Int J Clin Exp Med 2019;12(4):4168-4173
www.ijcem.com /ISSN:1940-5901/IJCEM0082399

Original Article

Computerized tomography findings for missed diagnosis of pulmonary tuberculosis: analysis of 234 cases

Sai-Bin Wang[1], Qian Ye[2]

Departments of [1]Respiratory Medicine, [2]Medical Records Quality Management, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang University, Jinhua, Zhejiang Province, PR China

Received July 10, 2018; Accepted December 10, 2018; Epub April 15, 2019; Published April 30, 2019

Abstract: Computerized tomography (CT) has been proven as a valuable technique in the clinical diagnosis of pulmonary tuberculosis (PTB), but missed diagnosis on CT is still inevitable. Here, the incidence of missed diagnosis of PTB on CT scans was examined and it was determined that the CT findings easily resulted in missed diagnosis. A retrospective study was conducted to evaluate CT findings of 234 patients with confirmed PTB. Based on the initial diagnosis, patients were divided into the PTB group and the missed PTB group. Using multiple logistic regression CT findings of PTB revealed missed diagnosis. A total of 76 (32.5%) PTB patients were missed. Lung mass (odds ratio (OR), 8.194; 95% confidence interval (CI), 2.714-24.739; $P < 0.001$), bronchiectasis (OR, 4.548; 95% CI, 1.724-11.994; $P = 0.002$), and interstitial lung disease (OR, 19.206; 95% CI, 1.513-243.776; $P = 0.023$) as seen on chest CT scans, were independently associated with missed PTB. In conclusion, there was a high missed diagnosis rate of PTB based on clinical diagnosis. Findings of lung mass, bronchiectasis, and interstitial lung disease as observed in CT scans were associated with increased risk of missed PTB.

Keywords: CT, pulmonary tuberculosis, missed diagnosis

Introduction

Pulmonary tuberculosis (PTB) remains a global burden, particularly in developing countries [1, 2]. Early diagnosis of PTB is crucial [3], however diagnosis of PTB is not always an easy task because bacteriological confirmation of PTB remains challenging, and clinical symptoms and imaging findings of patients may also be non-specific [4]. Therefore, missed diagnosis of PTB is common in clinical practice.

Radiological examination, particularly computed tomography (CT) scan, has been proven as a valuable technique in the clinical diagnosis of PTB [3]. However, it can often be difficult to differentiate PTB form some other pulmonary diseases, such as lung tumors, interstitial lung disease, bronchiolitis, or pulmonary infection resulting from other pathogenic microorganisms (aspergillus species, non-tuberculosis mycobacteria, viruses) [5], because their imaging features could be overlapping. Therefore, it is necessary to analyze the imaging findings of missed PTB.

A number of studies have revealed the radiological features of PTB [1, 3, 6, 7]. However, few studies discuss CT findings that easily were missed diagnose of PTB. The aim of the present study was to determine CT features of missed PTB, improve the physician's familiarity with the spectrum of "missed PTB" CT findings, and reduce missed diagnosis.

Materials and methods

Study population

The clinical and radiological data of 234 confirmed PTB patients from January 2011 through December 2013 at a tertiary care hospital were reviewed [5]. Among these, a total of 76 patients were initially missed diagnosis by the pulmonary physician. This retrospective study was approved by the Institutional Review Board (IRB no. E-2015059). All patient information was anonymous, and informed consent was therefore waived.

Table 1. Baseline characteristics and CT findings of the study participants

Characteristics	Values
Age, (year)	56.07 ± 17.11
Man, n (%)	141 (60.26)
BMI, (kg/m^2)	21.84 ± 2.75
Smoking, n (%)	
Never	141 (60.26)
Former	37 (15.81)
Current	56 (23.93)
Missed diagnosis of PTB	76 (32.48)
Patients with coexisting disease, n (%)	
Diabetes mellitus	37 (15.88)
Malignancy	48 (20.60)
Cerebrovascular disease	48 (20.60)
Chronic kidney disease	3 (1.29)
Chronic lung disease	4 (1.72)
Rheumatologic disease	3 (1.29)
CT findings, n (%)	
Bronchiolitis	37 (15.81)
Pneumonia	62 (26.50)
Lung nodule	125 (53.42)
Lung mass	26 (11.11)
Anthracofibrosis	4 (1.71)
Bronchiectasis	35 (14.96)
Interstitial lung disease	5 (2.14)
Airway stenosis	15 (6.41)
Atelectasis	40 (17.09)
Pleural effusion	47 (20.09)
Parenchymal fibrocalcification	31 (13.25)

BMI, body mass index.

