
Original Article

STABILITY FOR LONG-TERM STORAGE AND REPRODUCIBILITY OF POSITIVITY IN THE PANEL TEST SLIDE PREPARED WITH THE POLYACRYLAMIDE-BASED ARTIFICIAL SPUTUM¹Hiroyuki YAMADA, ²Hiroko MATSUMOTO, ¹Satoshi MITARAI, and ³Akiko FUJIKI

Abstract [Objective] A novel artificial sputum has been developed using polyacrylamide, cultured THP-1 cell and BCG-Pasteur. Smears prepared with this artificial sputum are similar to actual sputum and has feasibility to set any positivity grades. Long-term storage and reproducibility of the positivity was examined to support further availability.

[Method] The artificial sputa were stored for up to 9 months at room temperature, 4°C and -20°C. Then, smears were prepared and their macroscopic and microscopic appearance were examined compared with smears from freshly prepared artificial sputum. Furthermore, smears with different positivities (\pm , 1+, 2+ and 3+) were prepared and examined by several trained technicians, and the reproducibility of the original sputum positivity was determined.

[Results] Macroscopic and microscopic appearance of smears prepared from long-term stored artificial sputum showed little changes compared with smears of freshly prepared artificial sputum. The positivity of these smears fell in their original grade. A total of 91 smears were prepared from artificial sputum with different positivity and examined by trained technicians. Although 3 out of 36 \pm smears were

determined as negative, all of the remaining smears were evaluated correctly.

[Discussion] This study confirmed that the artificial sputum and the smears have long-term storage stability and reproducibility in the positivity. These results suggest that the artificial sputum can be widely used to perform external quality assessment in many countries, including high prevalence countries.

Key words : Smear examination, Artificial sputum, Long-term storage, Reproducibility

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Original Article

A STUDY ON CLINICAL FEATURES OF *MYCOBACTERIUM KANSASII*
PULMONARY DISEASE IN WOMEN

Hiroyuki KAMIYA, Soichiro IKUSHIMA, Tetsu SAKAMOTO, Kozo MORIMOTO,
Tsunehiro ANDO, and Masaru ORITSU

Abstract [Objectives] To clarify clinical features of *M. kansasii* pulmonary disease in women.

[Methods] We performed a retrospective analysis of *M. kansasii* pulmonary disease in women comparing with that in men. We focused on 8 female cases of *M. kansasii* pulmonary disease during the past 7 years from June 1998 to August 2005.

[Results] The cases of *M. kansasii* pulmonary disease in women have increased in the latter few years. The mean age of female cases was higher than that of male cases, 65.6 and 53.1 years old, respectively. The number of female cases with smoking history was lower than that of male cases, 37.5% and 90.0%, respectively. Two female cases had underlying pulmonary diseases, as compared with 10 male cases, 25.0% and 33.3%, respectively. The radiological findings in female cases included 2 cavitary opacities, 1 infiltrative opacity and 5 nodular, bronchiectatic opacities, as compared with 27 cavitary opacities, 1 infiltrative opacity, 1 solitary nodular opacity and 1 nodular, bronchiectatic opacity in male cases. MAC was also detected in 2 female cases, who presented with nodular, bronchiectatic opacities. On the other hand, there were 6 female cases, in which no other NTM was detected. 3 cases showed cavitary or infiltrative opacities, which improved with the following 3 tuberculous drugs INH, RFP, and EB (HRE), while others showed nodular, bronchiectatic opacities, in which 2 cases showed radiological exacerbations

without any treatment and another one revealed an improvement with HRE.

[Conclusions] *M. kansasii* pulmonary disease in women tends to be identified in elderly who smoke less and have no underlying pulmonary diseases, and most of radiological findings in female cases revealed nodular, bronchiectatic opacities. Summing up all these findings, clinical features of *M. kansasii* pulmonary disease in women was considered to resemble that of MAC infection, and it was speculated that the increase of *M. kansasii* pulmonary disease in women has some relationship with that of MAC infection in middle or lingular lobe. However, it was confirmed that some cases of *M. kansasii* pulmonary disease in women might primarily present with nodular, bronchiectatic lesions, regardless of MAC infection.

Key words: *Mycobacterium kansasii* pulmonary disease, Female cases, Nodular, bronchiectatic opacities, Colonization

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TRANSMISSION OF TUBERCULOSIS FROM SMEAR-NEGATIVE BACILLUS-POSITIVE PULMONARY TB PATIENTS

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Abstract [Objectives] To elucidate TB transmission from smear-negative bacillus-positive patients.

