Review Article

MULTI DRUG RESISTANT TUBERCULOSIS

Takashi YOSHIYAMA

Abstract The proportion of multi drug resistant tuberculosis (MDR-TB) among new TB cases is 0.5% in Japan and 3% overall the world and with the increasing trend of TB cases that were born in endemic countries of TB, the risk of MDR-TB is increasing in Japan. Drug susceptibility test has been done traditinoally with phenotypic method but the genotypic method is prevailing globally in 2010s and Xpert® MTB/RIF has been introduced in Japan from 2016. When the case is detected as Rifampicin resistant, we need to start treatment with isoniazid, ethambutol, pyrazinamide, kanamycin, ethionamide, cycloserine and para-amino salycilic acid together with rifabutin until we know the drug susceptibility test result consideirng the risk of drug resistance and in order to avoid further acquisition of drug resistance. Globally, 9 months regimen including moxifloxacin, clofazimine, pyrazinamide, high dose isoniazid, ethambutol, ethionamide/prothionamide is used with good treatment result. In Japan, high cost of bedaquiline and delamanid, non-approval of bedaquiline and delamanid for non-MDR-TB who cannot be treated with isoniazid and rifampicin with adverse drug reactions, and non-approval of linezolid, clofazimine and moxifloxacin for tuberculosis are the barriers to the appropriate prevention and treatment of MDR-TB. Drug resistance to new drugs is appearing globally and we need to consider these resistant cases and avoid further acquisition of drug resitance, and role of surgery will continue in this setting.

Key words: Multi drug resistant tuberculosis, Xpert® MTB/RIF, Acquisition of drug resistance

Fukujuji Hospital, Japan Anti-Tuberculosis Association

Correspondence to: Takashi Yoshiyama, Fukujuji Hospital, Japan Anti-Tuberculosis Association, 3−1−24, Matsuyama, Kiyose-shi, Tokyo 204−8522 Japan.
(E-mail: yoshiyama1962@yahoo.co.jp)

Review Article

ISSUES IN TREATMENT OF TUBERCULOSIS IN JAPAN

Eriko SHIGETO

Abstract Treatment of tuberculosis is under control of government in Japan by administrative standards for tuberculosis care with public expenses payment system and DOT by public health center nurses. But the treatment success rate of initial treatment is lately around 50 percent which is substantially lower than recommended target level. Though high mortality in aged is the utmost cause and failure plus dropout is less than 5%, proportion of patients still on treatment at 12 months is around 10%. Long-term treatment of drug-susceptible tuberculosis may be caused by treatment without PZA, and/or inadequate cope with adverse reaction by general practitioner. Provision of information on standard treatment, more detailed guides of countermeasures to side effects and liaison between general practitioner and TB experts or Regional Tuberculosis Advisory Committees are required.

Treatment of drug-resistant tuberculosis needs different viewpoint. Drug-resistant tuberculosis patients are treated by personalized regimen based on drug-resistant test, but molecular based drug sensitivity tests are not widely used despite being approved for RFP, INH and PZA. Several drugs including moxifloxacin and linezolid recommended in WHO guidelines for drug-resistant tuberculosis are used by some experts but insufficiently because they are off-label. Consideration is necessary for these laboratory tests and off-label drugs to be available when needed. Delamanid and bedaquiline are approved for pulmonary MDR-TB and under control of tuberculosis expert through responsible access program by the pharmaceutical company. From September 2014 to February 2018, 135 cases were eligible to use delamanid and no acquisition of resistance is reported till June 2018. These new drugs are properly used under the control of experts, but its cost can be heavy burden on outpatient who must pay 5% of medical expenses. Abatement of economic burden for these patients is required.

DOTS is widely and well done lately, but recent issue is the support for foreign born patients who now account for more than 50% in 20−29yr age group. Language barrier is common, and knowledge of patient's religious constraints and customs are required. Tuberculosis treatment literacy materials in various languages are recently becoming available but the need for medical interpreter is not fulfilled.

Political will is required for implementation of adequate treatment in response to new technology and change of patient background.