CT-based diagnoses of these patients included bronchiolitis, pneumonia, lung mass, lung nodule, anthracofibrosis of the airway, bronchiectasis, atelectasis, interstitial lung disease, airway stenosis, pleural effusion, and fibrocalcific parenchymal PTB [5].

The following variables were collected: age, sex, smoking history (never, current and former), body mass index, comorbidities (diabetes mellitus, chronic kidney disease, chronic lung disease, malignancy, cerebrovascular disease, and rheumatologic disease). Final diagnosis of PTB was based on positive sample cultures of *Mycobacterium tuberculosis*, or positive real-time PCR for *Mycobacterium tuberculosis*, or improvement of symptoms after standard anti-TB treatment [8].

Statistical analysis

Statistical analysis was performed using SPSS 21.0 software (IBM Corporation, Armonk, NY, USA). Continuous variables and categorical variables are expressed as the mean ± standard deviation and the number (percentage), respectively. Between-group comparisons were performed using unpaired *t*-tests (normal distribution) or Wilcoxon rank sum test (non-normal distribution), Pearson Chi-square tests or the Fisher's exact, as applicable. Variables with a *P* value of < 0.1 in the univariate analyses were included in the multiple logistic regression, and $P < 0.05$ was considered statistically significant.

Results

Among the 234 patients, 76 (32.5%) PTB patients were missed diagnosis. The rates of CT findings in missed diagnosis were as follows: anthracofibrosis 100.0% (4/4), interstitial lung disease 80.0% (4/5), lung mass 65.4% (17/26), bronchiectasis 57.1% (20/35), atelectasis 55.0% (22/40), airway stenosis 53.3% (8/15), bronchiolitis 43.2% (16/37), pneumonia 40.3% (25/62), pulmonary parenchymal fibrocalcification 38.7% (12/31), lung nodule 23.2% (29/125), and pleural effusion 19.1% (9/47). Patient's demographics and CT findings are shown in **Table 1**.

Lung nodule, lung mass, anthracofibrosis, bronchiectasis, pleural effusion, atelectasis and interstitial lung disease, as seen on CT, positively correlated with the misdiagnosis of PTB as assessed by univariate analysis (**Table 2**, $P < 0.05$). In addition, age, sex, and coexisting malignancy were statistically significant (**Table 2**, $P < 0.05$). However, in multiple logistic regression analysis only lung nodule, lung mass, bronchiectasis and interstitial lung disease, as observed on CT, were revealed to be independently associated with risk of missed PTB (**Figure 1**, $P < 0.05$). In addition, age, sex, body mass index and coexisting malignancy were associated with the risk of missed PTB (**Table 3**, $P < 0.05$).

Other CT findings, such as anthracofibrosis, atelectasis, airway stenosis, bronchiolitis, pneumonia, pulmonary parenchymal fibrocalcification, and pleural effusion were not statistically significant between the non-PTB group and the PTB group ($P > 0.05$).

