

Bacteriologically-negative Pulmonary Tuberculosis—The Singapore Tuberculosis Control Unit Experience

W Y Pek,*^{MBBS, MRCP (UK)}, C B E Chee,**^{FAMS, MBBS, FRCP}, Y T Wang,***^{FAMS, MBBS, FRCP}

Abstract

Introduction: Patients with radiological features suggestive of active pulmonary tuberculosis (PTB) from areas with a high prevalence of the disease have a high clinical likelihood of PTB regardless of the bacteriological findings. It is the established practice in many countries to initiate therapy in such patients. Our study aimed to determine if treatment for bacteriologically-negative PTB in our local population was appropriate and to identify features at presentation that would be predictive of active PTB, as defined by good and appropriate response to anti-tuberculous treatment. **Materials and Methods:** A retrospective review of a randomised sample consisting of 100 bacteriologically-negative PTB patients given a course of anti-tuberculous treatment at the Singapore Tuberculosis Control Unit (TBCU). Based on their treatment response and outcome, patients were classified as probable active or unlikely active PTB. Patients' characteristics, clinical presentation and radiological findings were analysed for their association with likelihood of probable active PTB. **Results:** Fifty-six per cent of patients in this study had probable active PTB. The decision to treat this group of patient was appropriate. There was no serious adverse reaction in the patients treated. The presence of symptoms, especially cough at presentation, a history of contact with tuberculosis and cavitation on chest radiograph, were associated with an increase risk of probable active disease. **Conclusion:** The TBCU's practice to treat patients suspected of having radiological PTB in the setting of negative sputum smear and culture seems to be appropriate in the majority of cases.

Ann Acad Med Singapore 2002; 31:92-6

Key words: Anti-tuberculous treatment, Negative culture, Negative sputum smear, Pulmonary tuberculosis

Introduction

The management of a patient as for pulmonary tuberculosis (PTB) in the setting of negative bacteriology would have to take into account not only the likelihood that the patient has active PTB, but also the consequences of a mistaken diagnosis and the adverse effects of TB treatment. Patients with radiological features suggestive of active PTB from locales with a high prevalence of the disease have a high clinical likelihood of PTB regardless of the bacteriological findings.¹⁻⁴ It is the established practice in many countries to initiate therapy in such patients.

Nine hundred and fifty-four cases of PTB were treated at the Singapore Tuberculosis Control Unit (TBCU) in 1996. Four hundred and seventeen (41.9%) of these patients were bacteriologically negative, with at least two sets of negative sputum smears and cultures. Empiric therapy was initiated in these patients based on clinical suspicion and radiological

abnormalities. They were continued on their TB treatment even after the initial culture was known to be negative. As these numbers were high compared to the previous 5 years when the rate of negative bacteriology in treated patients averaged about 30%, we were concerned that we might be inappropriately over-treating our patients and hence, subjecting them to the adverse effects associated with anti-tuberculous chemotherapy.

The main aim of our study was to determine if our practice of empiric treatment for bacteriologically-negative PTB was appropriate in our population. Our secondary aim was to identify clinical and radiological features at presentation that would be predictive of active PTB, as defined by good response to TB treatment. In addition, we sought to determine if one could identify patients likely to have active disease based on radiological interpretation alone.

* Registrar, Department of Respiratory Medicine

** Senior Consultant, Department of Respiratory Medicine

*** Senior Consultant and Head, Department of Respiratory Medicine

Director, Tuberculosis Control Unit, Singapore

Tan Tock Seng Hospital

Address for Reprints: Dr Pek Wee Yang, Department of Respiratory Medicine, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.

E-mail: Wee_Yang_Pek@notes.ttsh.gov.sg

Materials and Methods

Patients

We conducted a retrospective medical record review of patients treated presumptively for PTB but who were sputum smear-negative and culture-negative at TBCU in 1996. We identified patients with negative bacteriology among all the cases treated from the computerised TBCU registry. One hundred patients were randomly selected from this bacteriologically-negative cohort. Their medical records, including chest radiographs, were retrieved and systematically reviewed. The patients in this study presented to TBCU with chest radiographs suspicious of PTB, had at least two sets of negative sputum smears and cultures at presentation, and had not received any antituberculous treatment in the past. Based solely on clinical and radiological grounds by the attending physicians, they were all given a standard course of anti-tuberculous treatment,⁵ continued on treatment even when the initial sputum specimens were culture-negative and followed-up for a minimum of 12 months from the time of presentation at TBCU.

Demographic data captured for analysis included age, gender, ethnicity and socio-professional grouping. The mode of presentation, referral source, presence and duration of symptoms, history of contact with persons with PTB, presence of cough, sputum or haemoptysis, weight loss, fever and asthenia were determined. Patients' smoking and alcohol drinking habits, the presence of co-morbid conditions, and prior treatment with antibiotics were also established from the review of the case records.

