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Chest imaging comparison between non-tuberculous and tuberculosis *mycobacteria* in sputum acid fast bacilli smear-positive patients

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Abstract. – OBJECTIVE: The aim of this study was to distinguish and compare the chest imaging features of non-tuberculous mycobacteria lung disease (NTM-LD) and pulmonary tuberculosis (PTB) in patients with sputum acid fast bacillus (AFB)-smear positive since an earlier differential diagnosis between these two is very important in clinical practice.

PATIENTS AND METHODS: A total of 4167 previously untreated cases with AFB smear-positive sputum were collected from January 2011 to January 2014, in Shanghai Pulmonary Hospital, Tongji University, China. Among them, 124 cases were identified with NTM-LD after specimen culture and strain identification. A cohort of 210 patients with PTB was randomly selected from the remaining 4043 cases with PTB as comparator. The clinical and chest computed tomography (CT) imaging data were compared.

RESULTS: The most prevalent pathogens in patients with NTM-LD were Mycobacterium abscessus (42%, 52/124) and Mycobacterium intracellulare (34%, 42/124). Univariate analysis showed patients with NTM-LD more frequently had bronchiectasis (85.5% vs. 45.7%, $p < 0.001$), thin-walled cavity ($D \geq 3$ cm) (16.9% vs. 7.6%, $p = 0.011$) compared to PTB patients. Additionally, the location of lesion also differed and the right middle lobe (23.9% vs. 16.3%, $p < 0.001$) and left lingual segment bronchiectasis (19.9% vs. 8.2%, $p < 0.001$) were more prominent in NTM-LD. Multivariate analysis showed, bronchiectasis (OR = 8.521, 95% CI: 4.209-17.250, $p < 0.001$) and thin-walled cavity ($D \geq 3$ cm) (OR = 3.561, 95% CI: 1.394-9.097, $p = 0.008$) were also the independent predictors for the diagnosis of NTM-LD.

CONCLUSIONS: Bronchiectasis in the right middle lobe or left lingual segment and thin-walled cavity with a diameter of more than 3 cm are the frequently the chest CT features in patients with NTM-LD, which might be helpful for an early diagnosis in patients with AFB-smear positive.

Key Words:
Non-tuberculous mycobacterial lung disease, Pulmonary tuberculosis, Acid fast bacilli smear-positive sputum, Chest computed tomography.

Introduction

Infection caused by non-tuberculous mycobacteria (NTM), especially non-tuberculous mycobacterial lung disease (NTM-LD), is gradually increased in clinical practice due to a rise in number of susceptible/immunocompromised individuals such as AIDS patients together with the adoption of novel test technologies[1]. NTM are widely distributed in nature and have been isolated from natural water, tap water and soil. NTM is divided into two species: the fast-growing and slow-growing species[2]. The representatives of slow-growing non-tuberculous mycobacteria (NTM) include *Mycobacterium avium*, *Mycobacterium intracellulare*, and *Mycobacterium kansasii*. The representatives of fast-growing non-tuberculous mycobacteria species include Abscesses mycobacteria, *Mycobacterium fortuitum*, and *Mycobacterium chelonae*. Both species are opportunistic pathogens[3].

It is difficult to diagnose non-tuberculous mycobacteria caused lung infections from pulmonary tuberculosis (PTB) at early stage due to their similar clinical manifestations. Currently microscopic examination of sputum smear for acid fast bacillus (AFB) is the most commonly used preliminary screening method for mycobacterial lung infection[4]. However, AFB-positive only provides the presence of

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pulmonary mycobacterial infection, but does not distinguish *Mycobacterium tuberculosis* from NTM[5-8]. However, bacterial culture and strain identification remain the unique way to identify NTM; the procedure needs a long time and almost as long as about two months. Thus, clinically suspected PTB with positive sputum AFB are often prescribed with empirical anti-tuberculosis medicine while waiting for bacteria identification results. Therefore, a considerable number of the NTM-LD patients receive unnecessary anti-TB treatment[9]. On the other side, adverse drug reactions are also a big challenge for patients with anti-tuberculosis drugs. Consequently, non-essential health care cost is increased because of the treatment of drug-induced complications[10,11].

Therefore, alternative diagnostic methods that help differentiate NTM from PTB in their early stage are urgently needed. Previous reports with limited cases have shown a trend that the clinical manifestations and CT imaging features between PTB and NTM might be different[12-15]. In this study, we analyzed the CT characteristics in 124 patients with NTM-LD and 210 patients with PTB and tried to distinguish NTM from PTB early on in patients with AFB smear-positive sputum.

