〈Regular Article〉

Clinical characteristics of tuberculosis patients in a tertiary hospital

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ABSTRACT We retrospectively assessed the clinical characteristics of tuberculosis patients in a tertiary hospital. The subjects consisted of 80 patients who *Mycobacterium tuberculosis* was isolated from clinical specimens and who received a definite diagnosis of tuberculosis in our tertiary hospital without isolated bedrooms between January 2010 and June 2018. The average age of the 80 patients was 68.3 years old, consisting of 43 males and 37 females (6 non-Japanese). Sixty-eight patients had underlying diseases, and malignant diseases were most frequently recognized. Seven patients were diagnosed as outpatients and the remaining patients were diagnosed after admission. The final diagnose consisted of 56 patients with pulmonary tuberculosis and 35 patients with extrapulmonary tuberculosis (tuberculous lymphadenitis, tuberculous pleurisy, miliary tuberculosis, etc.). Concerning the results of interferon-γ release assays (IGRAs), while the positive response rate of QFT was 75%, that of T-SPOT was 81%. The clinical specimens used to diagnose tuberculosis were as follows: expectorated sputum, 26 patients; bronchoscopic specimens, 32; biopsy tissue, 17; and others, 5. The interval from the first consultation to diagnosis was three months at the maximum and within one month in most patients. Regarding radiological findings, pulmonary lesions including miliary tuberculosis showed various atypical findings: 39 of 66 patients with bilateral lesions; 50 with no cavity lesion; and 13 with the extent of the lesion exceeding the unilateral lung field.

Tuberculosis patients in our tertiary hospital had many underlying diseases such as malignant or autoimmune diseases and were receiving immunosuppressive treatment. Therefore, because IGRAs do not always show a positive response and radiological findings also do not show typical findings, it is important to investigate acid-fast bacilli for various clinical specimens and actively perform diagnostic methods including bronchoscopy in order to prevent nosocomial infection.

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Key words：Tuberculosis, Clinical Characteristics, Tertiary Hospital

INTRODUCTION

The incidence of tuberculosis (TB) declined gradually from 31.0 per 100,000 people in 2000 to 12.3 per 100,000 people in 2018 in Japan[1]. However, nine million people newly develop TB every year worldwide and one-third of the global

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population is thought to be infected with TB[2]. According to World Health Organization (WHO) reports, while TB appeared in many patients with HIV-coinfection in South-East Asia and Africa, it was characterized by appearing most frequently among elderly patients in some Western Pacific countries[2]. Concerning risk factors of TB reactivity, malnutrition and immunodeficiency play important roles based on previous reports[3, 4]. However, there have been few recent reports on the clinical characteristics of tuberculosis patients in tertiary hospitals in Japan. Because *Mycobacterium tuberculosis* shows an air-bone infection type, it is important to investigate the clinical findings of TB patients and be aware of the known clinical characteristics to prevent hospital infection in tertiary hospitals. Therefore, we retrospectively investigated the clinical characteristics of TB patients in our tertiary hospital.

MATERIALS AND METHODS

The subjects consisted of 80 patients who *Mycobacterium tuberculosis* (MTB) was isolated from clinical specimens and who received a definite diagnosis of TB in Kawasaki Medical School Hospital between January 2010 and June 2018. We retrospectively investigated the backgrounds, laboratory findings including interferon-γ release assays (IGRAs), microbiological findings, radiological findings, length from the first visit to diagnosis of TB, and outcomes of these TB patients. The timing of TB diagnosis was judged by the culturing or polymerase chain reaction (PCR)-based identification of MTB from clinical specimens. Regarding the judgment of IGRAs (QFT or T-SPOT), we followed the guidelines proposed by the Centers for Disease Control and prevention (CDC) for QFT[5] and the UK guidelines for T-SPOT to diagnose TB published by NCCCC[6]. Because there are no isolation rooms for tuberculosis patients in our tertiary hospital, we investigated the outcome at transfer hospitals in cases of hospital transfer as far as possible.