Criteria for Treatment Response and the Likelihood of Active Disease

We determined whether a patient had active PTB⁶ according to their clinical and radiological response to anti-tuberculous treatment. Patients were deemed likely to have probable active PTB if they fulfilled all of the following criteria:

- 1) Radiological improvement consistent with a therapeutic response to anti-tuberculous medications as assessed by at least two independent assessors;
- 2) Stability of, or increase in weight during treatment;
- 3) Resolution of symptoms within 3 months of initiating treatment if symptoms were present;
- 4) Absence of another diagnosis during the treatment and follow-up period that could account for the clinical and radiological changes observed.

Patients who failed to demonstrate a radiological response following treatment were classified as unlikely active PTB. This group included asymptomatic patients who did not improve radiologically after treatment. When another diagnosis was present, the patient was labelled as such.

Radiological Assessment

Two chest physicians, not involved in the treatment of these patients and blinded to the clinical data, independently assessed the presenting chest radiograph of each patient in the study. The radiological findings were defined in terms of size and extent of the lesions, the location of the infiltrates and the presence of cavitation. The likely activity of the tuberculous focus was graded from definitely active to definitely inactive. The chest radiographs, before treatment initiation and after completion of treatment, were examined and compared to determine if there was any radiological improvement compatible with treated tuberculosis. In cases where there was discordance in opinion with regard to radiological improvement between the first two assessors, a third independent assessor would review the chest radiographs and his decision was used for the final analysis. This was necessary in 14 cases.

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences (Windows version). Descriptive summary measures of central tendency, frequency and associations between study variables and outcome with tests of statistical significance were computed as appropriate. Kappa coefficient of agreement was computed for radiological assessment by the two independent assessors. Clinical symptoms and radiological findings were analysed for their association with probable active PTB. Risk ratio for probable active tuberculosis was computed for each individual factor with significant association. In addition, we determined if the radiological activity as interpreted by the independent assessors could help to identify patients with probable active PTB. Significance was taken at $P < 0.05$ and the risk ratio was given with the 95% confidence interval.

Results

Patient Characteristics and Symptomatology

The patients' demographic data are shown in Table I.

There was no significant difference in terms of age, sex, ethnicity and socio-economic status and co-morbidity between symptomatic and asymptomatic patients in this study.

Fifty-three patients were asymptomatic persons who were referred for abnormal chest radiographs discovered during mobile chest radiograph screening (25), contact tracing (16) and pre-employment medical check-up (12). Among the 47 symptomatic patients, the most common presenting symptom was cough, which was present in 45 (95.7%) patients. Other symptoms, such as asthenia, weight loss and fever, were present in 19 (40.4%), 11 (23.4%) and 5 (10.6%) patients, respectively. The mean duration of

TABLE I: DEMOGRAPHIC CHARACTERISTICS SHOWN SEPARATELY FOR SYMPTOMATIC AND ASYMPTOMATIC PATIENTS

Variable	Symptomatic (%) (n = 47)	Asymptomatic (%) (n = 53)
Sex		
Male	78.7	71.7
Female	21.3	28.3
Ethnic group		
Chinese	87.5	83.0
Malay	8.5	13.2
Others	4.2	3.8
Age group (y)		
25 and below	8.6	15.1
35-44	25.5	20.8
45-54	10.6	17.0
55-64	17	15.1
65 and above	38.3	32.1
Socio-professional status		
Blue collar	44.7	50.9
White collar	19.1	13.2
Retired	25.5	24.5
Others	10.6	11.3
Smoker	46.8	43.4
Alcohol drinker	10.6	5.7

symptoms was 7.7 weeks before attendance at the Tuberculosis Control Unit.

Half of all patients (51) were given a course of oral antibiotics prior to the initiation of anti-tuberculous treatment, but their chest radiograph remained suspicious of PTB. Bronchoscopy was performed in 2 cases to exclude lung cancer and computed tomographic (CT) scan of the thorax was performed in one of them.

Radiological Features at Presentation

The patients' radiological characteristics are shown in Table II.

Eighty cases (80%) had acinar infiltrates in the upper zone, predominantly over the right lung. Seventy-five cases (75%) had disease estimated at more than 5 cm². Cavitation was rare and was found in only 7%. A large proportion (79%) of the presenting chest radiographs reviewed was considered to be definitely or likely active by the two independent assessors. An alternative diagnosis was deemed likely in one case and was subsequently shown to be due to cancer of the lung. Three chest radiographs were interpreted as normal with no disease.

The kappa coefficient of agreement for the assessment of radiological improvement by the two independent assessors indicates fair to good agreement ($\kappa = 0.48$).

