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Prevalence and Its Predictors of Extrapulmonary Involvement in Patients with Pulmonary Tuberculosis

Extrapulmonary organ involvement in human immunodefiaency virus (HIV)-infected patients with pulmonary tuberculosis (TB) is reported to be 26%, however, the clinical predictors of extrapulmonary involvement in pulmonary TB patients has not been reported yet. We tried to determine the clinical predictors of presence of extrapulmonary involvement in patients with pulmonary TB. Cross-sectional study was performed including all adult patients with culture-proven pulmonary TB diagnosed between January 1, 2004 and July 30, 2006, at a tertiary referral hospital in South Korea. The presence of extra-pulmonary TB involvement was diagnosed based on bacteriological, pathological, or clinical evidence. Among 320 patients with a culture-proven pulmonary TB, 40 had extrapulmonary involvement. Patients with bilateral lung involvement were more likely to have extrapulmonary involvement, with an adjusted odds ratio (OR) of 4.21 (95% confidence interval [CI], 1.82-9.72), while patients older than 60 yr (adjusted OR, 0.27; 95% CI, 0.08-0.89), patients with cavitary lesions (adjusted OR, 0.37; 95% CI, 0.16-0.84), and with higher levels of serum albumin (adjusted OR, 0.45; 95% CI, 0.25-0.78) had less frequent involvement. Clinicians should be aware of the possibility of extrapulmonary involvement in TB patients with bilateral lung involvement without cavity formation or lower levels of serum albumin.

Key Words : *Tuberculosis; Tuberculosis, Miliary; Diagnosis*

Min Jae Kim, Hye-Ryoun Kim, Seung Sik Hwang*, Young Whan Kim, Sung Koo Han, Young-Soo Shim, and Jae-Joon Yim

Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine and Lung Institute, Seoul National University College of Medicine, Seoul; Department of Social and Preventive Medicine*, College of Medicine, Inha University, Incheon, Korea

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Address for correspondence
Jae-Joon Yim, M.D.
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine and Lung Institute, 103 Daehak-ro, Jongno-gu, Seoul 110-744, Korea
Tel : +82.2-2072-2059, Fax : +82.2-762-9662
E-mail : yimjj@snu.ac.kr

INTRODUCTION

Extrapulmonary tuberculosis (EPTB) comprises 9.7-46% of all cases of tuberculosis (TB) (1-3). Although tuberculous bacilli could spread to any organs, the common organs involved with EPTB include lymph nodes, pleura, bones and joints, brain and meninges, gastrointestinal organs, liver, genitourinary organs, peritoneum, and pericardium. Although TB lymphadenitis or TB pleuritis respond relatively well to anti-TB treatment, some forms of EPTB (e.g., TB meningitis) are notorious for their association with high morbidity and mortality (4, 5). Furthermore, miliary TB, the extreme form of EPTB, presents a great challenge to human health because of its high mortality rate of 18-24%, even in recent reports (6-9).

Extrapulmonary organ involvement (10) in human immunodeficiency virus (HIV)-infected patients with pulmonary TB is reported to be 26%, however, the clinical characteristics of patients with pulmonary TB at risk of simultaneous extrapulmonary organ involvement have not been studied in detail, although the initiation of treatment following early identification of extrapulmonary involvement is crucial. The aim of this study was to determine the prevalence and clinical predictors of the presence of extrapulmonary involvement in patients with pulmonary TB.

MATERIALS AND METHODS

Study settings, subjects, and data collection

All adult patients with culture-proven pulmonary TB diagnosed between January 1, 2004 and July 31, 2006 at Seoul National University Hospital, a tertiary referral hospital were included for this study. We retrospectively reviewed the medical records of these patients, which included demographic data, results of laboratory tests, and so on. We also reviewed the radiographic examinations of the patients. The protocol of this study was approved by the institutional review board of Seoul National University Hospital.