Patients and Methods

Patients

From January 2011 to January 2014, in total 13509 AFB smear-positive sputum specimens from previous untreated cases were collected in Shanghai Pulmonary Hospital, Tongji University, China. The sputum requires at least two tests to show varying degrees of AFB smear positive. All AFB smear-positive sputum specimens were cultured and strain identified, 124 cases were identified with NTM-LD, and 4043 were PTB. Patients with PTB (210 in all) were randomized and collected as comparator (according to their hospital registration number, last digit being 6, 1:15 proportional sampling). All patients were supported with CT image data from radiology department of our hospital. This study has been approved by the Ethics Committee of Shanghai Pulmonary Hospital, Tongji University School of Medicine, China. All participants had given their written, informed consent and agreed to information collection in the study.

Diagnosis of Pulmonary TB and NTM-LD

All of the sputum specimens were handled with acid-fast bacilli staining. A TB polymerase chain reaction (PCR) was performed with in-house IS6110-based PCR assays. Mycobacterial cultures were performed using the Löwenstein-Jensen medium. Patients were diagnosed with pulmonary TB according to mycobacteria culture results and guidelines from the Chinese Medical Association. NTM diagnosis was based on mycobacterial culture results and guidelines from the American Thoracic Society's (ATS) guidelines[16].

CT scanning: The chest CT scan data were originally obtained from imaging department of Shanghai Pulmonary Hospital. All CT examinations were performed within 3 months of the AFB smear test. High-resolution CT scans were performed on all patients using Philips brilliance CT instruments or Siemens Definition AS CT instruments. Scan parameters used were: 120 kV, 200-240 mA, slice thickness 2 mm using high-resolution reconstruction algorithm, thickness 1 mm. Full-lung CT scan was performed with the patient being in supine position, breath-holding in maximum inspiration, from the apex to the upper abdomen. Lung window (window level 700 HU, window width 1200), mediastinal window (window level 50 HU, window width 450) were adopted to observe CT images. The CT scan images were reviewed independently by three experienced radiologists and pulmonary specialists who were blind to the patient's microbiology results. The final decisions regarding the chest CT scan findings were determined by consensus.

Statistical Analysis

Statistical analyses were conducted using SPSS 17.0 software for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using a chi-square test or Fisher's exact test, and continuous variables were compared using an independent unpaired *t*-test. Univariate analysis was performed to evaluate the characteristic CT findings. Multivariate analysis was conducted using a logistic regression model to determine the independent predictive factors for patients with PTB and NTM infections. *p*-values of less than 0.05 were considered significant.

Results

Patients with NTM-LD (124 in all) included 70 men and 54 women, with a median age of 59 years

Table I. Clinical characteristics of patients with pulmonary tuberculosis and NTM lung diseases.

	TB n = 210	NTM lung disease n = 124	*p*-value
Age	54	59	0.996
Male	162 (77.1)	70 (56.4)	<0.001
Ever smoker	79 (37.6)	44 (35.4)	0.726
Diabetes mellitus	48 (22.9)	23 (18.5)	0.407
Malignancy	7 (3.3)	1 (0.8)	0.266
Autoimmune disease	2 (0.9)	1 (0.8)	1.000
COPD	26 (12.4)	23 (18.5)	0.150
Pneumoconiosis	2 (0.9)	1 (0.8)	1.000

old. The median age in 210 patients with PTB was 54 years, and included 162 men and 48 women. The clinical characteristics were similar between the two groups regarding age, smoking history, cancer and other underlying diseases except a higher percentage of male patients in TB group (Table I). In NTM-LD patient's group, the most common infection was *Mycobacterium abscessus* infection (42%, 52/124) and *Mycobacterium intracellulare* infection (34%, 42/124) (Table II).

Laterality and distribution of CT manifestations in patients with NTM-LD or PTB are summarized in Table III. CT manifestations were described as the presence or absence of the following phenomena: a tree-in-bud pattern, nodules (D1-3 cm), bronchiectasis, thin-walled cavity (D < 3 cm), thin-walled cavity (D ≥ 3 cm), thick-walled cavity (D < 3 cm), thick-walled cavity (D ≥ 3 cm), consolidation, patches, nodules (D < 1 cm), atelectasis, ground-glass opacity, reticular opacity, volume reduction, mediastinal lymphadenopathy, hilar lymphadenopathy, calcified lymph node, cystic changes, pleural effusion, interstitial fibrosis, pneumothorax and pleural thickening.