Concerning microbiological examinations, clinical specimens such as expectorated sputum, bronchoscopy, tissue, and pleural fluid were directly examined by Ziehl-Neelsen staining. The specimens used for culture were digested and decontaminated by the sodium hydroxide method. The samples were used to inoculate slants of 1% Ogawa egg medium, and bacteria were identified and differentiated based on growth characteristics and conventional biochemical tests. Drug sensitivity tests for isolated *M. tuberculosis* were performed using Bit-spectrum-SR (Kyokuto Pharmaceutical Industrial Co., Ltd.). The levels of resistance to antituberculous drugs such as streptomycin (SM), isoniazid (INH), rifampicin (RFP), ethambutol (EB), kanamycin (KM), enviomycin (EVM), ethionamid (TH), cycloserine (CS), paraaminosalicylate (PAS), and levofloxacin (LVFX) were assessed.

Regarding the radiological findings on admission, the portion, extension of lesion, and radiological findings according to the Japanese Society for Tuberculosis (JST) were evaluated based on both chest radiographs and computed tomography (CT). Finally, we reviewed the radiological findings such as cavities, calcifications, pleural effusions, and lower lung field dominance described by Segerra *et al.*[7].

The study protocol was approved by the Ethical Committee of Kawasaki Medical School (Approval No. 2554).

RESULTS

We present the background of patients with TB encountered in our hospital in Table 1. During the observation period, 80 patients were enrolled in this study. They consisted of 43 males (54%) and 37 females (46%) with a mean age of 68.3 years old. Most patients (85%) had underlying diseases (respiratory diseases: 26% and non-

Table 1. Backgrounds of tuberculosis patients in our tertiary hospital

Backgrounds	Number of patients (n=80)
Age (Mean ± S.D.)	68.3 ± 19.0
Sex (Male：Female)	43:37
Smoking history (+)	47 (59%)
Alcohol abuse (+)	6 (8%)
Underlying disease (+) (with repetition)	68 (85%)
Respiratory disease	21 (26%)
CDPD	9
Old pulmonary tuberculosis	5
Others	7
Non-respiratory disease	64 (80%)
Malignant disease	12
Gastrointestinal disease	11
Cerebral vascular disease	10
Diabetes mellitus	10
Collagen disease	10
Renal disease (including CRD)	5
HIV infection	2
Others	4
Immunosuppressive treatment	12 (15%)
Previous treatment for tuberculosis (+)	6 (8%)

COPD: Chronic obstructive pulmonary disease, HIV: Human immunodeficiency virus

Table 2. Diagnosis on admission or initial consultation with tuberculosis patients (n=80)

Diagnosis	Number of patients (n=80)
Tuberculosis	40 (50%)
Pulmonary tuberculosis	31 (39%)
Tuberculous pleurisy	2
Miliary tuberculosis	5
Tuberculous lymphadenitis	2
Non-tuberculous disease	40 (50%)
Pneumonia	15 (19%)
Pulmonary nontuberculous mycobacterial disease	6
Necrotizing lymphadeniitis	5
Lung cancer	3
Pleuritis	2
Meningitis	1
Others	8

respiratory diseases: 80%) and 12 (15%) received immunosuppressive treatment. The detection methods consisted of clinical symptoms such as fever and productive cough (75%) in most patients and periodical examination or follow-up period for other underlying diseases (25%). Seventy-three patients (91%) were admitted to our hospital for a final diagnosis, and the remaining 7 patients were diagnosed with TB in the outpatient department. Although most patients could be diagnosed within one month (73/80; 91%), the remaining seven patients required over one month to receive a diagnosis of TB and there was an inpatient with HIV infection and myelodysplastic syndrome and another inpatient with lower lung field tuberculosis who required three months after admission for TB diagnosis in this study. The rate of diagnosis on admission was the same between TB and non-TB disease (50 vs. 50%, respectively). In the patients with non-TB disease, pneumonia was the most frequent and, secondly, pulmonary non-TB disease was diagnosed in several patients (Table 2). It was

Table 3. Radiological findings of tuberculosis patients (66 patients with pulmonary lesion)

Radiological findings		Number of patients (n=66)
Portion	Right	21 (32%)
	Left	6 (9%)
	Bilateral	39 (59%)
Classification*	Ⅰ	1 (2%)
	Ⅱ	15 (23%)
	Ⅲ	50 (75%)
Extension of lesion‡	1	28 (42%)
	2	25 (38%)
	3	13 (20%)
Other findings	Carcification	16 (24%)
	Pleural effusion	5 (8%)
	Lower lung field dominant	5 (8%)