Key words: Pyrazinamide, Treatment success rate, Adequate treatment, Drug-resistant tuberculosis, Medical system for tuberculosis treatment

National Hospital Organization Higashihiroshima Medical Center

Correspondence to: Eriko Shigeto, National Hospital Organization Higashihiroshima Medical Center, 513 Jike, Saijyo-cho, Higashihiroshima-shi, Hiroshima 739−0041 Japan.
(E-mail: eshigetou@hiro-hosp.jp)

Review Article

EDUCATION FOR TUBERCULOSIS AND NON-TUBERCULOUS MYCOBACTERIAL DISEASES

— Comparison between Lung Tuberculosis and Non-Tuberculous Mycobacterial Lung Diseases —

Jiro FUJITA

Abstract The diagnosis of an acid-fast bacterial infection should be performed comprehensively, using medical history, physical findings, microbiological examination, and radiological findings. However, the final diagnosis of mycobacterial diseases is traditionally based on a microbiological examination or pathological finding, but radiological findings can assist this. In recent years, a pathologic-radiologic correlation has been established through the detailed analysis of chest high-resolution CT (HRCT); specifically, the radiological findings of pulmonary tuberculosis patients compared with their pathological findings. Now, it is possible to estimate pathological findings from HRCT images. In other words, the radiological findings of pulmonary tuberculosis contain fundamentals of chest radiological diagnosis. Potentially, understanding the radiological findings of pulmonary tuberculosis will, in turn, deepen the entire understanding of chest imaging diagnoses. Indeed, to learn more about mycobacterial lung diseases, we should first understand the clinical features of the non-tuberculous mycobacteria often experienced in general clinical practice. Then, the clinical experiences of the National Hospital Organization will be useful to examine pulmonary tuberculosis cases, intensively. By strengthening the National Hospital Organization Hospitals' function as training hospitals, our knowledge of tuberculosis and other mycobacterial lung diseases will deepen.

Key words: Pulomanry tuberculosis, Non-tuberculous mycobacteria, Education, Radiological findings, Differential diagnosis

Department of Infectious, Respiratory, and Digestive Medicine, Control and Prevention of Infectious Diseases, Graduate School of Medicine, University of the Ryukyus; University of the Ryukyus Hospital

Correspondence to: Jiro Fujita, Department of Infectious, Respiratory, and Digestive Medicine, Control and Prevention of Infectious Diseases, Graduate School of Medicine, University of the Ryukyus, 207 Uehara, Nishihara-cho, Nakagami-gun, Okinawa 903−0215 Japan.
(E-mail: fujita@med.u-ryukyu.ac.jp)

Original Article

MYCOBACTERIAL EXAMINATION OF INTRAOPERATIVE SPECIMENS AFTER A 1-MONTH STANDARD TREATMENT REGIMEN IN PATIENTS WITH SPINAL TUBERCULOSIS

Kazutaka IZAWA

Abstract [Objective] The purpose of this study was to compare the negative conversion rate between intraoperative specimens of spinal tuberculosis and sputum specimens of pulmonary tuberculosis after 1 month of treatment with a standard anti-tuberculosis drug regimen. [Patients and Methods] We retrospectively reviewed the records of 111 patients who underwent anterior spinal fusion for spinal tuberculosis. All patients received anti-tuberculosis drug using a standard regimen with either INH, RFP, PZA, EB or SM (Method A) or a standard regimen with INH, RFP, EB or SM (Method B). Overall, 76 patients were treated with Method A and 35 patients were treated with Method B. Forty-five out of the 111 patients had intrathoracic lesions: 40 of these patients were smear-positive and 5 were smear-negative as well as PCR-positive. Nineteen patients were classified as having extra-pulmonary lesions such as miliary tuberculosis or tuberculous pleuritis. Forty-seven out of the 111 patients did not have intrathoracic lesions. All the patients underwent surgery 1 month after the initiation of the anti-tuberculous treatment. The negative conversion rate was compared between the intraoperative specimens of spinal tuberculosis and sputum specimens of the 40 smear-positive patients with pulmonary tuberculosis. [Results] The negative conversion rate of intraoperative specimens after 1-month treatment for spinal tuberculosis was 7.2% (Method A: 10.5%, Method B: 0%). The negative conversion rates of the sputum specimens were 82.5% (Method A: 78.2%, Method B: 88.2%) at 1 month, 92.5% (Method A: 87.0%, Method B: 100%) at 2 months, and 97.5% (Method A: 95.7%, Method B: 100%) at 3 months after treatment initiation. A comparison of the negative conversion rates of the sputum specimen at 1 month and the intraoperative specimen at the same period showed a significant difference ($p < 0.01$). [Conclusion] The negative conversion rate for intraoperative specimen in patients with spinal tuberculosis after 1 month of standard treatment was less than that of pulmonary tuberculosis at that time period.

