB) vaccine (HVJ-liposome/ or HVJ-envelope/HSP65 DNA＋IL-12 DNA). The vaccine provided remarkable protective efficacy in mouse compared to BCG vaccine, and improved the histopathological tuberculosis lesions. This vaccine also exerted therapeutic effect in *vivo* against XDR-TB as well as drug-sensitive TB in mice.

Furthermore, by using the cynomolgus monkey (similar to human tuberculosis), this novel vaccine provided higher protective efficacy (mortality) than BCG mortality. Furthermore, the combination of HSP65＋IL-12/HVJ and BCG by the priming-booster method showed a synergistic effect in the TB-infected cynomolgus monkey (100% survival). These data indicate that our novel DNA vaccine might be useful against TB for human clinical trials.

Key words: Molecular epidemiology, Latent infection with mycobacteria, Serodiagnosis, Novel anti-tuberculous chemotherapeutic agents, Vaccine development

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