

Original Article

COMPARATIVE STUDY OF BACTEC MGIT 960 AST AND CONVENTIONAL PROPORTION METHOD USING OGAWA MEDIUM FOR THE DRUG SUSCEPTIBILITY TESTING OF *MYCOBACTERIUM TUBERCULOSIS* TO ISONIAZID

¹Satoshi MITARAI, ³Ikuo KOBAYASHI, ³Chiyoji ABE, ²Masako WADA, ⁴Katsuhiro SUZUKI,
⁵Tetsuya TAKASHIMA, ⁶Yoshiko KAWABE, ⁶Kazuko MACHIDA, ⁷Masao TANO,
⁸Shuichi TAKIGAWA, ⁹Arisu KAMADA, ¹⁰Eriko SHIGETOH, ¹¹Shunji FUJII, ¹²Kenichi MORI,
¹³Hisashi SUYAMA, ¹⁴Shuichi YANO, ¹⁵Takeo KAWASHIRO, and ¹⁶Hideo OGATA

Abstract [Objective] To evaluate the accuracy of drug susceptibility testing to isoniazid with BACTEC MGIT 960 (MGIT AST) comparing with the standard proportion method using Ogawa medium.

[Method] A total of 1,109 *M. tuberculosis* strains, which were selected from the collection of RYOKEN drug resistance survey in 2002, were selected and subjected to the susceptibility testing to isoniazid using MGIT AST and 1% Ogawa standard methods. The results from MGIT AST were compared with the judicial diagnosis by Ogawa. The sensitivity to detect drug resistance, the specificity for susceptible strain, the efficiency of overall agreement, and kappa coefficient were calculated to evaluate the performance. The treatment process, outcome and prognosis were analysed for the patients on whom the tests showed discrepant results.

[Results] Compared with the judicial results, the sensitivity, specificity, efficiency, and kappa coefficient of MGIT AST were 100%, 97.1%, 97.3%, and 0.798, respectively. The strains, which showed discrepant results between MGIT AST and Ogawa, were all susceptible by Ogawa and resistant by MGIT AST. A total of 11 out of 30 discrepant cases were followed clinically and no relapse cases were identified, irrespective of the modification of the treatment regimen. As for the proportion of primary INH drug resistance in the present study, it was 5.3% with MGIT AST but was 2.7% with Ogawa, and the difference was statistically significant ($p=0.005$).

[Discussion] The discrepancies on the results of drug susceptibility testing of *M. tuberculosis* strains to isoniazid between MGIT AST and 1% Ogawa proportion method have been reported. In the present study, the sensitivity, specificity, and overall efficiency of MGIT AST on the prevalent strains in Japan were all beyond 95%, and considered sufficient as the anti-tuberculosis drug susceptibility testing (AST), though

2.7% of discrepancy was observed. Even for the discrepant cases, there was no difference in the treatment outcome and prognosis. Thus, MGIT AST was confirmed as a reliable AST method comparable to Ogawa standard. However, MGIT AST might increase the proportion of INH resistance if it was used as a major AST method, compared with Ogawa.

Key words: Tuberculosis, Anti-tuberculosis drug susceptibility testing, Isoniazid, Low concentration, MGIT AST

¹Bacteriology Division, Mycobacterium Reference Centre, and ²Research Division, Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association (JATA), ³Diagnostic Systems, Nippon Becton Dickinson Company Ltd. ⁴Respiratory Medicine, National Hospital Organization (NHO) Kinki-chuo Chest Medical Center, ⁵Tuberculosis Medicine, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, ⁶Respiratory Medicine, NHO Tokyo National Hospital, ⁷Respiratory Medicine, NHO Higashi Nagoya National Hospital, ⁸Respiratory Medicine, NHO Nishibeppu National Hospital, ⁹Respiratory Medicine, NHO Sapporo Minami National Hospital, ¹⁰Respiratory Medicine, NHO Higashihiroshima Medical Center, ¹¹Respiratory Medicine, NHO Yamagata National Hospital, ¹²Respiratory Medicine, NHO Higashitokushima National Hospital, ¹³Respiratory Medicine, Nagasaki Municipal Medical Center, ¹⁴Respiratory Medicine, NHO Matsue National Hospital, ¹⁵Respiratory Medicine, NHO Higashisaitama National Hospital, ¹⁶Respiratory Medicine, Double-barred Cross Hospital, JATA

