Radiographic Features for Predicting Smear-Negative Pulmonary Tuberculosis

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Background: *Diagnosis of smear-negative pulmonary tuberculosis (TB) in some circumstances remains a challenge to physicians especially those working in limited-resource settings.*
Objective: *To investigate and examine radiographic characters as a predictor of true diagnosis of pulmonary tuberculosis in patients with negative sputum smears.*
Material and Method: *This retrospective cross-sectional study was conducted in patients with smear-negative pulmonary TB at Siriraj Hospital between January 2013 and June 2014. Patients with previous TB treatment, HIV co-infection, significant pleural effusion, and corticosteroid therapy equivalent to prednisolone greater than 15 mg/day were excluded. Demographic and clinical data were collected and radiographic features were reviewed and classified as active or inactive TB by a consensus of three independent reviewers. Various diagnostic parameters for true prediction of TB, as defined by culture confirmation and/or radiographic improvement, were then examined.*
Results: *There were 122 patients during the study period, 65 (53%) were male, 27 (22%) were asymptomatic, 20 (16%) had extrapulmonary involvement, and eight (7%) had concomitant diabetes mellitus. TB was confirmed in 92 patients (75%), 72 had positive culture and 20 had radiographic improvement. Miliary nodules and cavitary lesions had high specificity (100% and 100%, respectively) and low sensitivity (9.8% and 13%, respectively) for prediction of true TB. Focal interstitial and alveolar opacities had high positive predictive value (79.5 and 85%) and modest accuracy (62.3 and 47.5%).*
Conclusion: *Given that specific radiographic features are uncommon and non-specific features are common in smear-negative pulmonary tuberculosis, clinicians should supplement clinical symptoms, radiological features, and radiological responses with mycobacterium TB culture to verify diagnosis of TB.*

Keywords: *Radiographic features, Smear-negative pulmonary tuberculosis*

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Tuberculosis (TB) remains one of the major infectious diseases that threaten global health. According to a 2013 WHO report, approximately 60,000 new cases of TB cases were reported in Thailand with nearly half of pulmonary TB (PTB) patients having negative sputum smear[1]. The gold standard for diagnosis of PTB is isolation of *Mycobacterium tuberculosis* from sputum specimen by culture, a process that takes about three weeks using the current method[2]. In sub-optimal clinical situations, physicians who encounter patients suspected of having PTB with negative-smear status must decide whether to treat or not treat based on clinical and radiological information[3]. The practice of relying on clinical presentation and radiographic findings benefits not only the individual patient/case, but also helps to monitor and control TB at the community level. Because there is no standardize radiological criteria for active PTB, a significant drawback to this diagnostic approach is that an undetermined percentage of patients suspected to have TB may receive unnecessary treatment. Some patients with non-active disease have radiographic abnormalities that can persist or even become worse after complete and successful course of anti-TB therapy.

The objective of this study was to investigate and examine radiographic characters that predict active disease in patients with presumptive PTB with negative sputum smear. Comparison of radiographic features between culture-positive and culture-negative subgroups was the study's secondary objective.

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Material and Method

A retrospective cross-sectional study was conducted at Siriraj Hospital between January 2013

and June 2014 in patients who were justified to treat as smear-negative PTB by their respective physicians. We included patients older than 15 years of age who provided at least two sputum culture specimens, had complete course of treatment as designated by their physicians, and had both initial and end-of-treatment digital chest radiographs (CXRs). Patients with history of previous TB treatment, HIV co-infection, and/or other severe immunosuppressed states were excluded. The protocol for this study was approved by the Siriraj Institutional Review Board (Si 381/2014).

Demographic data and sputum culture results were gathered from medical and laboratory records. All initial CXR digital files were reviewed by the three authors of this study (two radiologists and one pulmonologist), all of whom were independently blinded to culture results and end-of-treatment CXRs, according to a structured protocol constructed by the authors (Table 2). This protocol classified findings into nine categories with a conclusion regarding whether patient was active or inactive PTB from global judgment, by at least two-thirds agreement of the reviewers. Active PTB was defined as positive culture result for *M. tuberculosis*. For patients with negative culture result, active PTB was also defined if there was significant radiographic improvement in end-of-treatment CXR relative to initial CXR as judged subjectively by the reviewers.

