Issue

DIFFICULTIES IN THE TREATMENT OF TUBERCULOSIS IN INFANTS

Shinya KONDO and Masaki ITO

Abstract Nowadays, methods of the diagnosis in infants with suspected tuberculosis and of the treatment are definitely established in Japan, where a number of childhood tuberculosis has been falling down (the incidence is less than 2 per 100,000). Still, infants less than one year are considered to be at high risk against tuberculosis. Actually, the number of tuberculosis among them is three times larger than those of one or two years old children. One of major reasons of difficulties in the treatment is the rapid progress of the disease because of underdeveloped cell-mediated immunity among them. Alveolar macrophage and lymphocyte and their cooperation in immunological functions do not develop enough to kill or confine *Mycobacterium tuberculosis*. As a result, the infection may progress to disease quickly, and then may spread systemically before the starting treatment. Anatomical underdevelopment of cranial arteries and narrow cerebrospinal passages easily cause cerebral infarction and hydrocephalus following meningeal inflammation due to tuberculosis. These neurological disorders may result in poor prognosis despite of administration of effective anti-tuberculosis medicines. Delay in the diagnosis also makes the treatment difficult in some infants whose tuberculin skin test shows false negative and radiographic manifestation of chest is not clear. During the treatment, systemic and enteric viral infections occur frequently among infants with tuberculosis, and liver functional disorders caused by these infections sometimes disturbs the treatment for tuberculosis. Recurrence of tuberculosis is very rare among infants who complete the full treatment at the age of more than one year. Finally, it is important for the early start of treatment for tuberculosis to recognize both susceptibility to tuberculosis and difficulties in the diagnosis in some infants less than one year.

Key words: Infants less than one year, Tuberculosis, Cell-mediated immunity, Delayed-type hypersensitivity, Tuberculous meningitis, Paradoxical worsening

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Original article

THE INCIDENCE RATE OF ACTIVE PULMONARY TUBERCULOSIS AMONG ADULT POPULATION WITH FIBROTIC LESIONS

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Abstract The incidence rate of "active" pulmonary tuberculosis (TB) cases with bacteriological confirmation or cavitary lesions on chest radiographs was studied among population screened with mass miniature radiography in Funai-Gun, Kyoto Prefecture from 1982 to 1993. The results were as follows: Among population of 40 and over, prevalence rate of all fibrotic lesions on chest radiographs among male (8.3%) was twice as high as that of female (3.8%). The rate of moderate or extensive fibrotic lesions among male (3.3%) was three times as high as that of female (1%). The higher the age of the population, the higher the prevalence rate of radiological fibrotic lesions both in male and female. In male, in particular, prevalence rate of moderate or extensive fibrotic lesions started to rise after 40 years of age, became much higher after 70 years of age and reached 8.1% after 80 years of age. In female, however, it started to rise at 50s (0.3%) gradually and reached only 2.3% after 80 years of age. The incidence rate of "active" pulmonary TB among male of 40 years and over with moderate or extensive fibrotic lesions (4.2 per 1000 person-years) was 16 times as high as male of 40 years and over with normal chest X-ray finding (0.26 per 1000 person-years). Similarly, the incidence rate of "active" pulmonary TB in female of 40 years and over with moderate or extensive fibrotic lesions was 24 times as high as among female with normal finding, and the difference was statistically significant ($p < 0.001$). From the data obtained and bibliographical review, benefits of INH prophylaxis were discussed.

Key words: Pulmonary tuberculosis, Incidence of tuberculosis, X-ray mass screening, Fibrotic lesions

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Original Article

EFFECT OF GLYCYRRHIZIN ON ANTI-TUBERCULOSIS DRUG-INDUCED HEPATITIS

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Abstract In cases in which hepatotoxicity developed during anti-tuberculosis chemotherapy, the rapid recovery of liver function is essential for the completion of the anti-tuberculosis chemotherapy protocol. Glycyrrhizin (Stronger Neo-Minophagen C: SNMC) is widely used in Japan for the treatment of patients with drug eruption or chronic hepatitis. However, a consensus on the clinical effects of glycyrrhizin for the treatment of anti-tuberculosis drug-induced hepatitis has not yet been reached. We studied 24 cases who showed abnormal liver function test results while undergoing anti-tuberculosis chemotherapy and who were treated with or without glycyrrhizin. We then compared recovery periods of liver function among both groups. The time required for liver function normalization in the patients who received glycyrrhizin (SNMC, 40 m*l* daily, intravenously) was 15.1 ± 4.5 days and the time required for normalization in the non-glycyrrhizin group was 15.2 ± 5.2 days. The difference was not significant and the fact indicated that glycyrrhizin is not useful for the treatment of anti-tuberculosis drug-induced hepatitis.