*: Radiological classification according to the Japanese Society for Tuberculosis
‡: 1; within half of unilateral lung field, 2; within unilateral lung field, 3; exceeding unilateral lung field

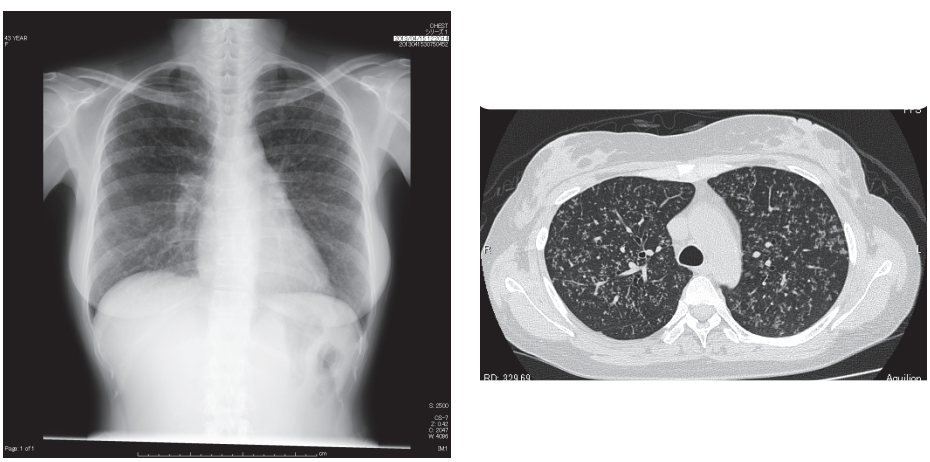

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Fig. 1. A 43-year-old woman showed diffuse small nodular shadows in the bilateral lung field on a chest radiograph (a) and diffuse small nodular shadows in the bilateral lung on chest CT (b). (Diagnosis: Miliary tuberculosis)

difficult to make a final diagnosis in these patients.

Concerning the results of IGRAs, QFT showed a positive response in 60 of the 80 patients (75%), but was negative in 16 and indeterminate in 4. On the other hand, T-SPOT showed a positive response in 64 of 79 patients (81%), but was negative in 13 and indeterminate in 2. Among the laboratory findings, while hypoalbuminemia (albumin ≦3.5 g/dL) related to the general conditions was recognized in 53/80 (66%) TB patients, lymphocytopenia (lymphocyte count ≦1000) related to the immune status was recognized in 35/80 (44%) TB patients.

Regarding the radiological findings, pulmonary lesions including miliary TB showed the following: (1) the lesion existed in both lungs in 39 of 66 patients (59%), the right lung in 21, and left lung in 6, (2) a cavity lesion was not frequently recognized in 16 of 66 patients (25%), (3) the lesion existed within one-third of the unilateral lung field in 28 of 66 patients (42%), within the unilateral lung field in 25 (38%), and exceeded the unilateral lung field in 13 (20%) (Table 3). Miliary TB was recognized in 10 of 66 patients (15%) (Fig. 1). So-called lower lung field pulmonary TB (8) was recognized in 5 of

