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Response to Empirical Anti-Tuberculosis Treatment in Patients with Sputum Smear-Negative Presumptive Pulmonary Tuberculosis

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Key Words
Pulmonary tuberculosis · Empirical treatment · Predictor · Radiology · Treatment outcome

Abstract
Background: In many cases, physicians initiate anti-tuberculosis (TB) treatment based only on symptoms or radiographic findings without confirmation of pulmonary TB by acid-fast bacilli (AFB) smear. It has not been well known which clinical characteristics could be used as predictors for positive culture or real TB in patients with sputum smear-negative presumptive pulmonary TB. ***Objective:*** We tried to elucidate treatment outcomes in patients with sputum smear-negative presumptive pulmonary TB and to find predictors of positive culture results. ***Methods:*** We reviewed data of the patients who had been treated as presumptive TB with negative AFB smear on the basis of clinical and radiographic features from December 1998 to December 2000 at a university hospital in Korea. We reviewed medical records and radiographs of patients and analyzed possible predictors for positive culture. ***Results:*** One hundred and one patients were enrolled. Among them, pulmonary TB was confirmed by culture in 32 patients (31%). Thirty-one (96.9%) out of 32 culture-positive patients showed clinical or radiographic improvement as did 50 (72.5%) out of 69 culture-negative patients. The predictor for a positive culture result is the presence of patchy consolidation in an initial radiograph (p = 0.025; OR 2.89; 95% CI 1.14–7.28). ***Conclusions:*** The empirical anti-TB treatment in patients with sputum smear-negative presumptive pulmonary TB was effective and adequate, especially presented with patchy consolidation in initial chest radiographs in Korea.

Introduction

The World Health Organization estimates that one third of the world's population is infected with the *Mycobacterium tuberculosis.* Among them, 8 million people get new cases of active tuberculosis (TB) annually, and 2 million people die of TB each year [1]. TB is the world's foremost cause of death from a single infectious agent among adults [2, 3].

The only confirmation of TB diagnosis is given by the bacteriological examination, but a suspicion of TB is frequently based on clinical and radiological grounds [4]. The acid-fast bacilli (AFB) smear of respiratory specimen, including sputum, induced sputum and bronchial washing specimen, is the essential modality for the prompt diagnosis of pulmonary TB. However, the sensitivity of

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the AFB smear result is known to be poor, varying between 30 and70% depending on a number of factors relating to how the test is implemented [5]. Even though the culture of tuberculous bacilli is more sensitive (80–85%), being able to detect as few as 10 bacteria per milliliter of sputum [6, 7], it usually takes 3–6 weeks to receive culture results. Considering the fact that half of all patients with TB can present with negative sputum AFB smear [8], physicians should start anti-TB treatment in sputum AFB smear-negative patients with a high suspicion of TB not only for the benefits of the patients, but also for the control of TB in the community.

The empirical treatment of presumptive pulmonary TB is especially important in Korea, where the prevalence of pulmonary TB is still as high as 0.5%, and only one third of the patients with pulmonary TB are sputum AFB smear positive [9]. Although there have been few reports of the treatment response of presumptive pulmonary TB and predictors of positive *M. tuberculosis* culture results among patients with a negative sputum AFB smear result in a low or high TB-prevalent area with high prevalence of HIV infection [10–14], there has been no report in an industrialized nation with moderate-to-high TB prevalence and with very low prevalence of HIV infection. The purpose of our study was to elucidate treatment outcomes of presumptive pulmonary TB based on clinical and radiographic features and to find predictors of positive culture in Korean patients with negative sputum AFB smear.

Methods

Study Setting and Subjects

The subjects included in the study were patients who were aged 15 years or older and visited the Seoul National University Hospital, a university-affiliated referral hospital, between December 1998 and December 2000 with suspicion of pulmonary TB. In these patients, we retrospectively reviewed the clinical records and radiographs of the patients who had at least three negative sputum AFB smear results and started anti-TB medication by individual physicians' decision on the basis of symptoms and/or radiographic features. We excluded patients who were diagnosed to have pulmonary TB by AFB smear of other specimen or tissue biopsy. All sputum smears were concentrated and examined by trained microbiology technicians. Each sputum smear was cultured by Ogawa media and maintained at least 8 weeks to detect the presence of growing organisms.