Key words: Anti-tuberculosis drug, Liver dysfunction, Drug-induced hepatitis, Glycyrrhizin, Hepatoprotective agent

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A CASE OF PULMONARY TUBERCULOSIS INITIALLY PRESENTED WITH SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE (SIADH)

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[2] Masayuki MATSUMOTO, [3] Masahide YASUI, and [3] Masaki FUJIMURA

Abstract A 90-year old man was admitted to a hospital because of consciousness loss with hyponatremia. Although his symptom promptly improved with Na supply, his chest X-ray film showed pulmonary infiltration and direct microscopy of sputum smear was positive for acid-fast bacilli, then he was referred our hospital and was admitted. We made a clinical diagnosis of pulmonary tuberculosis with SIADH based on detailed examinations. But he should neither respiratory symptoms nor fever. He was medicated with the standard antituberculosis drugs with fluid restriction, and his tuberculosis and hyponatremia were improved gradually.

We should be more careful about pulmonary tuberculosis irrespective of its severity as a cause of SIADH.

Key words: Pulmonary tuberculosis, Syndrome of inappropriate secretion of antidiuretic hormone (SIADH), Hyponatremia

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Short Report

EFFECTS OF ANTISENSE OLIGO DNA ON THE ANTIMICROBIAL ACTIVITY OF REACTIVE OXYGEN INTERMEDIATES AND ANTIMYCOBACTERIAL AGENTS AGAINST *MYCOBACTERIUM AVIUM* COMPLEX

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Abstract There has not yet been systematic studies which attempt to elucidate detailed profiles of the interaction between antimicrobial drugs and macrophage microbicidal mechanisms. We examined the effects of antisense oligo DNAs (AsDNAs) against *oxyR* and *ahpC* on the susceptibility of *Mycobacterium avium* complex (MAC) to the H_2O_2-halogenation system and combined antimycobacterial drugs〔clarithromycin (CAM) ＋ rifampicin (RFP)〕, both separately and in combination. It was found that AsDNA treatment of MAC did not affect the susceptibility of the organisms to any of the antimicrobial systems tested. Since the present AsDNAs did not efficiently reduce the expression of AhpC mRNA, attempts to increase bacterial uptake of AsDNAs are necessary to achieve significant increase in the drug susceptibility of MAC organisms due to AsDNA treatment.

Key words: *Mycobacterium avium* complex, Antisense oligo DNA, H_2O_2-halogenation system, Clarithromycin, Rifampicin

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The 77th Annual Meeting Invited Lecture

TUBERCULOSIS CONTROL STRATEGY IN ASIA FOR THE 21ST CENTURY
— Tuberculosis Control in the Western Pacific Region of World Health Organization —

Shigeru OMI

Abstract The unprecedented and rapid changes at the global level posed a big challenge to public health. The tuberculosis disease as one of major health problems today should be viewed from this context. These global challenges include 1) population issue particularly on growth and ageing; 2) epidemiological issue such as health transition; and, 3) social and environmental issues such as rapid urbanization and global warming. Furthermore, we should also take into account other changes such as the role of the government in the health service delivery, clinical or cure-oriented approach to prevention, increasing consumer demand and health financing.

The burden of tuberculosis is devastating. Everyday in the Western Pacific Region (WPR), about 1000 people lose their life due to tuberculosis. Most of them are between the ages 14–54, which are the so-called economically productive age group. The economic impact, therefore, is significant. In addition TB is a disease of poverty of which the risk of getting TB is higer in poor who have less access to TB services due to financial barrier and lack of knowledge. Despite this devastating situation, TB has a significant and cost effective tool called DOTS. WPRO put highest priority in TB control programme not only because of the facts mentioned above but I also consider TB as an agenda carried over from the last century. I would like, then, to commit myself to this cause for the betterment of the future of the next generation.