Key words: Spinal tuberculosis, Standard treatment, Intraoperative specimen

Original Article

RETROSPECTIVE ANALYSIS OF TREATMENT OF LATENT TUBERCULOSIS INFECTION IN JAPAN, SEVERE LIVER DYSFUNCTION DURING ISONIAZID TREATMENT

Internal Medicine Group of Ryoken

Abstract [Objective] Multi central retrospective analysis was done for the treatment of latent tuberculosis infection (LTBI) in Japan. Severe liver dysfunction during Isoniazid treatment of LTBI was analyzed.

[Target] Those who started isoniazid (INH) in 2014 and 2015 in the hospital belonging to Internal Medical Group of Ryoken was analyzed.

[Result] The frequency of severe liver dysfunction with AST or ALT more than 500 IU/L was observed among 6% of persons aged 50−69 years old, among 4% of those aged 40−49 years old, and around 1% of those older than 70 years and those 30−39 years old, and no persons among younger than 30 years old. The frequency of severer liver dysfunction with AST or ALT more than 1000 IU/L and total bilirubin more than 3 mg/d*l* was observed among 1.3% of persons aged 50−69 and more among females (1%) than males (0.1%). All cases recovered with conservative treatment although the maximum of total bilirubin was 17 mg/d*l* .

Key words: Latent tuberculosis infection, Isoniazid, Severe liver dysfunction

Correspondence to: Takashi Yoshiyama, Fukujuji Hospital, Japan Anti-Tuberculosis Association, 3−1−24, Matsuyama, Kiyose-shi, Tokyo 204−8522 Japan.
(E-mail: yoshiyama1962@yahoo.co.jp)

Original Article

INVESTIGATION OF POTENTIAL PROGNOSTIC FACTORS FOR THE INCREASINGLY PREVALENT MILIARY TUBERCULOSIS IN JAPAN

[1]Eri INOUE, [2]Nobuharu OHSHIMA, [1]Miki IKEDA, [1]Masato WATANABE, [1]Masahiro KAWASHIMA, [1]Junko SUZUKI, [1]Kimihiko MASUDA, [1]Akira YAMANE, [1]Hirotoshi MATSUI, and [1]Hideaki NAGAI

Abstract [Objectives] Although the prevalence of tuberculosis has been decreasing in Japan, the prevalence of miliary tuberculosis (TB) has been gradually increasing. Therefore, it would be important that we know prognostic factors for miliary TB to provide suitable treatment and general management. To identify prognostic factors, we retrospectively studied 106 cases of miliary TB in our hospital. [Methods] We reviewed the medical records of 106 patients who had been diagnosed with miliary TB and undergone in-hospital treatment at our medical institution between April 2004 and March 2013. We conducted retrospective comparative analyses of age, sex, smoking history, complications, history of immunosuppressant use, presence or absence of hypoxemia, Eastern Cooperative Oncology Group Performance Status (PS), blood cultures, blood tests, administration of rifampicin (RFP) and isoniazid (INH), and time delay from symptom presentation to diagnosis between the patients who survived and were discharged (survivor group) and those who died in hospital (non-survivor group). In addition, we examined factors which contributed to longer survival period. [Results] The patients in the non-survivor group (n=41) were older and less nourished and had poorer oxygenation, poorer PS, and smaller number of peripheral blood lymphocyte count than the patients in the survivor group (n=65). And the rate of administration of RFP in the non-survivor group was lower than that in the survivor group. Administration of RFP was related to the longer survival time in the non-survivor group. [Conclusions] Nutritional status, oxygenation, PS, peripheral blood lymphocyte count, and RFP administration were identified as prognostic factors of miliary TB. Administration of RFP appeared to be most important for the survival.