Table 2. Univariate analysis of possible risk factors of missed diagnosis of PTB

Variables	Missed diagnosis of PTB		*P*-value
	Yes (n = 76)	No (n = 158)	
Age, (year)	64.28 ± 11.73	52.13 ± 17.90	< 0.001
Sex, n (%)			0.005
Female	40 (52.63)	53 (33.54)	
Man	36 (47.37)	105 (66.46)	
BMI, (kg/m^2)	22.33 ± 3.08	21.60 ± 2.56	0.057
Smoking, n (%)			0.507
Never	47 (61.84)	94 (59.49)	
Former	14 (18.42)	23 (14.56)	
Current	15 (19.74)	41 (25.95)	
Patients with coexisting disease, n (%)			
Diabetes mellitus			0.120
No	68 (89.47)	128 (81.53)	
Yes	8 (10.53)	29 (18.47)	
Malignancy			0.001
No	51 (67.11)	134 (85.35)	
Yes	25 (32.89)	23 (14.65)	
Cerebrovascular disease			0.418
No	58 (76.32)	127 (80.89)	
Yes	18 (23.68)	30 (19.11)	
Chronic kidney disease			0.553
No	76 (100.00)	154 (98.09)	
Yes	0 (0.00)	3 (1.91)	
Chronic lung disease			0.307
No	76 (100.00)	153 (97.45)	
Yes	0 (0.00)	4 (2.55)	
Rheumatologic disease			0.553
No	76 (100.00)	154 (98.09)	
Yes	0 (0.00%)	3 (1.91)	
CT findings, n (%)			
Bronchiolitis			0.128
No	60 (78.95)	137 (86.71)	
Yes	16 (21.05)	21 (13.29)	
Pneumonia			0.124
No	51 (67.11)	121 (76.58)	
Yes	25 (32.89)	37 (23.42)	
Lung nodule			0.001
No	47 (61.84)	62 (39.24)	
Yes	29 (38.16)	96 (60.76)	
Lung mass			< 0.001
No	59 (77.63)	149 (94.30)	
Yes	17 (22.37)	9 (5.70)	
Anthracofibrosis			0.011
No	72 (94.74)	158 (100.00)	
Yes	4 (5.26)	0 (0.00)	
Bronchiectasis			< 0.001

Based on CT scan, lung mass (odds ratio (OR), 8.194; 95% confidence interval (CI), 2.714-24.739; *P* <0.001), bronchiectasis (OR, 4.548; 95% CI, 1.724-11.994; *P* = 0.002), and interstitial lung disease (OR, 19.206; 95% CI, 1.513-243.776; *P* = 0.023) on CT scans were associated with increased risk of missed PTB. However, lung nodules (OR, 0.214; 95% CI, 0.097-0.471; *P* < 0.001) were associated with decreased risk of missed diagnosis.

Discussion

The present study shows a relatively high rate of clinical missed diagnosis of PTB. CT-based features of lung nodule, lung mass, bronchiectasis and interstitial lung disease were independently associated with the risk of missed PTB. Specifically, lung nodule was associated with decreased risk of missed PTB; while the other three CT findings were associated with increased risk of missed diagnosis.

Tuberculosis remains a major cause of morbidity and mortality worldwide. Approximately 9 million new cases of TB and 1.5 million TB-related deaths were recorded globally in 2013 [2]. In clinical practice, bacteriological diagnosis of tuberculosis infection is not always avail-

No	56 (73.68)	143 (90.51)	
Yes	20 (26.32)	15 (9.49)	
Interstitial lung disease			0.039
No	72 (94.74)	157 (99.37)	
Yes	4 (5.26)	1 (0.63)	
Airway stenosis			0.090
No	68 (89.47)	151 (95.57)	
Yes	8 (10.53)	7 (4.43)	
Atelectasis			< 0.001
No	54 (71.05)	140 (88.61)	
Yes	22 (28.95)	18 (11.39)	
Pleural effusion			0.029
No	67 (88.16)	120 (75.95)	
Yes	9 (11.84)	38 (24.05)	
Parenchymal fibrocalcification			0.426
No	64 (84.21)	139 (87.97)	
Yes	12 (15.79)	19 (12.03)	

PTB, pulmonary tuberculosis; BMI, body mass index.

able. Indeed, a substantial fraction of patients with PTB were diagnosed based on the clinical and radiological data of patients. Consequently, PTB patients who do not have typical clinical manifestations and CT features are prone to be missed. Anti-tuberculous chemotherapy increases survival dramatically in patients with PTB, and early anti-tuberculosis treatment is very important [2, 3]. Therefore, it is crucial to improve the accuracy of clinical diagnosis of PTB. Analysis of atypical chest CT features of PTB may help to improve missed diagnosis.