TABLE II: RADIOLOGICAL CHARACTERISTICS OF ALL PATIENTS

	No. of patients (n = 100)
Extent of disease	
<5 cm ²	25*
5 to 15 cm ²	43
>15 cm ²	32
Cavitation	
Yes	7
No	93
Radiological activity	
Definitely active	50
Likely active	29
Likely inactive	11
Definitely inactive	10*

* 3 chest radiographs considered normal and 1 was considered to have lesion not due to tuberculosis.

Ninety-three per cent of our study patients completed the prescribed course of treatment. Ninety-two per cent of all patients had received the standard regimen of either 6 months or 9 months of anti-tuberculous chemotherapy. Treatment was self-administered in all cases. All patients were reviewed at TBCU at monthly intervals where their clinical progress and any adverse reaction was assessed, and weight recorded.

Adverse Drug Reactions

Sixteen of the patients studied developed adverse reaction to the anti-tuberculous drugs. Ten patients had skin rash or itch, 3 had giddiness, 2 complained of gastrointestinal upset and 1 patient had symptomatic hepatitis. Four of these patients had their treatment terminated early because of the side effects. The mean duration of treatment in the 4 patients was 3 months. However, none of the adverse reactions resulted in hospitalisation. It is important to note that among the 16 patients with adverse reaction, 12 were found to have probable active PTB with both radiological as well as clinical response to treatment.

Response to Treatment

Based on the criteria for treatment response defined in this study, 56 patients had probable active PTB. This group of patients included 32 symptomatic and 24 asymptomatic subjects (Table III). They all showed radiological improvement after treatment, consistent with a therapeutic response to anti-tuberculous drugs.

Forty-two patients had no radiological improvement after treatment, and were categorised as unlikely active PTB.

An alternative diagnosis was found in 2 patients. One of them was a 73-year-old smoker who showed radiological

TABLE III: PATIENT GROUPS BASED ON TREATMENT RESPONSE

	Total no. of patients	Patients with symptoms
Probable active PTB ¹⁺²⁺³⁺⁴	56	32
Unlikely active PTB	42	15
Lung cancer	2	
Total	100	

PTB: pulmonary tuberculosis

1. Radiological improvement as assessed by at least 2 independent assessors.
2. Stability of, or increase in weight during treatment.
3. Resolution of symptoms within 3 months of treatment if symptoms were present.
4. Absence of another diagnosis during the treatment and follow-up period.

worsening despite treatment and was diagnosed to have stage III squamous cell carcinoma of the lung bronchoscopically after 3 months of TB treatment. The other patient was a 61-year-old non-smoking female who was found to have stage III adenocarcinoma of the lung 9 months after treatment for tuberculosis was completed.

Risk Factors

The presence of symptoms at presentation was found to be associated with probable active PTB in this group of bacteriologically-negative patients. The risk ratio of 1.50 (95% CI, 1.054-2.144) was statistically significant. There was a greater likelihood that a patient with cough as the presenting symptom had probable active PTB with a risk ratio of 1.52 (95% CI, 1.068-2.150). A positive history of contact with tuberculosis was significant in predicting the presence of probable active PTB with a risk ratio of 1.84 (95% CI, 1.369-2.477).

In terms of radiological features, the presence of cavitation (although uncommon) was associated with probable active PTB with a risk ratio of 1.545 (95% CI, 1.545-2.122).

A significant association was found between the radiological activity as interpreted by the independent assessors and the presence of probable active PTB. When the independent assessors deemed the presenting chest radiograph active, a patient was 1.8 times more likely to have probable active PTB ($P < 0.05$) (Table IV). No association was found between the likelihood of probable active tuberculosis and the other radiological features like size and location of the lesion.

No association was found between ethnicity, gender, age, presence of co-morbidity, smoking status and the likelihood of probable active PTB in this study.

TABLE IV: RADIOLOGICAL ACTIVITY AND LIKELIHOOD OF PROBABLE ACTIVE PTB BASED ON TREATMENT RESPONSE

Radiological activity*	Probable active PTB		Total
	Yes	No	
Active	49	30	79
Inactive	7	14	21
Total	56	44	100

PTB: pulmonary tuberculosis

* Radiological activity as determined by the independent assessors.