Key words: Miliary tuberculosis, Prognostic factors, Rifampicin, Lymphocyte count

Original Article

CORRELATION BETWEEN GENOTYPIC *ERM* GENES AND PHENOTYPIC INDUCIBLE CLARITHROMYCIN RESISTANCE OF CLINICAL NON-PHOTOCHROMOGENIC RAPIDLY GROWING MYCOBACTERIUM ISOLATES WHICH WERE IDENTIFIED *MYCOLICIBACTERIUM FORTUITUM* BY DDH MYCOBACTERIA

[1]Shiomi YOSHIDA, [1]Kazunari TSUYUGUCHI, [2]Mika KIHARA, [2]Motohisa TOMITA, [1]Yoshikazu INOUE, [3]Seiji HAYASHI, and [3]Katsuhiro SUZUKI

Abstract [Objectives] The aim of this study was to identify the *erm* genes conferring the resistance variation in clinical non-photochromogenic rapidly growing mycobacterium (NPRGM) isolates identified *Mycolicibacterium fortuitum* by DDH mycobacteria kit.

[Material] All NPRGM isolates were collected from 14 consecutive bronchiectasis patients at the National Hospital Organization Kinki-chuo Chest Medical Center, Osaka, Japan, between 1 January 2016 and 31 December 2017.

[Methods] All of isolates were confirmed using *rpoB*, *hsp65*, and 16S−23S ITS region gene sequencing. Also, these isolates were evaluated the presence of *erm* genes and determined the minimum inhibitory concentration to clarithromycin according to CLSI 2011 M24−A2.

[Results] The presence of *erm* consensus regions among the 13 clinical isolates were determined, and heterogeneous *erm* genes including *erm* (39) and *erm* (40) presented in them which belonged to five species of NPRGM. However, the finding that the inducible resistance of NPRGM by *erm* methylases could not be confirmed by conventional susceptible testing.

[Discussion] It therefore appears necessary to develop more proper inducible resistant evaluation to clarithromycin of NPRGM and accurate identification for selecting appropriate antimicrobial therapies.

Key words: *Mycolicibacterium fortuitum*, Non-photochromogenic rapidly growing mycobacterium, Clarithromycin, Inducible resistance, *erm* gene, DDH mycobacteria

[1]Clinical Research Center, [2]Department of Clinical Laboratory, [3]Department of Respiratory Medicine, National Hospital Organization Kinki-chuo Chest Medical Center

Correspondence to: Shiomi Yoshida, Clinical Research Center, National Hospital Organization Kinki-chuo Chest Medical Center, 1180 Nagasone-cho, Kita-ku, Sakai-shi, Osaka 591−8555 Japan.
(E-mail: yoshida.shiomi.vg@mail.hosp.go.jp)

結核 第93巻 第11-12号 2018年11-12月

Original Article

EFFICACY AND SAFETY OF SITAFLOXACIN FOR *MYCOBACTERIUM AVIUM* COMPLEX PULMONARY DISEASE

Mitsuaki YAGI, Taku NAKAGAWA, Yuta HAYASHI, Noritaka YAMADA, Osamu TARUMI, Yasutaka FUKUI, and Kenji OGAWA

Abstract [Objective] We investigated the actual condition, the efficacy, and the safety of use of sitafloxacin (STFX) for *Mycobacterium avium* complex pulmonary disease (MAC-PD).

[Materials and Methods] Eighty nine patients who were newly prescribed STFX for MAC-PD were retrospectively investigated about reasons for prescribing STFX, efficacy as an alternative drug for standard therapeutic agents, efficacy of add-on therapy for refractory cases, and adverse events.

[Results] STFX were the most frequently prescribed in 54 patients (61%) as an alternative drug for standard therapeutic agents. Of the 46 patients who were able to follow up, 21 patients completed treatment. In refractory cases, no cases achieve negative sputum conversion, although symptom improvement was observed in 4 cases and radiological improvement was confirmed in 3 cases. Adverse events of STFX were seen in 50 (56%) of 89 patients. Diarrhea was the most common adverse event (22%). Twenty-three patients were discontinued due to adverse events.

[Conclusion] STFX for MAC-PD shows a certain effect as an alternative drug, and add-on therapy for refractory cases. However, there was a limit to the efficacy, and many adverse events were seen.