Data Collection and Statistical Analysis

We reviewed medical records of enrolled patients, which included an admission note, microbiology results (smear and culture) and chest radiography interpretation by board-certified radiologists. We analyzed demographic characteristics of patients such as age and sex as well as clinical features including symptoms, laboratory and radiographic findings. The results of chest radiographs were classified into 5 categories – patchy consolidation, nodular opacities, streaky nodular opacities, cavitary lesion and miliary nodules. These categorizations were independently verified by two radiologists who were blinded to the culture results and treatment responses. Improvement was defined by radiographic findings. The serial radiographs were reviewed by two radiologists who decided treatment response, improvement or no improvement, independently. If their opinions were discordant, they made a new conclusion after discussion.

Univariate comparisons between the culture-positive group and the culture-negative group were performed using Pearson's χ^2 test or Fisher's exact test for categorical variables and Student's t test for continuous variables. All tests of significance were two sided, and a p value less than 0.05 was considered statistically significant. Multiple logistic regression analysis was also conducted using SPSS (version 11.0) to identify predictor variables for positive culture results in patients with AFB smear-negative presumptive pulmonary TB.

Table 1. Characteristics of patients with sputum smear AFB-negative presumptive pulmonary TB

		n = 101
Age, years[1]	48.0 (21–85)	
Sex	male	66 (65.3)
	female	35 (34.7)
History of previous tuberculosis	yes	13 (12.9)
	no	88 (87.1)

Figures in parentheses are percentages.
[1] Presented as mean, with range in parenthesis.

Results

One hundred and one patients with smear-negative presumptive pulmonary TB were enrolled. The characteristics of patients including clinical findings and radiographic results are summarized in table 1. The mean age of the patients was 48.0 years with a male to female ratio of 66 (65.3%) to 35 (34.7%). Thirteen patients (12.9%) had a history of pulmonary TB and subsequent anti-TB treatment. All these 13 patients reported that they had completed anti-TB medication; however, we could not review their previous medical records. Sixty-three (62.4%) patients were symptomatic, and the most common symptom was cough. Streaky nodular opacities (50.5%) and patchy consolidation (40.6%) were the most frequently observed radiographic findings. All 101 patients were

Table 2. The treatment outcome of smear-negative presumptive pulmonary tuberculosis

	Culture positive n = 32 (32)	Culture negative n = 69 (68)	Total n = 101
Radiologic improvement*	26/32 (81.3)	36/69 (52.2)	62/101 (61.4)
Clinical improvement	24/24 (100)	24/28 (85.7)	48/52 (92.3)
Radiologic or clinical improvement**	31/32 (96.9)	50/69 (72.5)	81/101 (80.2)
Treatment period, mean, months	9.5	8.8	9.0
Treatment period, range, months	6–16	6–41	6–41
Duration of follow-up, mean, months	27.8	31.4	30
Duration of follow-up, range, months	6–52	6–70	6–70
Recurrence	1	0	1

Figures in parentheses are percentages.
* p = 0.008; ** p = 0.004.

treated for at least 6 months with anti-TB medication based on isoniazid, rifampicin, ethambutol and pyrazinamide. The mean treatment period was 9.0 months. These patients were followed up by 1 of 5 respiratory care specialists on a monthly basis, and mean follow-up duration including treatment period was 30 months.

Among 101 patients, pulmonary TB was confirmed by culture in 32 patients (31%). Thirty-one (96.9%) out of 32 culture-positive patients showed clinical or radiographic improvement as did 50 (72.5%) out of 69 culture-negative patients (p = 0.004; table 2). TB was recurred in 1 patient from the culture-positive group, whose culture was converted to be positive at the 49th month after termination of chemotherapy. One patient died of leukemia during the follow-up period after cure of pulmonary TB.