PTB lesions can be seen in a variety of imaging manifestations On CT scans [1]. Of primary PTB, typical imaging manifestations on CT scan include parenchymal consolidation (**Figure 2A**), predominantly located in the middle and lower lobes. Parenchymal consolidation could be linear, patchy, nodular, or a mass in radiology [9]. Whereas reactivation tuberculosis tends to predominantly locate in the apical and posterior segments of the upper lobes (**Figure 2B**), and the superior segments of the lower lobes (**Figure 2C**). However, approximately 5% of cases of reactivation tuberculosis were not typically distributed in the anterior segment of the upper lobes or the lower segment of the basal lobes [10]. Cavitation is generally evident in approximately half of the patients with reactivated tuberculosis [1]. Reportedly, residual cavities and bronchiectasis (**Figure 2D**, **2E**) were found in 12-22% and in 71-86% of PTB patients on thin-section CT scan, respectively [1]. In addition, bronchial stenosis, obstructive atelectasis and pneumonia (**Figure 2F**) are equally common findings on CT scan as PTB complications [1]. Typically tuberculoma is a solitary lesion, but may be multiple, and often surrounded by small nodules (**Figure 2G**), containing calcifications [11]. Moreover, unilateral pleural effusion (**Figure 2H**) on CT is also a frequent imaging finding when tuberculosis is infected with pleura [1]. CT findings of PTB are not only related to the type of PTB, but also to host immune status [1]. Actually, atypical manifestations are common in immune-compromised patients. For example, PTB patients with diabetic mellitus have a higher prevalence of multiple cavities than those without diabetic mellitus, and frequently non-segmental distribution of the lesions [12-14]. On the other hand, PTB could show signs similar to other pulmonary diseases such as lung cancer on CT. Indeed, quite a few cases of PTB had been initially misdiagnosed as lung cancers [15].

In the current study, the missed diagnosis rate of PTB based on clinical diagnosis was found to be relatively high (32.5%). Patients with lung mass, bronchiectasis, and interstitial lung disease, as seen on chest CT scan, had a significantly increased risk of missed PTB. Conversely, lung nodule was associated with a decreased risk of missed diagnosis, which implies that physicians may be more consciously suspicious of PTB through lung nodules. Since CT features of lung mass, bronchiectasis and interstitial lung disease may increase the risk of missed PTB, physicians may need to consider increasing the weight of these CT findings in support of TB diagnosis.

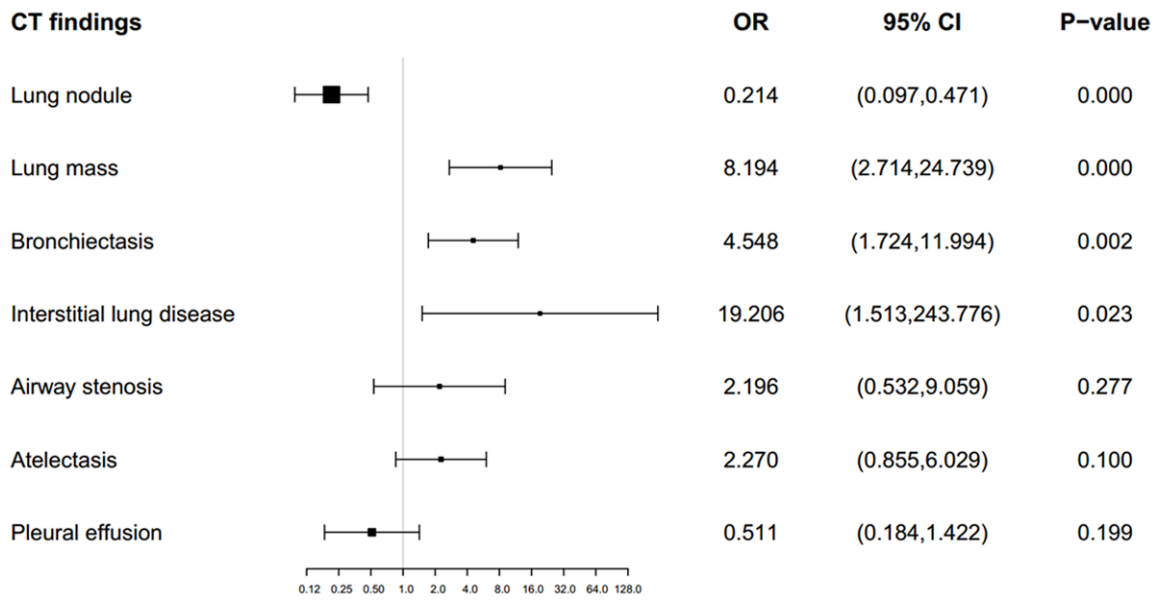

Figure 1. Risk of CT findings in missed diagnosis of pulmonary tuberculosis.