Key words: *Mycobacterium avium* complex pulmonary disease, Sitafloxacin, Alternative medicine, Refractory case, Adverse events

Department of Respiratory Medicine, National Hospital Organization Higashinagoya National Hospital

Correspondence to: Mitsuaki Yagi, Department of Respiratory Medicine, National Hospital Organization Higashinagoya National Hospital, 5−101, Umemorizaka, Meito-ku, Nagoya-shi, Aichi 465−8620 Japan.
(E-mail: yagim@e-nagoya.hosp.go.jp)

Case Report

A CASE OF CONCOMITANT ADULT T-CELL LEUKEMIA-LYMPHOMA LYMPHOMA TYPE AND TUBERCULOUS LYMPHADENITIS

[1]Masayoshi HIGASHIGUCHI, [2]Shigeru NAKANE, [1]Tomoshige MATSUMOTO, and [1]Takashi FUJII

Abstract An 82-year-old man was diagnosed with active pulmonary tuberculosis and tuberculous lymphadenitis because *Mycobacterium tuberculosis* was detected in both the sputum and pus collected from the incision site in the neck. He was treated with a combination of isoniazid, rifampicin, and ethambutol. However, even after 2 months of treatment, the lymphadenopathy worsened with new lesions arising. The histopathological examination of cervical lymph nodes revealed T-cell non-Hodgkin lymphoma. He tested positive for anti-human T-lymphotropic virus type 1 (HTLV-1) antibody. The diagnosis of adult T-cell leukemia-lymphoma (ATL) lymphoma type was made. He was treated with supportive care alone because of his poor performance status. Approximately 2 months later he died. HTLV-1 infection, which underlies ATL, might have contributed to the development of tuberculosis in this case as HTLV-1 infection is associated with immunosuppression. When a patient does not improve after treatments, physicians should perform histological examination to avoid making a premature diagnosis and overlooking underlying serious diseases.

Key words: Adult T-cell leukemia-lymphoma, Tuberculous lymphadenitis, Human T-lymphotropic virus type 1; HTLV-1

Case Report

A CASE OF BILATERAL TUBERCULOUS PLEURISY WITH DEVELOPMENT TO PLEURAL AND PERITONEAL TUBERCULOMA DURING ANTI-TUBERCULOSIS TREATMENT

[1]Yusuke OKAYAMA, [1]Takashi KINOSHITA, [1]Takayuki TOYAMA, [1]Youhei IMAMURA, [1]Masaki TOMINAGA, [2]Shohei TAKATA, [1]Tomoaki HOSHINO, and [1]Tomotaka KAWAYAMA

Abstract An initial aggravation after anti-tuberculosis chemotherapy is characterized as a paradoxical reaction, and a progressive tuberculoma is recognized as one of the initial aggravations.

A patient aged 37 years, female without history of tuberculosis and immunosuppressive diseases visited our clinic due to persistent fever and non-productive coughing. She was admitted due to bilateral pleural effusions. There was no evidence of tuberculosis antigens from sputum and pleural effusions. Bilateral tuberculous pleurisy was suspected, because of high levels of adenosine deaminase of both pleural effusions (right 73.2 IU/L and left 77.5 IU/L) and positive results in QuantiFERON®-GIT (ESAT-6: 1.03 IU/mL). She was discharged after interventions of anti-tuberculosis chemotherapy with pyrazinamide, rifampicin, isoniazid and ethambutol.

However, she was re-admitted due to new symptoms of right chest discomfort and abnormal shadows at right pleura on chest x-ray findings one month after the interventions. Diagnosis of right progressive chest and abdominal tuberculoma was made from the detections of tuberculosis DNA by polymerase chain reaction techniques from punctured fluids of the abdominal shadows. The tuberculoma disappeared 1 year and 4 months after consolidated anti-tuberculosis chemotherapy. This case was, here, presented as a diagnostic difficulty that development to pleural and peritoneal tuberculoma one month after initiation anti-tuberculosis chemotherapy on bilateral tuberculous pleurisy might be considered as paradoxical reactions, which was different from progressive diseases.

Key words: Bilateral tuberculous pleurisy, Peritoneum tuberculoma, Pleural tuberculoma, Paradoxical response

[1]Division of Respirology, Neurology, and Rheumatology, Department of Medicine, Kurume University School of Medicine; [2]National Hospital Organization Fukuoka-higashi Medical Center

Correspondence to: Takashi Kinoshita, Division of Respirology, Neurology, and Rheumatology, Department of Medicine, Kurume University School of Medicine, 67 Asahi-cho, Kurume-shi, Fukuoka 830−0011 Japan.
(E-mail: tkino@med.kurume-u.ac.jp)