The clinical characteristics of patients with positive or negative culture results are shown in table 3. Symptomatic patients were more common in the culture-positive group than in the culture-negative group (81.3 vs. 53.6%, p = 0.008). In addition, a patchy consolidation in the chest radiograph was more frequent in the culture-positive group (59.4 vs. 31.9%, p = 0.009). In the multivariate analysis, a patchy consolidation in simple chest radiography was an independent predictor of a positive culture result (OR 2.89; 95% CI 1.14–7.28). Neither sputum (OR 1.24; 95% CI 0.91–1.67) and weight loss (OR 1.03; 95% CI 0.67–1.57) nor branching linear opacity (OR 1.12; 95% CI 0.44–2.87) and lymph node enlargement (OR 1.00; 95% CI 0.29–3.45) in chest CT was associated with a positive culture result. In additional analysis, a patchy consolidation in an initial chest radiograph was the predictor for a radiographic improvement with empirical anti-TB treatment (OR 4.13, 95% CI 1.64–10.4) as well, whereas streaky nodular opacity was the predictor of no improvement with treatment (OR 0.30; 95% CI 0.13–0.71).

Among the patients with negative culture results, nontuberculous mycobacteria were isolated in 3 patients, and 1 patient was diagnosed as having a sarcoidosis. In 12 patients, adverse effects of TB medication such as hepatitis, leucopenia, pruritis, acneiform skin lesions were notified; however, they were not so severe as to change or stop anti-TB medications.

Discussion

The prompt initiation of treatment for pulmonary TB is crucial not only for the benefits of the patients, but also for the control of tuberculosis in the community. The fact that the smear-negative but culture-positive TB was responsible for 17% of the tuberculosis transmission underscores the importance of initiation of anti-TB medication in the case of AFB smear-negative presumptive pulmonary TB [15]. However, for patients with a high clinical suspicion of TB, clinicians face the dilemma of starting empirical treatment or waiting for the culture results for up to 6–8 weeks. Even after 6–8 weeks, clinicians again face the dilemma of continuing or stopping empirical treatment if a final culture showed negative results. Although newer rapid diagnostic tools such as the nucleic acid amplification method [16–18] and serodiagnosis using ELISA have been introduced recently [19–23], there have been mixed results about their usefulness in diagnosis of smear-negative pulmonary TB, and they are not yet considered as standards of practice. [24] Therefore, the

Table 3. Comparison between patients with positive or negative culture

	Positive culture n = 32	Negative culture n = 69	p value	OR	95% CI
Age, mean, years	46.4	48.7	0.565		
Age, range, years	21–81	23–85			
Sex, M:F	20:12	46:23	0.682	0.88	0.49–1.59
History of treated TB[1]	3 (14.3)	10 (10.5)	0.750	0.70	0.25–1.94
Lab.[2]					
WBC, ×1,000/μl	6.5 (4.4–9.1)	6.5 (3.7–10.1)	0.989		
ESR, mm/h	31.9 (1.0–120.0)	24.4 (1.0–117.0)	0.493		
CRP, mg/dl	2.8 (0.1–8.0)	1.7 (0.1–4.9)	0.336		
Symptoms[1]					
Yes*	26 (81.3)	37 (53.6)	0.008	2.61	1.19–5.77
Cough*	17 (53.1)	21 (30.4)	0.029	1.38	1.004–1.89
Sputum	15 (46.9)	22 (31.9)	0.146	1.24	0.91–1.67
Hemoptysis	6 (18.8)	10 (14.5)	0.586	1.11	0.74–1.67
Weight loss	4 (12.5)	8 (11.6)	1.000	1.03	0.67–1.57
Febrile sense	5 (15.6)	6 (8.7)	0.318	1.29	0.74–2.24
Dyspnea	1 (3.1)	7 (10.1)	0.430	0.76	0.57–1.03
Chest pain	2 (6.3)	4 (5.8)	1.000	1.03	0.57–1.84
Night sweat	2 (6.3)	2 (2.9)	0.589	1.38	0.51–3.71
Pattern of radiograph[1]					
Streaky nodular	15 (39.7)	36 (68.4)	0.620	0.87	0.49–1.54
Patchy opacity*	19 (59.4)	22 (31.9)	0.009	2.14	1.19–3.83
Nodular lesion	6 (18.8)	15 (21.7)	0.731	0.88	0.42–1.86
Cavity	5 (15.6)	9 (13.0)	0.762	1.15	0.53–2.48
Miliary lesion	0 (1.6)	2 (2.6)	1.000	0.97	0.97–1.01
Location[1]					
Right upper lobe	16 (50.0)	39 (56.5)	0.540	0.84	0.47–1.48
Right middle lobe	4 (12.5)	10 (14.5)	1.000	0.89	0.37–2.15
Right lower lobe	7 (21.9)	14 (20.3)	0.855	1.07	0.54–2.12
Left upper lobe	13 (40.6)	25 (36.2)	0.672	1.13	0.64–2.03
Left lower lobe	4 (12.5)	6 (8.7)	0.721	1.30	0.57–2.95
CT	12	24			
Branching linear[1]	7 (37.5)	13 (34.8)	0.813	1.12	0.44–2.87
Lymphadenopathy[1]	2 (6.3)	4 (5.8)	1.000	1.00	0.29–3.45