Key words: Tuberculosis Control, Western Pacific Region, DOTS strategy

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The 77th Annual Meeting Educational Lecture

HIV INFECTION AND TUBERCULOSIS

Hideaki NAGAI

Abstract The number of people infected with human immunodeficiency virus (HIV) is gradually increasing in Japan, and the morbidity rate from tuberculosis in the Japanese people is high. Accordingly, the number of cases with both infections is considered to increase in the future. Our hospital has already encountered 31 cases of HIV associated tuberculosis.

HIV infects mainly CD4-positive cells. The extreme decrease in the cell count results in serious cellular immunological disorder. CD4-positive cell disorder induces disorders of B lymphocytes, cytotoxic T cells, natural killer cells, and macrophage functions. These destructive conditions show the state of immunodeficiency including macrophage that are most important for defense of acid-fast bacterial infection. Migration and activation of macrophages with cytokines derived from T cells are impaired to induce the following phenomena: hypoplasia of granuloma, failure of tubercule bacillus suppression, the spread to regional lymph nodes (hilar or mediastinal lymph nodes), and hematogenous dissemination. On this occasion, caseous necrosis and cavitation are unlikely to occur, and false-negative tuberculin reaction is often observed.

The incidence of severe cases, which include miliary tuberculosis, tuberculous meningitis, etc., and extrapulmonary tuberculosis, are high among acquired immunodeficiency syndrome (AIDS)- associated tuberculosis cases. HIV-infected tuberculosis cases are generally regarded as endogenous exacerbation, but they include primary infection and reinfection as well. Even during the treatment for drug-sensitive strains particularly, some cases may have reinfection with multidrug-resistant bacteria, suggesting that caution should be taken against this point. Conversely, the association of tuberculosis is a factor for the poor prognosis of HIV infection, since it facilitates the development of HIV infection. If the bacteria belong to a drug-sensitive strain, the infection with them responds well to antituberculous drugs, the same as in tuberculosis cases without HIV infection, showing a favorable prognosis. However, the mortality rate of infection with multidrug-resistant tuberculosis is extremely high.

The combined use of a protease inhibitor, i.e., anti-HIV drug, with rifampicin is regarded as contraindication for the treatment because rifampicin strongly induces hepatic cytochrome P-450 and increases the metabolism of protease inhibitors and nonnucleoside reverse transcriptases to markedly decrease the blood concentrations. Accordingly, the treatment for tuberculosis should take priority over that for HIV infection in HIV-infected tuberculosis, and highly active antiretroviral therapy (HAART) may be administered after the treatment of tuberculosis. When HAART is necessary for the treatment during the tuberculosis treatment, rifampicin had better be exchanged to rifabutin because the effect of rifabutin to induce cytochrome P-450 is less potent than that of rifampicin.

A report has recently shown that the exacerbation of pyrexia and chest X-ray findings was transiently observed approximately 2 weeks after potent anti-HIV therapy for HIV- infected tuberculosis, which included a protease inhibitor. The reason for the exacerbation has been believed to be that the impaired function of CD4-positive cells is improved by the administration of anti-HIV drugs to raise temporarily the reaction of the vital part to *M. tuberculosis*.

A tuberculin skin test (TST) reaction size of ≧5 mm of induration is considered positive (i.e., indicative of *M. tuberculosis* infection) in persons who are infected with HIV. Persons with a TST reaction size ≧5 mm who have not previously received treatment for *M. tuberculosis* infection should receive tuberculosis preventive treatment. Prevention by BCG vaccination is regarded as contraindications for HIV-infected patients, because disseminated *M. bovis* infection may be associated with them.

Many HIV-positive patients infected with tuberculosis show uneventful healing, when *M. tuberculosis* is the sensitive strain. However, since some patients show the rapid course of tuberculosis, clinical physicians keep the early detection of tuberculosis for HIV-infected patients and the association of HIV infection for tuberculosis patients in their mind, respectively.