Correspondence to: Satoshi Mitarai, Bacteriology Division, Mycobacterium Reference Centre, Research Institute of Tuberculosis, JATA, 3-1-24 Matsuyama, Kiyose-shi, Tokyo 204-8533 Japan. (E-mail: mitarai@jata.or.jp)

SIGNIFICANCE OF TUBERCULOSIS SCREENING OF OUTPATIENTS IN AREAS WITH HIGH PREVALENCE OF TUBERCULOSIS

¹Nobuaki NAKATA, ¹Fumiaki INORI, ¹Fusao NAKAMURA, ²Shigeyoshi HARIHARA,
³Yukio HIRAYAMA, ⁴Akira SUZUKI, ⁵Akira SHIMOUCI, and ⁶Toshio TAKATORIGE

Abstract [Objective] The Osaka Socio-Medical Center Hospital is a medical care facility located in the Airin area of Osaka city where the prevalence of tuberculosis is high, and treats day laborers and homeless people mainly, either free of charge or with a small fee. To investigate whether this hospital can play a role to reduce the prevalence of tuberculosis in this area, we investigated the case rate of active tuberculosis in outpatients of the hospital.

[Subjects and Methods] Of 1,673 patients who first visited the Orthopaedic Outpatient Clinic between March 31, 2005 and June 15, 2006, 538 patients consented to undergo screening and underwent chest X-ray examination (screening group). We also analyzed chest X-ray examination in 2,000 patients examined at the Department of Internal Medicine during the same period (control group).

[Results] Of the 538 patients in the screening group (523 males and 15 females), 13 male patients (2.4%) requiring treatment were detected. Of the 2,000 patients in the control group, 85 patients (84 males and 1 female) (4.3%) requiring treatment were detected.

[Conclusion] The tuberculosis case rate (2.4%) in the

screening group was similar to that of tuberculosis screenings (1.1–1.8%) in the Airin area in 2004. The case rate in the control group was two times higher. Since the prevalence is very high in patients of this hospital, the hospital should play a significant role in the health care of tuberculosis patients in this community by reinforcing the screening system and enriching the outpatient clinic system.

Key words: Tuberculosis, Screening, Airin, Free-of-charge or small-fee medical care facility, Day laborers

¹Department of Orthopaedic Surgery, ²Department of Internal Medicine, ³Clinical Laboratory, ⁴Social Consultation, Osaka Socio-Medical Center Hospital, ⁵Osaka City Public Health Office, ⁶Public Health, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University

Correspondence to: Nobuaki Nakata, Department of Orthopaedic Surgery, Osaka Socio-Medical Center Hospital, 1–3–44 Haginochaya, Nishinari-ku, Osaka-shi, Osaka 557–0004 Japan. (E-mail: n-nakata@med.osaka-cu.ac.jp)

ASSOCIATION BETWEEN CLUSTERED STRAIN OF *M.TUBERCULOSIS*
AND INFECTIONOUSNESS INDEX OF TUBERCULOSIS CASES
IN A POPULATION-BASED *IS 6110*-RFLP ANALYSIS

^{1,2}Eri TSUKISHIMA, ^{1,3}Yuu MITSUHASHI, ¹Koichi YANO, ¹Aiko TAKASE,
⁴Arisu KAMADA, ⁴Masaru AMISHIMA, ⁵Yasushi AKIYAMA
⁵Michihiro FUJINO, ⁴Katsuyuki TOBISE, and ⁵Fujiya KISHI

Abstract [Objective] Isolates of *M. tuberculosis* were analyzed for their DNA fingerprints to facilitate understanding of ongoing transmission of tuberculosis in Sapporo (population 1.87 million), Japan, where the incidence rate of tuberculosis was 15.0 per 100,000 in 2004.

[Subject] Out of all tuberculosis patients registered in the city from November 1998 to December 2003, isolates from culture-positive respiratory tuberculosis cases for whom written informed consent had been obtained, were analyzed by restriction fragment length polymorphism (RFLP). The study included 345 cases (249 men and 96 women) whose isolates were available for DNA patterns.

[Method] Using standard *IS6110*-RFLP typing, cases whose isolates shared identical fingerprints were considered to belong to the same cluster. Proportions of clustered cases were evaluated according to their clinical and socio-economical characteristics.