Definition of extra-pulmonary involvement of TB

The presence of extra-pulmonary involvement in patients with pulmonary TB was based on the following criteria: 1) demonstration of acid-fast bacilli or the growth of *Mycobac-*

terium tuberculosis from tissue; 2) presence of granulomas with or without caseation necrosis in tissue; 3) positive polymerase chain reaction (PCR) results for the DNA of *M. tuberculosis* from tissues; or 4) a clinical diagnosis by duty physicians based on symptoms, laboratory, radiographic findings, and treatment response to anti-TB medications. Tuberculous pleuritis was not classified as EPTB because pleura is believed to be involved by direct invasion from frequently accompanying pulmonary parenchymal TB or hypersensitivity reaction by *M. tuberculosis* rather than blood stream dissemination (11-13).

Statistical analyses

Univariate comparisons between the group with pulmonary TB and extrapulmonary involvement and the group with pulmonary TB without extrapulmonary involvement were performed using Pearson's chi-square test or Fisher's exact test for categorical variables and Student's t-test for continuous variables. Variables analyzed included demographic characteristics, laboratory results, and radiographic findings. Using variables with p values of <0.20 from the univariate comparisons, multiple logistic regression models were constructed to identify predictors of the presence of extrapulmonary involvement. In logistic regression, backward elimination was used to select variables to be maintained in the final model, using a p value of <0.10 as the criterion for statistical significance of associations. The area under the receiver operator characteristic (ROC) curve was used to evaluate the performance of the models. To successfully split patients into more homogeneous subgroups, classification and regression trees (CART) were used to build a binary classification tree through recursive partitioning. All tests of significance were two sided and $p<0.05$ was considered statistically significant. We used statistical software Stata 9.0 (Stata Corporation, College Station, TX, U.S.A.) to perform the multiple logistic regression and R 2.4.1 (The R foundation for statistical computing) to construct the CART.

RESULTS

Three hundred and twenty patients were diagnosed with culture-proven pulmonary TB at Seoul National University Hospital between January 1, 2004 and July 31, 2006. Their median age was 45 yr and 198 (62%) were male: 85 patients (26.6%) had underlying diseases including HIV infection, diabetes, chronic liver diseases, and so on; 83 patients (25.9%) had previously diagnosed and treated TB (Table 1).

Forty (12.5%) of the 320 patients with pulmonary TB had extrapulmonary involvement. Miliary involvement of the lung was the most common manifestation of EPTB (12 patients, 30%). TB lymphadenitis (8 patients), intestinal TB (8 patients), and TB laryngitis (8 patients) followed. The tuberculous involvement of extrapulmonary organs was confirmed bacteriologically in 11 patients (27.5%) and diagnosed based on positive PCR for *M. tuberculosis* DNA in 7 patients (Table 2).

We compared the clinical characteristics and laboratory results between the 40 pulmonary TB patients with extrapulmonary involvement and the 280 patients without. There was no difference between the two groups in terms of age, underlying diseases, history of previous TB, and drug susceptibility pattern. However, bilateral lung involvement was more common in patients with extrapulmonary involvement (77.5% vs. 46.4%, $p<0.001$). In addition, the mean hematocrit, albumin, and cholesterol values were lower in the pa-