Table 3. Multivariable analysis of risk factors for missed diagnosis of PTB

Variables	Odds ratio	95% CI	*P* Value
Sex	0.037	0.170-0.845	0.018
Age	0.952	0.926-0.977	< 0.001
BMI	0.786	0682-0.906	0.001
Malignancies	0.237	0.097-0.581	0.002
Lung nodule	0.214	0.097-0.471	< 0.001
Lung mass	8.194	2.714-24.739	< 0.001
Anthracofibrosis	< 0.001	< 0.001-Inf	0.982
Bronchiectasis	4.548	1.724-11.994	0.002
Interstitial lung disease	19.206	1.513-243.776	0.023
Airway stenosis	2.196	0.532-9.059	0.277
Atelectasis	2.270	0.855-6.029	0.100
Pleural effusion	0.511	0.184-1.422	0.199

PTB, pulmonary tuberculosis; BMI, body mass index.

The present study is subject to several limitations due to the original study design [5, 16]. First, the retrospective nature of the study suggests that some potential confounders such as clinical manifestations of patients had not been considered, and potential misdiagnoses such as false-positive PCR data could not be excluded, as well as some complications might be underestimated. Second, this study was conducted at a single institution in an area of intermediate PTB burden in East Asia, which, therefore, may limit the application of these CT findings in areas of differing PTB prevalence. Third, CT findings were evaluated only by an experienced radiologist, which may result in a potential CT-diagnosis bias [5]. Thus, further validation in prospective studies should be considered.

Conclusively, the incidence of missed PTB based on clinical evaluations was relatively high. Lung mass, bronchiectasis, and interstitial lung disease, as seen on chest CT scan, may often be associated with increased risk of missed PTB. When patients present these CT features, physicians may need to be more cautious in ruling out PTB.

Acknowledgements

This work was supported by the Medical and Health Science and Technology Plan Project of Zhejiang Province (No. 2018RC079), the Youth Research Fund of Jinhua Hospital of Zhejiang University (No. JY2017205), and the Science and Technology Key Project of Jinhua City (No. 20163011).

Disclosure of conflict of interest

None.

Address correspondence to: Sai-Bin Wang, Department of Respiratory Medicine, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang Uni-

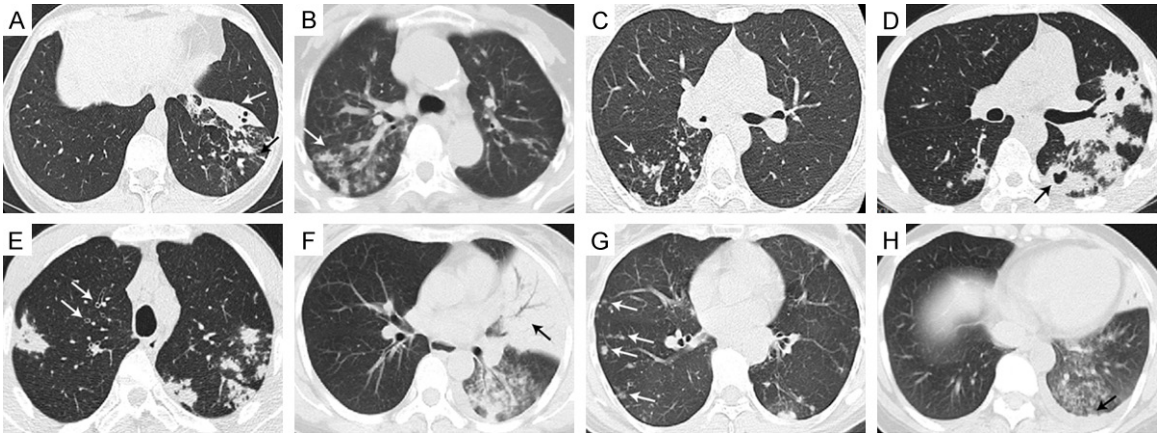

Figure 2. Typical CT findings for pulmonary tuberculosis. (A) Parenchymal linear (black arrow) and patchy (white arrow) consolidation. Tuberculosis infection (white arrows) in the apical and posterior segments of the right upper lobe (B), and the superior segments of the right lower lobe (C). (D) A cavitation in the left lung (black arrow), surrounded by irregular thick walls. (E) Bronchiectasis in the right lung (white arrows) on thin-section CT scan. (F) Obstructive atelectasis (black arrow) and pneumonia in the left lung. (G) Multiple nodules in the right lung (white arrows). (H) Tuberculosis infection in the left lung, accompanied with unilateral pleural fluid (black arrow).