Data were expressed descriptively. Sensitivity and specificity as determined by two-by-two table were used to identify radiographic features for predicting active PTB. Positive predictive value (PPV), negative predictive value (NPV), and accuracy were also determined. Agreement of reviewers was assessed by kappa number determination. Comparison between culture-positive and culture-negative groups was performed using Chi-square or Fisher's exact test. A p-value <0.05 was considered statistically significant. All statistical analyses were performed by SPSS software version 16.0 (SPSS, Inc., Chicago, IL, USA).

Results

One hundred twenty two patients fulfilled the inclusion criteria during the study period, with slight male preponderance and mean age of 50 years. No obvious symptom was established in 27 patients (22%), 20 (16%) had concomitant extrapulmonary TB, and eight (7%) had diabetes mellitus as a co-morbidity (Table 1).

According to the three independent reviewers, initial CXRs were judged as active PTB in 101 patients (83%). Final active PTB was identified in 92 patients, with 72 having positive culture results and 20 having radiographic improvement after completing course of treatment. The reviewers judged as active PTB in 85 out of 92 true active PTB (92%) and in 16 out of 30 (53%) of non-PTB patients. All active PTB patients were cured at the end of treatment.

Miliary nodules, cavitary lesions, ipsilateral adenopathy, and ipsilateral pleural effusion were radiographic features with high specificity, but low sensitivity and accuracy in determining active PTB. Focal interstitial and alveolar opacities had high PPV and accuracy, with low NPV (Table 2). An inter-rater reliability for focal interstitial opacities was 0.64 (95% CI 0.39-0.89, p<0.001). Radiographic features between positive and negative culture results were not significantly different (Table 3).

Discussion

Mycobacterial load[4] and infectivity[5] of smear-negative PTB patients were far less than the results from smear-positive PTB patients. However, if left untreated, progression to smear-positive cavitary disease would have been inevitable[6]. Physician threshold whether to treat, to investigate, or to observe depends on various factors, including the pattern of radiographic abnormalities[7]. However, no single exceptional diagnostic tool exists, among bronchoscopy[8], adenosine deaminase activity[9], polymerase chain reaction[10], TB prediction score[11], antibody detection[12], gastric aspirates[13], and the quest for that diagnostic tool continues[14].

In the present study, we evaluated treatment outcomes of smear-negative presumptive PTB patients, based on individual decisions of physicians. Rate of over-diagnosis by physicians in charge as determined by negative culture results and no radiographic improvement was 24.6%, and decreased to 17.2% according to the judgment of experienced reviewers. These figures are comparable to 21.1%[15] and 28.8%[16] in earlier studies from Thailand during

Table 1. Demographic and clinical data from 122 smear-negative PTB patients

Character	Number
Age (years), mean ± SD	50±19
Male:female	65:57
Patients with extrapulmonary involvement, n (%)	20 (16)
Patients with concomitant diabetes mellitus, n (%)	8 (7)
Number of asymptomatic patients, n (%)	27 (22)

Table 2. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of various radiographic features in predicting active PTB