Table 1. Demographic and clinical characteristics of enrolled patients

	320 patients
Age, yr, median (range)	45 (20-74)
Male/female	198 (62%)/122 (38%)
Underlying diseases	85 (26.6%)
HIV infection	5 (1.6%)
Diabetes	38 (11.9%)
Chronic liver disease	9 (2.8%)
Connective tissue disease	13 (4.1%)
Chronic renal failure	1 (0.3%)
Asthma	6 (1.9%)
COPD	2 (0.6%)
Cancer	20 (6.3%)
Post-transplantation state	5 (1.6%)
On immunosuppressant	19 (5.9%)
Previous history of TB	83 (25.9%)
Diagnosis of pulmonary TB	
Negative AFB smear but positive culture of *M. tuberculosis*	167 (52.2%)
Positive AFB smear and positive culture of *M. tuberculosis*	153 (47.8%)
Drug susceptibility tests	
Sensitive to all drug	221 (69.1%)
Resistant but not MDR	30 (9.4%)
MDR	69 (21.6%)
Presence of extrapulmonary involvement	40 (12.5%)
Radiographic characteristics	
Presence of cavitary lesion	126 (39.4%)
Extent of radiographic lesion	
Confined to unilateral lung	159 (49.7%)
Extended to bilateral lung	161 (50.3%)
Laboratory tests (mean±standard deviation)	
Leukocytes (×1,000/μL)	7.60±3.33
Neutrophil (×1,000/μL)	5.08±2.75
Lymphocyte (×1,000/μL)	1.64±0.95
Hemoglobin (g/dL)	12.92±2.16
Hematocrit (%)	39.37±5.78
Total protein (g/dL)	7.16±0.89
Albumin (g/dL)	3.84±0.61
Cholesterol (mg/dL)	162.96±40.41
Creatinine (mg/dL)	0.97±0.42

HIV, human immunodefiaency virus; COPD, chronic obstructive pulmmary disease; TB, tuberculosis; AFB, acid-fast bacilli; MDR, multi-drug resistance.

tients with extrapulmonary involvement (Table 3).

The final multiple logistic regression model showed that after adjustment only the presence of cavitary lesions, absence of bilateral lung involvement, and lower albumin levels were associated with extrapulmonary involvement in patients with pulmonary TB. Patients with bilateral lung involvement were more likely to have extrapulmonary involvement, with an adjusted odds ratio (OR) of 4.21 (95% confidence interval [CI], 1.82-9.72), while patients older than 60 yr (adjusted OR, 0.27; 95% CI, 0.08-0.89) and patients with cavitary lesions were less likely to have extrapulmonary involvement (adjusted OR, 0.37; 95% CI, 0.16-0.84). In addition, patients with higher levels of albumin had less frequent extrapulmonary involvement (adjusted OR, 0.45; 95% CI, 0.25-0.78) (Table 4). The fitness of the final model was good in terms of multiple logistic regression (area under the ROC curve, 0.76; 95% CI, 0.68-0.84) as well as CART analysis (area under the ROC curve, 0.73; 95% CI, 0.65-0.82) (Fig. 1).

Table 2. Sites and methods of diagnois of extrapulmonary involvement in 40 patients

Involved organ*	40 patients (100%)
Miliary involvement	12 (30%)
Lymph node	8 (20%)
Intestine	8 (20%)
Larynx	6 (15%)
Soft tissue	5 (12.5%)
Bone and joint	4 (10%)
Peritoneum	1 (2.5%)
Meninges	1 (2.5%)
Method of diagnosis	
Bacteriologically confirmed	11 (27.5%)
Positive PCR for *M. tuberculosis* DNA in tissue	7 (17.5%)
Pathologically diagnosed	9 (22.5%)
Clinically diagnosed	13 (32.5%)
Disseminated Miliary nodules in chest radiographs	9 (22.5%)
Others†	4 (10%)

*, When a patient had more than one organ involved, all of them were counted independently; †, 2 patients with intestinal TB diagnosed based on typical colonosopic findings and the other 2 patients with TB laryngitis without AFB bacilli and caseating granuloma in pathologic examinations.
PCR, polymerase chain reaction; TB, tuberculosis; AFB, acid-fast bacilli.

Table 4. Risk factors for combined extra-pulmonary involvement in patients with pulmonary TB (multiple logistic regression-final model)

Variable	Odds ratio	95% CI	*p* value
Age (yr)			
20-39	1.0 (ref.)	-	
40-59	0.71	0.62-1.59	0.411
+60	0.27	0.08-0.89	0.031
On immunosuppressant	2.86	0.87-9.41	0.084
Radiographic characteristics			
Presence of cavitary lesion	0.37	0.16-0.84	0.018
Extended to bilateral lung	4.21	1.82-9.72	0.001
Results of laboratory tests			
Albumin per increase of 1 g/dL	0.45	0.25 - 0.78	0.005

TB, tuberculosis; CI, confidence interval.