Discussion

Some patients with clinical and radiological features suggestive of active PTB have negative sputum smear and culture for tubercle bacilli. Sputum smear under microscopy is relatively insensitive for the detection of mycobacterial organism, and approximately 5000 to 10,000 organism per millilitre must be present for smear to be positive on microscopy.⁷ Sputum cultures for *Mycobacterium tuberculosis* are more sensitive than sputum smear, but may also be negative in up to one-fifth of patients with active PTB.^{2-4,8,9} It has been suggested that up to 3 to 6 specimens should be sent for bacteriologic analysis in cases that are smear negative initially to increase the yield of a positive diagnosis.¹⁰

Patients with negative sputum smear can still spread the disease to others and hence be a public health threat.¹¹ Early presumptive treatment is of benefit in that it stops progression of the disease at an early stage and decreases the potential for spread in the community. However, this must be weighed against the possible side effects and over-treatment in patients with inactive disease.

In studies on short-course chemotherapy done in the early 1980s, 35% of patients with untreated radiological active PTB with negative smears had an eventual positive culture after variable period of follow-up.¹⁻³ In the study by Cowie and associates⁸ on initially smear-negative and culture-negative PTB, 58% of suspected tuberculosis cases developed bacteriologically-confirmed PTB after 65 months of follow-up. The study by Dutt and colleagues⁹ reported that 30% of patients who had negative sputum smear and cultures showed radiological as well as clinical response to anti-tuberculous treatment, suggesting active infection and confirmed the correctness of empiric treatment in this group of patients. These studies suggested that a significant number of patients (from high prevalence area) with radiological PTB had active disease despite a negative bacteriology on initial testing. Our study sought to determine the appropriateness of presumptive treatment in this group of patients in our population and to better

characterise patients at risk of active PTB.

The TBCU's practice to presumptively treat patients suspected of having radiological PTB in the presence of negative sputum smear and culture seems to be appropriate for 56% of all cases. The remaining 42 patients probably included those with latent TB infection, scarring or both. Patients on presumptive treatment for PTB, however, need to be monitored more closely, and other modalities of investigation may be required in order to avoid missing serious alternative diagnosis like cancer. Our study shows that bacteriologically-negative patients are more likely to have active infection if they are symptomatic at presentation, cough in particular. Patients with positive history of contact are at increased risk of active disease and should be empirically treated based on radiological findings alone. Presence of cavitation on chest radiograph has long been shown to be indicative of active tuberculosis and this appears to be true also in the bacteriologically-negative patients. Radiological activity, when assessed by experienced independent assessors, is an important indicator of active PTB and can help to identify patient with negative culture who should be given a full course of anti-tuberculous treatment.

We conclude that the empiric treatment of bacteriologically-negative and radiologically-suggestive PTB is appropriate in our community with moderately high prevalence for PTB. This practice generally does not lead to unnecessary delay in alternative diagnosis, nor does it expose the patient to unacceptable side effects of the anti-tuberculous treatment.

REFERENCES

1. Hong Kong Chest Service. A study of the characteristics and course of sputum smear-negative pulmonary tuberculosis. *Tubercle* 1981; 62: 155-67.
2. Hong Kong Chest Service/British Medical Research Council. A controlled trial of 2-month, 3-month, and 12-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis. Results at 60 months. *Am Rev Respir Dis* 1984; 130:23-8.
3. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A controlled trial of 3-month, 4-month, and 6-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis. Results at 5 years. *Am Rev Respir Dis* 1989; 139:871-6.
4. Gordin F M, Slutkin G, Schecter G, Goodman P C, Hopewell P C. Presumptive diagnosis and treatment of pulmonary tuberculosis based on radiological findings. *Am Rev Respir Dis* 1989; 139:1090-3.
5. Bass Jr J B, Farer L S, Hopewell P C, O'Brien R, Jacobs R F, Ruben F, et al. Treatment of tuberculosis and tuberculosis infection in adults and children. American Thoracic Society and the Centers for Disease Control and Prevention. *Am J Respir Crit Care Med* 1994; 149:1359-74.
6. American Thoracic Society. Diagnostic standards and classification of tuberculosis. *Am Rev Respir Dis* 1990; 142:725-35.
7. Yeager Jr H, Lacy J, Smith L R, Lemaistre C A. Quantitative studies of mycobacterial populations in sputum and saliva. *Am Rev Respir Dis* 1966; 95:998-1004.
8. Cowie R L, Langton M E, Escreet B C. Diagnosis of sputum smear- and sputum culture-negative pulmonary tuberculosis. *S Afr Med J* 1985; 68:878.
9. Dutt A K, Moers D, Stead W W. Smear- and culture-negative pulmonary tuberculosis: four-month short-course chemotherapy. *Am Rev Respir Dis* 1989; 139:867-70.
10. Blair E B, Brown G L, Tull A W. Computer files and analyses of laboratory data from tuberculosis patients. II. Analyses of six years' data on sputum specimens. *Am Rev Respir Dis* 1976; 113:427-32.
11. Behr M A, Warren S A, Salamon H, Hopewell P C, Ponce de Leon A, Daley C L, et al. Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. *Lancet* 1999; 353:444-9.