[Subjects and Methods] The subjects of this retrospective study were 8,339 TB patients registered in Aichi Prefecture between 1989 and 2003. Of these patients, 7,122 had pulmonary TB and 1,217 had extra-pulmonary TB. Bacteriological examination for the pulmonary patients revealed sputum smear-positive in 2,640, sputum smear-negative bacillus-positive (SNBP) in 1,794, and smear-negative bacillus-negative (SNBN) in 2,688.

All registration files were reviewed to identify epidemiological links of patients. When linked patients with an interval of the dates of registration of less than 10 years were found, the initial case was considered as the index case, and the other patients were regarded as secondary cases.

An index case rate (ICR) for a category of patients was defined as follows; $ICR = NI/NA$, where NA : Number of TB patients in a category A, and NI : Number of index cases in category A.

[Results] A total of 287 patients were considered as index cases, and the ICR was 3.4%. The ICRs were 2.3% for the SNBP patients, 7.5% for the smear-positive patients, 1.2% for the SNBN patients, and 1.1% for the extra-pulmonary tuberculosis patients. The SNBP patients had a significantly higher ICR than the SNBN patients ($p < 0.01$), and a significantly lower ICR than the smear-positive patients ($p < 0.001$). In the SNBP patients, the ICRs were 5.0% for those aged 40 to 49 years and 1.6% for those aged 50 to 59, and the difference was statistically significant ($p < 0.05$). All patients were grouped into two groups; younger patients with an age

of less than 50 years and elder patients with an age of 50 years or higher. The ICRs showed significant differences between the younger patients and the elder patients as follows: 4.3% vs 1.7% for the SNBP patients ($p < 0.01$), 15.5% vs 5.0% for the smear-positive patients ($p < 0.001$), and 1.9% vs 0.9% for the SNBN patients ($p < 0.05$). The chest X-ray showed cavitory lesion in 453 SNBP patients. The ICRs were 8.7% for 126 cavitory younger SNBP patients, 2.6% for 311 non-cavitory younger SNBP patients, 2.4% for 327 cavitory elder SNBP patients, and 1.5% for 1,030 non-cavitory elder SNBP patients. The ICR for the cavitory younger SNBP patients was significantly higher than those for the other three subgroups ($p < 0.01$ to $p < 0.001$).

[Conclusion] These findings suggest that TB transmission from SNBP patients depends on the patient's age and the cavity formation, and that patients aged less than 50 years with cavitory pulmonary TB is the most important target for the epidemiological research.

Key words : Smear-negative bacillus-positive pulmonary tuberculosis, TB transmission, Index case rate, Aging, Cavitory lesion, Gender difference.

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A CASE OF ADRENAL TUBERCULOSIS COMPLICATED WITH ACUTE EXACERBATION OF ADRENAL INSUFFICIENCY DURING THE INITIAL PHASE OF ANTI-TUBERCULOSIS THERAPY FOR PULMONARY TUBERCULOSIS

Reiko TAKI, Makiko SUGIURA, Tsunehiro SORITA, Sahoko CHIBA,
Naoko SAIJO, Yoko HIRAKI, and Masafumi YOSHIZAWA

Abstract A 36-year-old male was admitted to our hospital because of adrenal insufficiency. About one month before admission, he was diagnosed as pulmonary tuberculosis and started anti-tuberculosis therapy with isoniazid, rifampicin, ethambutol, and pyrazinamide. On the tenth day, general fatigue, abdominal pain, nausea and diarrhea developed, and laboratory examination showed hyponatremia [126 mEq/l]. Enhanced CT on admission revealed bilateral adrenal mass-like enlargement, and further examination showed high level of plasma ACTH, and low level of cortisol. These findings led to a diagnosis of adrenal insufficiency caused by adrenal tuberculosis. He was treated with hydrocortisone and his signs and symptoms rapidly improved. We suppose adrenal insufficiency became clinically apparent because rifampicin

reduced half-life of serum cortisol. Interestingly we observed rapid increase and decrease in size of bilateral adrenal glands on CT scan during the course.

Key words: Pulmonary tuberculosis, Adrenal tuberculosis, Addison's disease, Adrenal insufficiency, Rifampicin

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————— The 82nd Annual Meeting Invited Lecture —————

TUBERCULOSIS ELIMINATION IN THE UNITED STATES;
WHY, HOW, AND WHAT WILL IT TAKE?

Kenneth G. CASTRO

Abstract This overview of tuberculosis elimination in the United States consists of three parts. First I will briefly overview the neglect and related factors during 1970's and early 80's which resulted in the 1985–1992 unprecedented resurgence of tuberculosis following thirty years of a steady decline in the United States. Second, I will review what we did in response and the resulting trends. Third, I will focus on the Institute of Medicine (IOM) report entitled “Ending Neglect”, and identify the challenges to elimination and what will it take to finishing the job.