DISCUSSION

The presence of cavities in patients with pulmonary TB is

Table 3. Comparison of demographic and clinical characteristics between pulmonary tuberculosis (TB) patients with extrapulmonary involvement and without extrapulmonary involvement (univariate analysis)

	Pulmonary TB without extrapulmonary involvement (%)	Pulmonary TB with extrapulmonary involvement (%)	*p* value
Number of patients	280	40	
Sex			
Male	177 (63.2)	21 (52.5)	
Female	103 (36.8)	19 (47.5)	0.192
Age (yr)			0.499
20-39	109 (39.9)	16 (40.0)	
40-59	115 (41.1)	19 (47.5)	
+60	56 (20.0)	5 (12.5)	
Underlying diseases			
HIV infection	3 (1.1)	2 (5.0)	0.119
DM	34 (12.1)	4 (10.0)	1.000
Chronic liver disease	9 (3.2)	0 (0)	0.609
Connective tissue disease	9 (3.2)	4 (10.0)	0.065
Chronic renal failure	0	1 (2.5)	0.215
Asthma	6 (2.1)	0 (0)	1.000
COPD	2 (0.7)	0 (0)	1.000
Cancer	18 (6.4)	2 (5.0)	1.000
Post-transplantation state	4 (1.4)	1 (2.5)	0.489
On Immunosuppressant	12 (4.3)	7 (17.5)	0.005
History of TB	72 (25.7)	11 (27.5)	0.810
Drug susceptibility tests			
Sensitive to all	192 (68.6)	29 (72.5)	
Resistant but not MDR	25 (8.9)	5 (12.5)	0.413
MDR	63 (22.5)	6 (15.0)	
Radiographic characteristics			
Presence of cavitary lesion	115 (41.1)	11 (27.5)	0.100
Extent of radiographic lesion			
Confined to unilateral lung	150 (53.6)	9 (22.5)	<0.001
Extended to bilateral lung	130 (46.4)	31 (77.5)	
Results of laboratory tests			
(mean±standard deviation)	7.45±2.86	8.72±5.78	0.171
Leukocytes (×1,000/μL)			
Neutrophil (×1,000/μL)	4.97±2.64	5.85±3.41	0.061
Lymphocyte (×1,000/μL)	1.63±0.66	1.71±2.09	0.799
Hematocrit (%)	39.72±5.72	36.91±5.69	0.004
Total protein (g/dL)	7.19±0.86	6.96±1.04	0.200
Albumin (g/dL)	3.88±0.58	3.54±0.75	0.008
Cholesterol (mg/dL)	164.93±40.99	148.90±33.16	0.020
Cr (mg/dL)	0.96±0.45	0.94±0.47	0.699

DM, diabetes mellitus; COPD, chronic obstructive pulmmary disease; MDR, Multi-drug resistance.

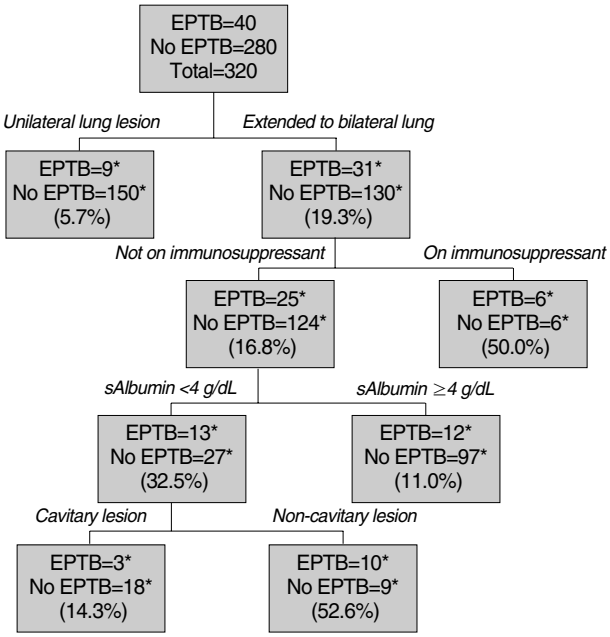

Fig. 1. Classification and regression trees (CART) analysis for predicting combined extra-pulmonary involvement in patients with pulmonary TB
EPTB, pulmonary TB with extra-pulmonary involvement; sAlbumin, serum level of albumin.