Radiographic features	% sensitivity (95% CI)	% specificity (95% CI)	% PPV (95% CI)	% NPV (95% CI)	% accuracy
Upper lobe minimal reticulation	4.3 (1.4-11.4)	83.3 (64.5-93.7)	44.4 (15.3-77.3)	22.1 (15.1-31.1)	23.8
Thin-walled cavity	13.0 (7.2-22.1)	100 (85.0-100)	100 (69.9-100)	27.3 (19.4-36.7)	34.4
Focal alveolar opacities	36.9 (27.3-47.7)	80.0 (60.9-91.6)	85.0 (69.5-93.8)	29.3 (20.0-40.1)	47.5
Focal interstitial opacities	67.4 (56.7-76.6)	46.7 (28.8-65.4)	79.5 (68.5-87.4)	31.8 (19.1-47.7)	62.3
Lung mass	1.1 (0.1-6.8)	100 (85.9-100)	100 (5.5-100)	24.8 (17.6-33.6)	25.4
Localized bronchiectasis	4.3 (1.4-11.3)	93.3 (76.5-98.8)	66.7 (24.1-94.0)	24.1 (16.9-33.1)	26.2
Ipsilateral mediastinal lymphadenopathy	3.3 (0.8-9.9)	100 (85.9-100)	100 (30.1-100)	25.2 (17.9-34.1)	27.1
Ipsilateral minimal pleural effusion	14.1 (8.0-23.3)	96.7 (80.9-99.8)	92.9 (64.2-99.6)	26.9 (19.0-36.4)	34.4
Miliary nodule	9.8 (4.8-18.2)	100 (85.9-100)	100 (62.9-100)	26.5 (18.9-35.8)	32.0

Table 3. Comparison of radiographic features between patients with positive and negative *Mycobacterium tuberculosis* culture results

Radiographic features	Positive culture (n = 72) frequency (%)	Negative culture (n = 20) frequency (%)	*p*-value
Upper lobe minimal reticulation	4 (5.6)	0 (0)	0.57
Thin-walled cavity	11 (15.3)	1 (5.0)	0.29
Focal alveolar opacities	26 (36.1)	8 (40.0)	0.75
Focal interstitial opacities	49 (68.1)	13 (65.0)	0.79
Lung mass	0 (0)	1 (5.0)	0.22
Localized bronchiectasis	4 (5.6)	0 (0)	0.57
Ipsilateral mediastinal lymphadenopathy	2 (2.8)	1 (5.0)	1.00
Ipsilateral pleural effusion	8 (11.1)	5 (25.0)	0.15
Miliary nodule	8 (11.1)	1 (5.0)	0.68

the non-HIV era, but lower than the 38.6% that was reported from Korea[3]. Outcome of treatment in non-HIV, smear-negative PTB in this study was excellent, as compared to the worse outcome for those with HIV co-infection in a study from Malawi[17].

Miliary nodules, cavitary lesions, ipsilateral adenopathy, and ipsilateral pleural effusion had high specificity and PPV for true prediction of active TB, but their sensitivities were variably low. This finding was consistent with a study from the United States that included patients with HIV-coinfection[11]. Presence of focal alveolar or interstitial opacities was more sensitive, but had lower specificity. In Korean study, patchy opacity was the only radiographic feature that predicted culture positivity (OR 2.89, 95% CI 1.14-7.28) and radiographic improvement after empirical anti-TB treatment (OR 4.13, 95% CI 1.64-10.4)[3].

These variations in sensitivity and specificity of radiographic features in smear-negative PTB in this study may have resulted from the exclusion of patients who had been previously treated for PTB, HIV co-infection, or some other significantly immuno-suppressed state. The level of experience of those who interpreted CXR findings is another confounding factor. Although our reviewers have worked in the field of TB for a long period, some subjective variation was observed among reviewers. The use of automated CXR interpretation software to reduce human bias was introduced in clinical settings in Africa with promising results[18]. Another potential limitation of this study is its retrospective design, since some clinical information and verification of patient clinical course could not be determined. We recommend the development and implementation of a management algorithm to optimize the number of patients correctly treated for smear-negative PTB.

Conclusion

For new patients and non-HIV patients suspected of having smear-negative PTB, specific

radiographic features for predicting diagnosis and need for treatment are uncommon. Clinicians should combine clinical symptoms and radiographic features for making a decision to treat empirically, but should verify TB diagnosis with culture results in addition to radiological and/or clinical responses.

What is already known on this topic?

Initial mode of diagnosis for smear-negative PTB depends largely on clinical features and radiologic findings.

What this study adds?

Radiologic findings for true prediction of active PTB in new and non-HIV patients are non-specific.

Potential conflicts of interest

None.