[Results] Out of 345 cases, 207 (60.0%) were classified into 59 clusters, and 15% of clustered cases having definite epidemiological links. Multiple logistic regression analysis in men showed that age and infectiousness were significantly related to clustering. The adjusted odds ratios (OR) [95% confidence intervals (CI)] were 0.17 [0.03–0.79] for 30–59 years, 0.15 [0.03–0.69] for 60 years or over and 2.35 [1.17–4.70] for those cases assigned as the highest level of transmis-

sion of tuberculosis from the infectiousness index of cases. For women the final model showed the adjusted OR [95% CI] were 0.52 [0.22–1.22] for those with previous history of tuberculosis and 0.33 [0.06–1.85] for diabetics. In male cases with a previous history of tuberculosis, most highly infectious cases were significantly associated with clustering (OR [95% CI], 4.53 [1.16–17.68]).

[Conclusion] The results suggest that highly infectious male tuberculosis cases with endogenous reactivation have contributed to recent transmission of tuberculosis in the studied area.

Key words: *Mycobacterium tuberculosis*, Molecular epidemiology, Restriction fragment length polymorphism, Infectiousness index of tuberculosis cases, Cluster rate

¹Sapporo Public Health Office, ²Health & Welfare Department, Kiyota Ward Office, City of Sapporo, ³Health & Welfare Department, Kita Ward Office, City of Sapporo, ⁴National Hospital Organization Sapporo-Minami National Hospital, ⁵Hokkaido Social Insurance Hospital

Correspondence to: Eri Tsukishima, Sapporo Public Health Office, 19 Odori Nishi, Chuo-ku, Sapporo-shi, Hokkaido 060-0042 Japan. (E-mail: eri.tsukishima@city.sapporo.jp)

Original Article

A SURVEY OF ANTI-TUBERCULOSIS DRUG-INDUCED SEVERE LIVER INJURY IN JAPAN

*Eriko SHIGETO, Committee for Treatment, Japanese Society for Tuberculosis

Abstract [Purpose] To clarify the incidence and clinical significance of anti-tuberculosis drug-induced liver injury.

[Subjects and Methods] Questionnaire was sent out by mail to 114 hospitals, to ask whether there were patient(s) from 1994 to 2003 with liver injury induced by anti-tuberculosis drugs with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level of more than 1,000 IU/l and/or total bilirubin level of more than 2 mg/dl. As for the cases of severe hepatic injury, their backgrounds and clinical courses were investigated.

[Results] Seventy cases were reported from 24 out of 68 hospitals which treated at least 8,095 tuberculosis patients in 2003. Incidence rate of severe liver injury by anti-tuberculosis drugs was 0.50 to 0.59 percent in three hospitals with good surveillance system, and overall incidence was estimated to be between 0.1 to 0.5 percent. We could analyze 33 cases; one was HB antigen positive, one had HCV positive liver cirrhosis, 2 had other hepatic disease, and 17 had other underlying disease including diabetes mellitus. Twenty-three were treated by regimens with isoniazid (INH), rifampicin (RFP) and pyrazinamide (PZA), and 8 by regimens without PZA but with INH and RFP and one was a multidrug-resistant case and was treated by regimen with ethionamide and PZA. The onset of liver injury was within 2 months after starting anti-tuberculosis chemotherapy in 28 (85%) cases. In twenty-eight cases which both ALT and total bilirubin level are known, total bilirubin level at the onset of liver injury was more than 2 mg/dl in 14 cases and most of the cases were

hepatocellular type of liver injury. Six out of 10 cases with total bilirubin level more than 5 mg/dl died by liver failure. Total bilirubin was less than 2 mg/g/l in two of the dead cases; in one case antituberculosis drug were continued despite elevated level of ALT and another case complicated with gastric bleeding. Treatment for liver injury was conservative in most cases, 6 were treated by plasmapheresis and no liver transplantation was carried out. Eight cases died of liver failure, one died of tuberculosis and only 15 were treated successfully for tuberculosis.

[Conclusion] Incidence rate was high compared with that by other drugs reported previously. The risk factor of liver injury by antituberculosis drugs was not detected, but elevated total bilirubin level more than 5 mg/dl was an alarming sign for poor prognosis.

Key words: Anti-tuberculosis drugs, Standard regimen, Drug-induced liver injury, Hepatic failure, Incidence

*Department of Respiratory Medicine, National Hospital Organization Higashihiroshima Medical Center

Correspondence to: Eriko Shigeto, Department of Respiratory Medicine, National Hospital Organization Higashihiroshima Medical Center, 513 Jike, Saijo-cho, Higashihiroshima-shi, Hiroshima 739-0041 Japan.