regarded as a marker for high bacillary burden and is reported to be associated with relapse after completion of treatment (14). Our observation that the extrapulmonary involvement was less frequently observed in cavitary pulmonary TB patients suggests that the higher bacillary burden *per se* does not make the host prone to extrapulmonary involvement. On the contrary, the presence of cavities was associated with a lower possibility of the spread of tuberculous bacilli to extrapulmonary organs in this study. Given that pulmonary cavities have been reported to be rare in TB patients with immune compromise (15, 16), the presence of cavities could be a hallmark of a certain level of intact immunity against tuberculous bacilli, guaranteeing protection from further dissemination to other organs. This hypothesis could be tested through future study comparing systemic as well as local immunity against *M. tuberculosis* between TB patients with or without pulmonary cavity should be performed through future studies. In fact, differences were already reported in expression of various genes between pulmonary TB patients and extrapulmonary TB patients (17).

In contrast to the presence of pulmonary cavities, bilateral lung involvement might better reflect attenuated host immunity than bacillary burden (18). Considering that various types of impaired cell-mediated immunity have been considered to play an important role in the development of EPTB (10, 19-22), the decreased host immunity suggested by the presence of bilateral lung involvement could be crucial in the dissemination of tuberculous bacilli to extrapulmonary organs. In fact, pulmonary TB patients on immunosuppressants were prone to have extrapulmonary involvement (p= 0.08) in this study, although we failed to get statistical significance because of the small numbers of patients on immunosuppressants.

Hypoalbuminemia is generally regarded as a marker of poor nutritional status in patients with TB (23, 24). In addition, hypoalbuminemia/protein malnutrition itself could impair host immunity against *M. tuberculosis* through decreased production of cytokines including interferon-γ (25) or the reduction of CD4 and CD8 T cell numbers observed in animal models (26). Hypoalbuminemia as a predictor for the presence of extrapulmonary organ involvement as observed in this study could be explained by probable immune dysfunction against tuberculous bacilli and matches previous reports showing lower albumin levels in patients with disseminated TB (27).

Results from our study that older patients with pulmonary TB have a lower risk of having a extrapulmonary involvement (adjusted OR, 0.27; 95% CI, 0.08-0.89) disagrees with previous reports that show that EPTB was higher in the elderly (28). In addition, the lower risk of EPTB in the elderly does not support immunity as a determinant of the spread of tuberculous bacilli to other organs because of the higher incidence of TB in the aged group (29, 30) and decreased immunity to tuberculous bacilli in older mice (31). This observation could be interpreted in two ways. First, the decreased risk for extrapulmonary involvement in the elderly could result from the small number of patients older than 60 yr (61 patients, 19.1%) in this study. In this setting, a small change in the number of patients with extrapulmonary involvement could make significant changes in the OR. Second, extrapulmonary dissemination with bilateral lung involvement but without cavity formation could be understood as a characteristic of TB bacilli rather than host immune status. The clinical manifestations might differ among TB patients infected with different strains of *M. tuberculosis*. For example, the 'Beijing strain' was reported to cause more severe pathology in mice (32) as well as more advanced radiographic lesions in humans (33). In this context, infection by specific strains of *M. tuberculosis* might cause intra- and extrapulmonary dissemination rather than cavity formation.

In conclusion, the extrapulmonary organ involvement in patients with pulmonary TB was more common in patients with bilateral lung involvement but without cavity formation or low levels of serum albumin. Clinicians should keep in mind the possibility of extrapulmonary involvement in these patients.

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