References

1. World Health Organization. Global tuberculosis report 2013. WHO/HTM/TB/2013.11. Geneva: WHO; 2013.
2. Chierakul N, Petborom P, Foongladda S, Udompunturak S. Are two sputum samples enough for diagnosing pulmonary tuberculosis. J Med Assoc Thai 2012; 95 (Suppl 2): S87-91.
3. Lee CH, Kim WJ, Yoo CG, Kim YW, Han SK, Shim YS, et al. Response to empirical anti-tuberculosis treatment in patients with sputum smear-negative presumptive pulmonary tuberculosis. Respiration 2005; 72: 369-74.
4. Toman K. Tuberculosis case-finding and chemotherapy;questions and answers. Geneva: World health Organization; 1979.
5. Grzybowski S, Barnett GD, Styblo K. Contacts of cases of active pulmonary tuberculosis. Bull Int Union Tuberc 1975; 50: 90-106.
6. Hong Kong Chest Service, Tuberculosis Research Centre, Madras, British Medical Research Council. A study of the characteristics and course of sputum smear-negative pulmonary tuberculosis. Tubercle 1981; 62: 155-67.
7. Long R. Smear-negative pulmonary tuberculosis in industrialized countries. Chest 2001; 120: 330-4.
8. Charoenratanakul S, Dejsomritrutai W, Chaiprasert A. Diagnostic role of fiberoptic bronchoscopy in suspected smear negative pulmonary tuberculosis. Respir Med 1995; 89: 621-3.
9. Pushpakom R, Bovornkitti S, Ong-ajyuth S, Vanittanakorn N. Adenosine deaminase activity in bronchoalveolar lavage fluid (BALF): test for diagnosis of pulmonary tuberculosis. Thai J Tuberc Chest Dis 1988; 9: 63-9.
10. Gengvinij N, Pattanakitsakul SN, Chierakul N, Chaiprasert A. Detection of *Mycobacterium tuberculosis* from sputum specimens using one-tube nested PCR. Southeast Asian J Trop Med Public Health 2001; 32: 114-25.
11. Kanaya AM, Glidden DV, Chambers HF. Identifying pulmonary tuberculosis in patients with negative sputum smear results. Chest 2001; 120: 349-55.
12. Chierakul N, Damrongchokpipat P, Chaiprasert A, Arjratanakul W. Antibody detection for the diagnosis of tuberculous pleuritis. Int J Tuberc Lung Dis 2001; 5: 968-72.
13. Chierakul N, Anantasetagoon T, Chaiprasert A, Tingtoy N. Diagnostic value of gastric aspirate smear and polymerase chain reaction in smear-negative pulmonary tuberculosis. Respirology 2003; 8: 492-6.
14. Dheda K, Ruhwald M, Theron G, Peter J, Yam WC. Point-of-care diagnosis of tuberculosis: past, present and future. Respirology 2013; 18: 217-32.
15. Pumpreug U, PakchananunnP, Amatayakul N. Treatment of sputum smear negative pulmonary tuberculosis. Thai J Tuberc Chest Dis 1991; 12: 95-105.
16. Kasetjaroen Y, Pungrassami P, Hirun pat C. The retrospective analysis of patients with initial sputum exam negative for AFB but treated as pulmonary tuberculosis based on radiographic finding. Thai J Tuberc Chest Dis 1992; 13: 207-18.
17. Hargreaves NJ, Kadzakumanja O, Whitty CJ, Salaniponi FM, Harries AD, Squire SB. 'Smear-negative' pulmonary tuberculosis in a DOTS programme: poor outcomes in an area of high HIV seroprevalence. Int J Tuberc Lung Dis 2001; 5: 847-54.
18. Maduskar P, Muyoyeta M, Ayles H, Hogeweg L, Peters-Bax L, van Ginneken B. Detection of tuberculosis using digital chest radiography: automated reading vs. interpretation by clinical officers. Int J Tuberc Lung Dis 2013; 17: 1613-20.