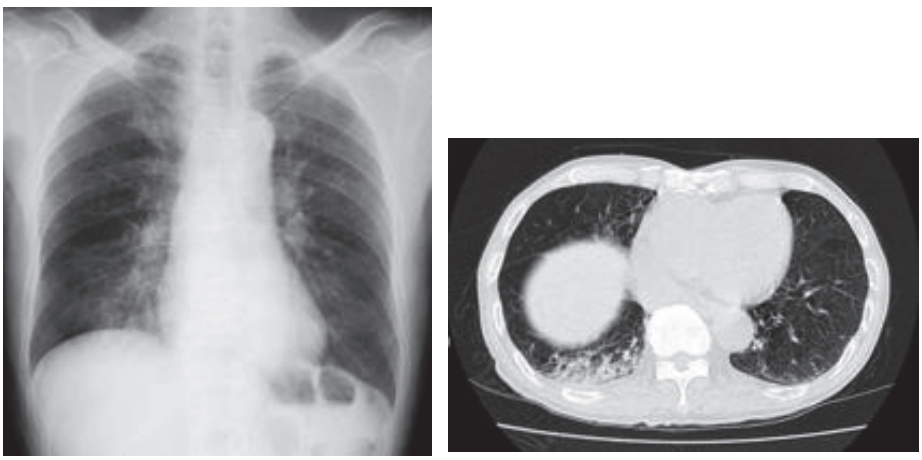

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Fig. 2. A 83-year-old man showed an infiltrative shadow in the right lower lung field on a chest radiograph (a) and a similar shadow in the right lower lobe with emphysematous change on chest CT (b). (Diagnosis: Lower lung field tuberculosis)

Table 4: Diagnostic methods for tuberculosis patients (n=80)

Clinical specimen	Number of patients (n=80)
Sputum	26 (33%)
Smear-positive, culture-positive	17
Smear-negative, culture-positive	9
Bronchoscopy	32 (40%)
Smear-positive, culture-positive	28
Smear-negative, culture-positive	4
Tissue	17 (21%)
Smear-positive, culture-positive	13
Smear-negative, culture-positive	4
Others (Pus, Cerebral spinal fluid, Pleural effusion, etc)	5 (6%)
Smear-positive, culture-positive	3
Smear-negative, culture-positive	2
Multidrug-resistant (INH ≧0.2 μg/mL, RFP ≧40 μg/mL)	0
INH-resistant (INH ≧0.2 μg/mL)	1
SM-resistant (SM ≧20 μg/mL)	3

66 patients (8%) (Fig. 2).

The methods to diagnose TB involved expectorated sputum in 26 patients, bronchoscopic specimens in 32, lung biopsy tissue in 17, and other clinical specimens in 5. Both smear and culture tests of clinical specimens were positive in 61 of the 80 patients (76%) and the remaining patients were negative for smear tests but culture tests were positive. However, there was one patient with an isoniazid (INH)-resistant strain and three patients with a streptomycin (SM)-resistant strain based on a drug sensitivity test (Table 4).

The final diagnose of the 80 patients consisted of 56 patients with pulmonary TB and 36 patients with extrapulmonary TB (tuberculous lymphangitis 11, miliary tuberculosis 10, tuberculous pleurisy 6,

Table 5. Final diagnosis of tuberculosis patients (n=80)

Final diagnosis	Number of patients (n=80)
Pulmonary tuberculosis	45
Miliary tuberculosis	10
Tuberculous lymphadenitis	8
Pulmonary tuberculosis + Tuberculous pleurisy	5
Spinal tuberculosis	3
pulmonary tuberculosis + Tuberculous meningitis	2
Pulmonary tuberculosis + Tuberculous lymphadenitis	2
Tuberculous pleurisy	1
Bronchial tuberculosis	1
Pulmonary tuberculosis + Bronchial tuberculosis	1
Cerebral tuberculosis + Tuberculous lymphadenitis	1
Pulmonary tuberculosis + Tuberculous peritonitis	1

spinal tuberculosis 3, tuberculous meningitis 2, and others 4) (Table 5).

Concerning the outcome of 80 TB patients, 59 patients were transferred to another hospital with isolation rooms for TB patients after diagnosis immediately and the remaining 21 patients started antituberculous therapy in our hospital. Although antituberculous therapy were performed for most TB patients except for 2 patients who died before treatment, the precise clinical course or state of treatment continuation was unknown for most TB patients transferred to another hospital. Finally, nine patients died due to severe TB or worsening of underlying diseases before the completion of antituberculous treatment.

DISCUSSION

We retrospectively analyzed the clinical findings of TB patients in our tertiary hospital without isolation rooms for TB patients through this study. Subsequently, we revealed the following clinical characteristics: 1) Most TB patients had underlying diseases, malignant diseases were frequently recognized, and TB patients who received immunosuppressive treatment developed miliary TB; 2) Diagnoses on admission led to the same frequency of non-TB disease and TB, and pneumonia was the most frequent non-TB disease; 3) TB patients tend to show poorer nutritional conditions such as hypoalbuminemia, and the results of IGRAs (QFT or T-SPOT) showed negative or indeterminate responses compared with previous reports[5, 6]; 4) Pulmonary lesions including miliary TB showed atypical shadows without a cavity in many TB patients; 5) The diagnostic method to obtain a definite diagnosis most frequently involved bronchoscopic specimens.