The IOM report recommends the United States to pursue and accelerate the elimination of tuberculosis, addressing the following; 1) maintain control while adapting to declining incidence of tuberculosis, 2) speed the decline through the increased treatment of persons with latent infection, 3) invest in research and development to develop new tools needed for ultimate elimination, with a focus on new reliable and rapid diagnostic tools for latent infection, new drug regimens, especially in light of the emergence of extensively drug-resistant tuberculosis, and a safe and effective vaccine for tuberculosis, 4) increase the United States engagement in global efforts, recognizing that the global reality is directly reflected in the United States, 5) mobilize support and measure

progress towards elimination. Each of these recommendations will be translated into the agenda for action with the illustrations for the real situations of the United States.

It is important to recognize that in spite of all this progress much work needs to be done and in order to finish the job on tuberculosis elimination we have the blueprints, we have the partners, and we must keep working to make the effective use of our resources.

I would like to close by quoting one of the favorite phrases in “Ending Neglect”; “The issue now confronting the nation, that is the United States, is whether we will allow another cycle of neglect to begin or instead whether we will take decisive action to eliminate tuberculosis.”

Key words: TB elimination, TB resurgence, Ending neglect

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INNATE IMMUNITY AND TUBERCULOSIS

^{1,2}Satoshi UEMATSU and ^{1,2}Shizuo AKIRA

Abstract The immune system is divided into innate and adaptive immunity. The innate immune system provides the first line of host defense against invading microorganisms before the development of adaptive immune responses. Innate immune responses are initiated by germline-encoded pattern recognition receptors (PRRs), which recognize specific structures of microorganisms. Toll-like receptors (TLRs) are one of the family of pattern-recognition receptors to sense a wide range of microorganisms, such as bacteria, fungi, protozoa and viruses. Recognition of *Mycobacterium tuberculosis* components by TLRs triggers activation of signal transduction pathways, which then induces dendritic cell maturation and cytokine production, resulting in development of adaptive immunity. TLRs are critically involved in the induction of

host defense to *M. tuberculosis*.

Key words: Innate Immunity, Pattern recognition receptor, Toll-like receptor

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————— The 82nd Annual Meeting Educational Lecture —————

HUMAN RIGHTS OF PATIENTS AND TUBERCULOSIS PREVENTION

Shigeru TAKAHASHI

Abstract The Act for Prevention and Medical Treatment of Patients of Infectious Diseases in Japan was revised in December 2006. Through this revise of the act, the articles for the measures against Bio-terrors were incorporated into the act, and the idea of respect of human rights of patients surely took root into the act.

At the same time, the Tuberculosis Prevention Act was abolished and the articles of this act were partly revised and incorporated into the Act for Prevention and Medical Treatments of Patients of Infectious Diseases. The procedural rights of tuberculosis patients and the role of jurists in the procedure of tuberculosis prevention were consolidated. It is

desirable that dialogues between jurists and those who are engaged in tuberculosis prevention should be accelerated by these legislations.

Key words: Human rights of patients, Tuberculosis prevention, Due process of law

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GRANULOMATOUS DISEASES AND PATHOGENIC MICROORGANISM

Chairpersons: ¹Yoshikazu INOUE and ²Moritaka SUGA

Abstract Granuloma formation is a chronic inflammatory reaction where macrophage system and other inflammatory cells are involved. After some antigen exposure and processing, T cells, macrophages, epithelioid cells, and giant cell are activated, and granulomas are formed. Granuloma is considered as a defense mechanism against antigens, which stay in the organs without inactivation. Granulomas including fibroblasts extra-cellular matrix surround and isolate the antigens.

Granulomas are classified to noninfectious granulomas and infectious granulomas. However recent studies revealed pathogenic microorganism are suspected to be a cause of granuloma in non-inflammatory diseases. Balance between pathogenic microorganisms and defense mechanisms of the host might be important in the special immunologic reaction. In some cases, it is hard to clearly classify infectious and non-infectious granulomas. Recently, Eishi et al. reported that latent infection of *Propionibacterium acnes* might be cause of sarcoidosis. Several hypersensitivity pneumonias are considered to be caused by exogenous microorganisms. The symposium was organized to know and clarify the new

mechanisms of non-infectious granulomatous lung diseases and pathogenic microorganisms. This report is a summary of a symposium entitled “Granulomatous Diseases and Pathogenic Microorganism”, organized in the 82nd Japanese Society for Tuberculosis (president Dr. Mitsunori Sakatani, M.D.).