ลักษณะภาพถ่ายรังสีทรวงอกที่ใช้ทำนายวัณโรคปอดชนิดย้อมเสมหะไม่พบเชื้อ

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ภูมิหลัง: *การวินิจฉัยวัณโรคปอดชนิดย้อมเสมหะไม่พบเชื้อในบางสถานการณ์ยังคงเป็นสิ่งท้าทายสำหรับแพทย์ โดยเฉพาะในสถานที่ที่มีทรัพยากรจำกัด*

วัตถุประสงค์: *เพื่อศึกษาลักษณะภาพถ่ายรังสีทรวงอกที่ช่วยในการวินิจฉัยโรคได้ถูกต้อง ในผู้ป่วยที่สงสัยวัณโรคปอดแต่ตรวจย้อมเสมหะให้ผลลบ*

วัสดุและวิธีการ: *ได้ทำการศึกษาแบบตัดขวางในผู้ป่วยที่วินิจฉัยและรักษาวัณโรคปอดชนิดตรวจย้อมเสมหะไม่พบเชื้อของโรงพยาบาลศิริราช ระหว่างเดือนมกราคม พ.ศ. 2556 ถึง มิถุนายน พ.ศ. 2557 โดยคัดออกผู้ป่วยรายที่มีประวัติการรักษาวัณโรคในอดีต ติดเชื้อเอชไอวีร่วมด้วย มีวัณโรคเยื่อหุ้มปอดร่วมด้วย และได้รับการรักษาด้วยคอร์ติโคสเตียรอยด์ในขนาด ≥15 มก./วัน ทำการรวบรวมข้อมูลลักษณะทางคลินิกและรังสีวิทยา ภาพถ่ายรังสีทรวงอกจะถูกทบทวนโดยผู้นิพนธ์ 3 ราย โดยอิสระแล้วมีมติว่าเข้าได้กับวัณโรคปอดระยะแพร่เชื้อหรือไม่ จากนั้นจึงหาความสัมพันธ์ของลักษณะภาพถ่ายรังสีทรวงอกแบบต่าง ๆ ที่ช่วยในการทำนายโรคโดยใช้ผลการเพาะเชื้อและการดีขึ้นของภาพถ่ายรังสีทรวงอกภายหลังการรักษาเป็นเกณฑ์*

ผลการศึกษา: *มีผู้ป่วยรวมทั้งสิ้น 122 ราย ในช่วงเวลาที่ทำการศึกษา โดยเป็นชาย 65 ราย (ร้อยละ 53) ไม่มีอาการ 27 ราย (ร้อยละ 22) พบวัณโรคนอกปอดร่วมด้วย 20 ราย (ร้อยละ 16) และมีโรคเบาหวานร่วมด้วย 8 ราย (ร้อยละ 7) การวินิจฉัยโรคขั้นสุดท้ายพบเป็นวัณโรคระยะแพร่เชื้อ 92 ราย (ร้อยละ 75) โดย 70 ราย ผลเพาะเชื้อเป็นบวกและอีก 20 ราย ภาพถ่ายรังสีทรวงอกดีขึ้นภายหลังการรักษาด้วยยาต้านวัณโรค การพบ miliary nodule และ cavitary lesion มีความจำเพาะสูง (ร้อยละ100 ทั้งคู่) แต่มีความไวต่ำ (ร้อยละ 9.8 และ 13) ในการวินิจฉัยวัณโรคปอดระยะแพร่เชื้อ ลักษณะ focal interstitial และ alveolar opacity มี positive predictive value สูงคือ ร้อยละ 79.5 และ 85 และ accuracy ปานกลางคือ ร้อยละ 62.3 และ 47.5 ตามลำดับ*

สรุป: *ลักษณะภาพถ่ายรังสีที่จำเพาะสำหรับการวินิจฉัยวัณโรคปอดระยะแพร่เชื้อพบได้น้อยในผู้ป่วยที่ตรวจย้อมเสมหะไม่พบเชื้อ เนื่องจากพบลักษณะภาพถ่ายรังสีทรวงอกที่ไม่จำเพาะได้บ่อยกว่า แพทย์จึงควรใช้การเพาะเชื้อจากเสมหะช่วยยืนยันโรคร่วมไปกับการตอบสนองของภาพถ่ายรังสีทรวงอก*