Key words: Tuberculosis, Human immunodeficiency virus, Acquired immunodeficiency syndrome, Protease inhibitor, Immune reconstitution syndrome

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The 77th Annual Meeting Symposium

UP-TO-DATE UNDERSTANDING OF TUBERCULOSIS IMMUNITY

Chairpersons: [1]Masao MITSUYAMA and [2]Kiyoko AKAGAWA

Abstract This symposium was organized to provide the up-to-date knowledge on tuberculosis immunity, especially on the understanding of cytokines or Th1 cells involved in pathophysiology/protective immunity and vaccine development.

Dr. Kazuo Kobayashi (Osaka City Univ.) reported their findings on the immune response to bioactive lipid component from *M. tuberculosis*, trehalose-dimycolate (TDM) and sulfolipid (SL) in mice. Their unique and novel finding was that TDM is capable of inducing T-dependent immune response in euthymic mice. The specific immune response in TDM-immune mice was consisting of CD4+ cell response and expression of chemokines, inflammatory cytokines and then TH1-related cytokines. In contrast, SL did not show such an activity. TDM may be one of the protective antigens and may modulate the specific immune response of the host.

Dr. Isamu Sugawara's group (JATA) has examined the involvement of various cytokines in the host response to aerosolic infection with virulent strain of *M. tuberculosis* by using cytokine-knockout mice. The single deletion of IFN-γ or TNF α resulted in a severe lesion of multiple necrosis without granuloma, and cytokine mRNA level other than knocked out cytokine was normal, suggesting that IFN-γ and TNF α are principally important cytokines. In knockout mice for IL-12 or IL-18, necrotic lesion was not induced after infection and the pathological change was not so significant as in IFN-γ/TNF α knockout mice. By using IFN-γ knockout mice, it became possible to generate a granulomatous lesion with central necrosis and cavity resembling the lesion in humans. These mouse model appeared to be useful in the analysis of pathophysiology of human tuberculosis.

Dr. Kazuyoshi Kawakami (Ryukyu Univ.) reported the importance of TH1 cytokines in anti-tuberculous immunity. By using IL-12, IL-18 knockout mice or double knockout mice, it was shown that IL-12 exhibits more important role than IL-18 in the protection. A possible contribution of IL-23 was also suggested. In most of the clinical cases of tuberculosis, the production of IL-12, IL-18 and IFN-γ is increased, however, the group of relatively lower cytokine production did not respond well to the treatment. In addition, the plasma level of one of the chemokines, IP-10, was shown to be an indicator for the severity of the disease. Thus, some cytokines appear to be employable for the novel treatment in the near future.

Dr. Saburo Yamamoto (NIH) summarized the recent advance in the understanding of biological function of CpG motifs. Immunostimulatory DNA is effective in the modulation of TH1/TH2 polarity and the enhancement of protective immunity to *M. tuberulosis* in animals. CpG motif (immunostimulatory DNA) appears to exert its activity by signaling cascade via TLR9 resulting in NF-κB activation and cytokine gene expression. Analysis of basic mechanism of action by CpG motif should pave the way to the clinical application in the future.

Dr. Masaji Okada (Kinki Chuo Hospital) reported the current situation in the development of novel vaccines against tuberculosis. They have extensively constructed and examined the efficacy of various types of vaccines including subunit, DNA and recombinant BCG vaccines. Various vector systems have been tested for DNA vaccine. As immunizing antigens, a-Ag, ESAT-6, HSP65, 38kD-lipoprotein and so on have been employed. A large body of experimental data are accumulating for final evaluation, and among them, it is noteworthy to mention that HSP65DNA+IL-12DNA was 100 times more effective than conventional BCG in animal model. Among subunit vaccines, Mtb72f vaccine appears to be one of the promising candidates. In addition to the trial with various candidates, they have established a new mouse model, SCID/human PBL. This model animal has been employed for the development of vaccine effective for the induction of ESAT-6-specific human T cells.