versity, Jinhua, Zhejiang Province, PR China. E-mail: saibinwang@hotmail.com

References

[1] Cardinale L, Parlatano D, Boccuzzi F, Onoscuri M, Volpicelli G, Veltri A. The imaging spectrum of pulmonary tuberculosis. Acta Radiol 2015; 56: 557-564.

[2] World Health Organization. Global tuberculosis report 2017. World Health Organization [Internet] 2017; Available from: http://www.who.int/tb/publications/global_report/en/.

[3] Skoura E, Zumla A, Bomanji J. Imaging in tuberculosis. Int J Infect Dis 2015; 32: 87-93.

[4] Korzeniewska-Kosela M, Krysl J, Muller N, Black W, Allen E, Fitzgerald JM. Tuberculosis in young adults and the elderly: a prospective comparison study. Chest 1994; 106: 28-32.

[5] Na HJ, Eom JS, Lee G, Mok JH, Kim MH, Lee K, Kim KU, Lee MK. Exposure to mycobacterium tuberculosis during flexible bronchoscopy in patients with unexpected pulmonary tuberculosis. PLoS One 2016; 11: e0156385.

[6] Verma N, Chung JH, Mohammed TL. Tree-in-bud sign. J Thorac Imaging 2012; 27: W27.

[7] Jeong YJ, Lee KS. Pulmonary tuberculosis: up-to-date imaging and management. AJR Am J Roentgenol 2008; 191: 834-844.

[8] George PM, Mehta M, Dhariwal J, Singanayagam A, Raphael CE, Salmasi M, Connell DW, Molyneaux P, Wickremasinghe M, Jepson A, Kon OM. Post-bronchoscopy sputum: improving the diagnostic yield in smear negative pulmonary TB. Respir Med 2011; 105: 1726-1731.

[9] McAdams HP, Erasmus J, Winter JA. Radiologic manifestation of pulmonary tuberculosis. Radiol Clin North Am 1995; 33: 655-678.

[10] Woodring JH, Vandiviere HM, Fried AM, Dillon ML, Williams TD, Melvin IG. Update: the radiographic features of pulmonary tuberculosis. AJR Am J Roentgenol 1986; 146: 497-506.

[11] Krysl J, Korzeniewska-Kosela M, Müller NL, Fitzgerald JM. Radiologic features of pulmonary tuberculosis: an assessment of 188 cases. Can Assoc Radiol J 1994; 45: 101-107.

[12] Ikezoe J, Takeuchi N, Johkoh T, Kohno N, Tomiyama N, Kozuka T, Noma K, Ueda E. CT appearance of pulmonary tuberculosis in diabetic and immunocompromised patients: comparison with patients who had no underlying disease. AJR Am J Roentgenol 1992; 159: 1175-1179.

[13] Kim J, Lee IJ, Kim JH. CT findings of pulmonary tuberculosis and tuberculous pleurisy in diabetes mellitus patients. Diagn Interv Radiol 2017; 23: 112-117.

[14] Huang LK, Wang HH, Lai YC, Chang SC. The impact of glycemic status on radiological manifestations of pulmonary tuberculosis in diabetic patients. PLoS One 2017; 12: 0179750.

[15] Rolston KV, Rodriguez S, Dholakia N, Whimbey E, Raad I. Pulmonary infections mimicking cancer: a retrospective three-year review. Support Care Cancer 1997; 5: 90-93.

[16] Eom JS, Na HJ. Data from: exposure to mycobacterium tuberculosis during flexible bronchoscopy in patients with unexpected pulmonary tuberculosis. Dryad Digital Repository [Internet] 2016; Available from: https://doi.org/10.5061/dryad.78fm3.