1. Imaging of Granulomatous Lung Diseases : Masanori AKIRA (Department of Radiology, National Hospital Organization Kinki-chuo Chest Medical Center)

High-resolution computed tomography (HRCT) is a useful tool in the evaluation of parenchymal changes in patients with a granulomatous lung disease. In sarcoidosis, the HRCT findings include small, well-defined nodules in relation to lymphatic roots, lymph node enlargement, and middle or upper lobe predominance. The appearances of subacute hypersensitivity pneumonitis include ill-defined centrilobular nodules, ground-glass opacity, and air trapping especially on expiratory CT scan. Those of Langerhans cell histiocytosis include bizarre thin-walled lung cysts, centrilobular nodules and upper lobe predominance. Each of granulomatous lung

disease has some characteristic HRCT appearances, but they all are non-specific for diagnosis. HRCT is also useful for grading of parenchymal changes in granulomatous lung diseases.

2. Histopathology of granulomatous lung diseases with special reference to differential diagnosis of infectious disease: Tamiko TAKEMURA (Department of Pathology, Japanese Red Cross Medical Center)

The lung is commonly involved by various granulomatous diseases of various etiology. It is difficult to pathologically differentiate these granulomatous diseases to conduct appropriate therapy, because of morphological similarity of epithelioid cell granuloma, variable etiology, and difficulty of identification of causative agents. Granulomatous diseases generally are divided into infectious and non-infectious ones for treatment.

Although infectious granulomas usually reveal necrosis and abscess, non-infectious ones occasionally also reveal necrosis. In cases with granulomas in the lung, it is necessary to explore the etiologic agents including environmental ones.

3. Sarcoidosis and *Propionibacterium acnes*: Yoshinobu EISHI (Department of Pathology, Tokyo Medical and Dental University)

P. acnes can cause latent infection in peripheral lung tissue and the mediastinal lymph nodes and persist intracellularly in a cell-wall-deficient form. This dormant form of *P. acnes* can be activated endogenously under certain environmental conditions (hormones, stress, living habits, etc.) and proliferate in cells at the sites of latent infection. Granulomatous inflammation occurs in sarcoidosis patients with hypersensitivity to intracellular proliferation of the cell-wall-deficient bacteria, which can infect other cells or organs when spread via the lymphatic or blood streams. The timely use of antibiotics may not only kill the bacteria proliferating at the site of disease activity, but also prevent endogenous activation of *P. acnes*. If long term administration of antibiotics eradicates dormant forms of the bacteria persistent in organs, it may lead to complete remission of sarcoidosis.

4. Farmer's lung and thermophilic actinomycetes: Takashi MOURI (Pulmonary Division, Iwate Prefectural Kitakami

Hospital), Kohei YAMAUCHI, Hiroshi INOUE (Third Department of Internal Medicine, Iwate Medical University, School of Medicine), Kazuki KONISHI (Morioka Tsunagi Onsen Hospital)

Farmer's lung is caused by the allergic reaction to inhalation of thermophilic actinomycetes. Acute symptoms are chill, fever, cough and dyspnea. Fine crackles is characteristic. Pathologically, alveolitis with lymphocytes infiltration and epithelioid cell granuloma and Masson's body are characteristics. Bronchoalveolar lavage analysis shows elevated lymphocytes and diverse CD4/8 ratio (high in average). Isolation from the environment improves the symptoms. Sometimes patients need steroid therapy, 0.5 to 1.0 mg/kg of prednisolone. Pulse therapy can be applied for severe cases. SLX analogue can prevent lymphocytes infiltration and granuloma formation in mice model. Some of acute farmer's lung show poor long term prognosis, showing emphysematous, fine granular or small nodules in chest CT. These chronic farmer's lung might be diagnosed as IIPs.

5. Hot tub lung: Takashi OGURA (Kanagawa Cardiovascular and Respiratory Center)

Hot Tub Lung (HTL) is a disorder caused by exposure to *Mycobacterium avium* complex (MAC) organisms contaminating hot tub water. Whether this disease represents true infection or hypersensitivity pneumonitis is controversial. Recent reports support the theory that this disease represents a hypersensitivity pneumonitis rather than infection. The physicians should suspect a hypersensitivity pneumonitis reaction to MAC in the investigation of patients with hypersensitivity pneumonitis of unknown cause.

Key words: Granulomatous lung diseases, Pathogenic micro-organism, Sarcoidosis, Farmer's lung, Hot tub lung

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