WBC = White blood cells; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

* $p < 0.05$. Among these 3 variables statistically significant in univariate analyses, only patch consolidation was an independent variable in multiple logistic regression (OR 2.89; 95% CI 1.14–7.28).

[1] Number of patients, with percentages in parentheses.

[2] Presented as means, with range in parentheses.

clinical predictor of positive culture results or improvement to empirical anti-TB medication has been anticipated.

We presented the treatment outcome of presumptive pulmonary TB in patients with pulmonary TB based on individual clinicians' decision. Among 101 patients with presumptive TB based on clinical and/or radiographic features, 63 (62.3%) patients showed radiographic improvement with empirical anti-TB treatment in our study. This response rate is higher than 30.4% [25] and 48% [13] of a low TB-prevalent area and lower than 78% [26] of a high-prevalent area. These variations of response rates among different countries might be a reflection of TB prevalence in a specific area; in this context, 62.3% in

Korean patients and 55% in Singapore people [27] are predictable. However, the fact that data from Malawi used strict criteria for starting empirical anti-TB treatment [26] (cough longer than 3 weeks and no response to antibiotics in addition to radiographic features) in contrast to other reports [13, 25, 27] might have increased the response rate.

There have been some suggested predictors for the presence of pulmonary TB in the case of negative AFB smear results, such as positive tuberculin skin test [10–12], HIV infection [10, 12], cervical or mediastinal lymphadenopathy [11, 12], cavitary lung lesion [27, 28], history of contact with tuberculosis [10, 27], cough more than 3 weeks [26] and weight loss [13]. However, these variables couldn't be used ubiquitously because of the different epidemiological characteristics of each population and are not predictors of the treatment outcome.

Among suggested predictors for the presence of pulmonary TB in the case of negative AFB smear results, only the patchy consolidation in an initial chest radiograph was the independent predictor for a positive culture result and a radiographic improvement to the empirical anti-TB treatment in patients with negative sputum smear results in our study. In addition, the streaky nodular opacity was associated with no improvement after empirical anti-TB treatment as Woodring et al. [29] stressed. The cavitary lesion also failed to reach statistical significance as a predictor for culture-positive TB or for a radiographic improvement. In addition, there was no association between the branching linear opacity in chest CT, one of the hallmarks of bronchogenic spread of tuberculous inflammation [30], and the presence of active pulmonary TB. This lack of associations might be explained by the small number of patients who performed chest CT, 36 out of 101 patients. Although our results stressed the importance of the patchy consolidation in the chest radiograph of patients with possible pulmonary TB and radiographic findings are sometimes very informative in mycobacterial diseases [31–33], radiographic findings alone, without compatible symptoms, would not be the only reason to start anti-TB treatment.

The shortcoming of this analysis was the fact that we used empirical anti-TB treatment which was not based on clear indication but on individual physicians' decision. This could have misclassified other diseases such as bacterial pneumonia, which might be treated with broad-spectrum antimicrobial activity of rifampicin, as a smear-negative TB.

In conclusion, the empirical anti-TB treatment to presumptive smear-negative pulmonary TB is appropriate in the majority of Korean patients, especially in those who presented with patchy consolidation in an initial chest radiograph.

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