(E-mail: shigetou_eriko@hiro-hosp.jp)

Case Report

TUBERCULOSIS OF THE STERNOCLAVICULAR JOINT

Takeshi KAWASAKI, Yuka SASAKI, Aya SHINOZAKI, Rei BEKKU,
Tomohiro HASHIMOTO, Takenori YAGI, and Fumio YAMAGISHI

Abstract Tuberculosis is seen in every part of the body, but sternoclavicular joint tuberculosis is rare. We report a case of tuberculosis of the sternoclavicular joint in 70-year-old woman having complained of the right sternoclavicular joint swelling. She had a previous history of pulmonary tuberculosis, and visited her doctor for right sternoclavicular joint swelling on February 2006. A chest CT scan showed a low density area with destructive osseous changes in the right sternoclavicular joint. Definite diagnosis could not be done by twice needle biopsy, but we diagnosed her as tuberculosis of the sternoclavicular joint based on the clinical course and the findings of the examination. As her condition did not improve after 3 months treatment with anti-tuberculous drugs, we conducted therapeutic surgical procedure. Definite diagnosis of sternoclavicular joint tuberculosis was made on the basis of the presence of mycobacteria in the histological specimen and PCR-TB positive result. We kept the wound opened and continued administration of anti-tuberculous drugs, and her condition

does not deteriorate. Tuberculosis should be considered in case of a patient with arthritis and previous history of tuberculosis, even if it is seen in rare location. Diagnostic and therapeutic surgical procedure should be taken into consideration, if there is no improvement of the condition after a diagnosis of bone and joint tuberculosis, and the administration of chemotherapy for tuberculosis.

Key words: Sternoclavicular joint tuberculosis, Bone and joint tuberculosis, Tuberculous arthritis

Department of Thoracic Disease, National Hospital Organization Chiba-East National Hospital

Correspondence to: Takeshi Kawasaki, Department of Thoracic Disease, National Hospital Organization Chiba-East National Hospital, 673 Nitona-cho, Chuo-ku, Chiba-shi, Chiba 260-8712 Japan. (E-mail: t-kawa@cehpnet.com.)

A CASE OF TUBERCULOUS PLEURISY WITH EOSINOPHILIC PLEURAL EFFUSION AND HEMATOLOGICAL EOSINOPHILIA

Eishi KATO, Noriko YAMADA, and Takahiko SUGIURA

Abstract A 30-year-old man suffered from a chest-pain on his left side and was also having a low-grade fever though he actually neglected these symptoms for a while. Later, he was referred to our hospital due to the detection of chest abnormal shadows through the mass examination of chest X-ray taken on 18th October, 2005. His chest X-ray showed bilateral pleural effusion and it was confirmed that the right pleural effusion was encapsulated by his chest CT. The patient's hematological examination performed during his initial visit, showed an increased level of WBC with blood eosinophilia. He also had a puncture of pleural effusion at the time of admission to the center. Moreover, pleural effusion on both sides was exudative and elevations of ADA and eosinophil count as well were traced. In the patient's right pleural effusion, mycobacterium tuberculosis direct (MTD) test was positive.

As there were no findings suggesting collagen disease, malignancy, parasite infection, and other complications, he was diagnosed as tuberculous pleurisy with eosinophilic pleural effusion and blood eosinophilia. He was treated with four antitubercular agents, namely, INH, RFP, EB and PZA. As the result, his pleural effusion and blood eosinophil counts

were decreased along with an improvement in inflammatory reaction. The most common conditions associated with eosinophilic pleural effusion are described as malignancy, collagen disease, paragonimiasis, drug induced pleurisy, asbestosis, pneumothorax, and trauma, while there are only a few reports about such eosinophilic pleural effusion caused by tuberculous pleurisy. In this case, he also showed blood eosinophilia. Based on these findings, we finally came to the conclusion that the case is a very rare and significantly unique case of eosinophilic pleurisy with blood eosinophilia.

Key words : Tuberculous pleuritis, Eosinophilic pleural effusion, Hematological eosinophilia

Department of Respiratory Disease, Aichi Cardiovascular and Respiratory Center

Correspondence to : Eishi Kato, Department of Respiratory Disease, Aichi Cardiovascular and Respiratory Center, 2135 Kariyasuga, Yamato-cho, Ichinomiya-shi, Aichi 491-0934 Japan.