Key words: Anti-tuberculous immunity, TH1, Cytokine, Vaccine

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TOWARDS SUCCESS OF TUBERCULOSIS TREATMENT

Chairpersons: [1]Toyoo SAKURAYAMA and [2]Takeko YAMASHITA

Abstract The most important aim of tuberculosis control is to increase treatment success rates. Therefore, it is necessary to prevent unfavourable outcomes and multi-drug resistant tuberculosis to achieve the goal. Our national average figure of tuberculosis success rates between 1991 and 1996 has been 79.9 percent, which did not reach the WHO recommended success rate of 85 percent. The geographical discrepancy became bigger by years and the high death rate among the elderly owes very much the low success rates. There are two major factors that contribute the relatively low success rates in Japan. One factor is age and another is high incidence rate in urban area. Our previous study showed that 30.2 percent of the total tuberculosis patients were over 70 of age with the higher death rate and lower success rate than those younger than 70. High default rates in urban area have greatly contributed to the low success rates. There was huge difference of highest success rate and lowest one, 86.7 and 53.4 percent, respectively.

Lively discussion towards tuberculosis elimination was done in this symposium. The major topics were unique regional activities and cost-effective analysis of DOTS in urban setting.

1. Hospital DOTS was presented by Ms. Yukiko Saito,

RN. She shared the experience of her DOTS practice and evaluation method of hospital DOTS in the Fukujuji hospital. Their questionnaire results showed that DOTS group had lower percentage of imperfect pill taking and indicated the importance of hospital DOTS for the smooth transition to outpatient DOTS.

2. Ms. Kazuyo Arima, RN presented her health center DOTS strategy (Fureai DOTS) in Osaka city. Osaka city has the highest tuberculosis incidence rate that is equivalent to that of Nepal due to the high incidence among street persons. Tuberculosis control has been the city's rolling cry. The components of Osaka tuberculosis control are; (1) indiscriminate DOTS for street people and smear positive patients (Airin DOTS and Fureai DOTS) and (2) the patients follow up meeting (Cohort Kaigi). The number of health care providers who adopted DOTS has been increasing because of their active campaign of DOTS. This also stimulates the motivation of public health nurse to involve tuberculosis control.

3. The patient management using follow up chart (Cohort Kansatsubo) was presented by Ms. Yoko Nagata, RN in Itabashi Ward Health Center. The results of follow-up observation in 2000 revealed low success rate (72.3 percent), high proportion of bacteriological non-confirmation, and low public health nurse involvement rate. These figures ameliorated in accordance with the introduction of their unique follow-up method. The better outcome may be because of better collaboration among public health nurses according to Ms. Nagata. Their next ambition is to establish the standardized care for tuberculosis patients throughout the Itabashi ward.

4. The endeavour of Kobe city was presented by Dr. Chika Shirai, MD. Kobe city set up their goals by conducting follow up meeting (Cohort Kentoukai) ; 85 percent of success rate, less than 5 percent of default and failure, 90 percent of patients with the public health nurse encounter, 100 percent in bacteriological confirmation and indiscriminate contact investigation. The default/failure rates reduced from 11 to 4 percent. She also emphasized on the prospective plan, e.g., combination of their cohort based follow up chart and tuberculosis surveillance system, DOTS, reporting and recording system up date, expansion of standardized tuberculosis treatment, collaboration with other organization for patients follow-up, and integration of tuberculosis diagnosis committee.

5. The cost-effectiveness analysis of Japanese DOTS among homeless persons in Osaka city was presented by Dr. Moriyo Kimura, MD in the Research Institute of Tuberculosis. The results showed that DOTS was more cost-effective than non DOTS mainly due to low default rate and short hospitalization. However, the success of DOTS is not simply because of implementation of DOTS strategy but the person to person relationship between public health nurses and tuberculosis patients is the most important issue. In other words, DOTS would be highly cost-effective only if public health nurse involvement existed. This presentation also suggests that DOTS in slum area may reduce the burdens of poverty that is an important factor of tuberculosis.

6. Final presenter, Dr. Isao Kurosu, MD, shared his experience in his hospital. He emphasized the importance of DOTS implementation as the standardized treatment. The most important point for the DOTS introduction is that each patient understands that DOTS equalizes patients opportunities and confirms their pull taking, according to him. His presentation was concluded with that the collaboration with other health personnel such as nurses and public health nurses should be the key for the success of hospital DOTS.

In summary, DOTS is an important and highly cost-effective strategy for tuberculosis control in Japan. The establishment of human relationship between patients and health care providers is the key issue. Doctors should collaborate with other health personnel to make the Japanese DOTS successful.

Key words: Hospital DOTS, Outpatient DOTS, Cohort chart, Cohort meeting, Cost-effective analysis

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