Concerning risk factors of TB pathogenesis, malignancy, collagen vascular disease, HIV infection, and diabetes mellitus were described in previous reports[8–10]. In patients with malignancy, both immunosuppression due to malignancy itself and the influence of anticancer therapy have been reported to reactivate *M. tuberculosis* during dormancy into an old TB lesion and evoke active TB. The complication rate of pulmonary TB during the follow-up of lung cancer was reported to be high (2~10%)[11, 12] and a similar finding was recognized in this study. On the other hand, immunosuppressive drugs such as corticosteroid or biological drugs were recently administered to many patients with collagen vascular disease. These drugs also decreased immunity against TB infection and evoked active TB (1.7~4-fold increase in risk within six months after the initiation of treatment) [13–15]. Therefore, the Japanese College of Rheumatology or the Japanese Society for Tuberculosis stated that a preventive

antituberculous drug (isoniazid 300 mg/day administration for six or nine months) was necessary for these patients when immunosuppressive drugs were administered[16, 17]. Centers for Disease control and Prevention (CDC) also recommended preventive antituberculous therapy for nine months and reported the clinical effectiveness for HIV-positive patients[18]. Because there were no patients receiving preventive antituberculous therapy among 12 patients with immunosuppressive treatment in this study, we consider the importance of preventive antituberculous therapy to reduce severe TB such as miliary TB. Although there were few TB patients with HIV infection in our tertiary hospital, the number of patients with HIV infection has recently increased in Japan. If these patients show a decrease of CD4 lymphocytes due to HIV infection, they easily develop active, severe TB including extrapulmonary TB[19]. Because they show atypical radiological findings without a cavity, we always have to be careful regarding the appearance of TB in these patients.

In spite of the retrospective nature of this study, we positively investigated the results of IGRAs (QFT or T-SPOT) for most TB patients. Subsequently, QFT showed a positive response in 75% and T-SPOT showed a positive response in 81%. These results are lower than in previous reports (>90%)[5, 6]. Komiya et al. also previously reported that the positive response rate of QFT was low in immunocompromised patients because of the decrease in lymphocyte counts or poorer nutritional conditions[20]. Because there were many TB patients with an immunocompromised state due to underlying diseases in this study, we think that the severity of underlying diseases influenced the results of IGRAs. Therefore, although IGRAs may be useful to support a diagnosis of TB disease, we have to be careful regarding the definite diagnosis of TB disease in tertiary hospitals.

Regarding the radiological findings related to pulmonary TB, miliary (Fig. 1) and lower lung field (Fig. 2) TB were frequently recognized in 10 (13%) and 5 (6%) patients, respectively. Typical findings such as a cavity showed a low rate (25%). Because TB patients in the tertiary hospital showed various atypical radiological findings, it was necessary to conduct acid-fast bacilli examinations using many clinical specimens.

We found that non-TB disease showed the same frequency as TB based on the diagnosis on admission or initial consultation in this study. Because there were eight patients (10%) who required over one month to receive the correct diagnosis, it was considered important to make a correct diagnosis by bronchoscopy. Fortunately, there were no TB patients with multi-drug resistant *M. tuberculosis* in our hospital in this study. Therefore, if we send patients to special hospitals with isolation rooms for TB patients as soon as possible, we can protect against nosocomial infection and initiate earlier antituberculous treatment.

There are a few limitations of our study. First, it was a retrospective study that used medical records for data collection. Secondly, we studied a small number of TB patients (80 patients) because our hospital is a tertiary hospital without isolation rooms for TB patients. Thirdly, we could not obtain complete data on the content of treatment or prognosis due to the transfer of patients to special hospitals with isolation rooms for TB patients after a definite diagnosis in most cases.

In conclusion, TB patients in our tertiary hospital had many underlying diseases such as malignant or autoimmune diseases and were receiving immunosuppressive treatment. Therefore, because IGRAs showed a lower positive response rate than previous data and radiological findings also did not show typical findings, it is important to apply diagnostic methods positively such as bronchoscopy as soon as possible.

CONFLICTS OF INTERESTS

There are no conflicts of interests regarding this study.

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