Table II. Results of NTM Species identification.

Species	Quantity (%)
Mycobacterium abscessus	52 (41.9)
Mycobacterium intracellulare	42 (33.9)
Mycobacterium avium	8 (6.5)
Mycobacterium kansasii	7 (5.6)
Mycobacterium fortuitum	5 (4.0)
Mycobacterium Gordon	6 (4.8)
Mycobacterium chelonae	2 (1.6)
Sue in Galveston mycobacteria	1 (0.8)
Paraffin mycobacteria	1 (0.8)

Univariate analysis (data expressed as PTB *vs.* NTM-LD) demonstrated that compared to PTB patients, bronchiectasis (45.7% *vs.* 85.5%, $p < 0.001$) and thin-walled cavity formation (D ≥ 3 cm) (7.6% *vs.* 16.9%, $p = 0.011$) were sig-

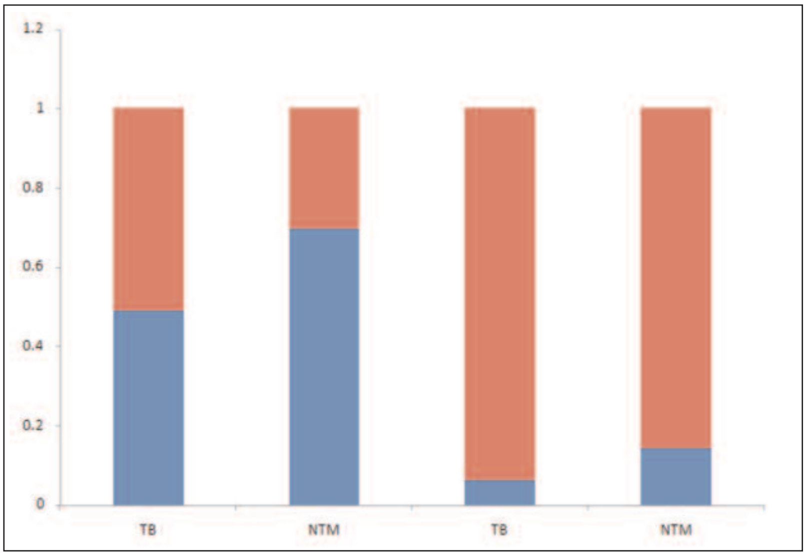

Figure 1. Bilateral bronchiectasis are more prominent in NTM-LD ($p = 0.004$) (and unilateral thin-walled cavity while no difference in term of laterality ($p = 0.618$).

Table III. Laterality and distribution of parenchymal lesions in patients with non-tuberculous mycobacterial lung diseases and pulmonary tuberculosis.

CT findings	Laterality		TB							Laterality		NTM						
	Bi	Uni	RUL	RML	RLL	LUL	LI	LLL	SUM	Bi	Uni	RUL	RML	RLL	LUL	LI	LLL	SUM
Tree-in-bud pattern	38	38	41	32	43	33	23	35	207	19	16	19	15	11	11	9	19	84
Nodules (D ≥ 1 cm)	19	56	36	10	27	25	9	22	129	21	29	23	10	21	14	2	23	93
Bronchiectasis	47	49	59	40	41	43	20	41	244	74	32	48	77	52	32	64	49	322
Thin-walled cavity (D < 3 cm)	6	30	16	1	9	10	3	9	48	1	24	12	3	3	7	1	4	30
Thin-walled cavity (D ≥ 3 cm)	1	15	8	1	2	7	0	2	20	3	18	8	3	5	7	1	3	27
Thick-walled cavity (D < 3 cm)	51	80	76	8	36	71	11	39	241	13	26	22	2	5	18	5	14	66
Thick-walled cavity (D ≥ 3 cm)	27	71	58	2	19	52	4	26	161	15	35	36	5	12	25	1	4	83
Consolidation	28	100	62	18	34	49	17	30	210	19	33	22	19	11	20	12	11	95
Patches	121	57	125	65	80	113	58	77	518	59	32	61	36	37	40	29	38	241
Nodules (D < 1 cm)	74	66	82	31	60	67	27	72	339	28	31	35	20	31	20	21	27	154
Atelectasis	0	20	6	4	1	5	3	3	22	0	1	1	0	0	0	0	0	1
Ground-glass opacity	9	16	8	6	14	5	4	10	47	1	9	5	3	4	2	2	1	17
Reticular opacities	5	9	5	3	5	7	2	10	32	0	1	0	0	0	0	0	1	1
Volume reduction	1	17	6	5	5	13	12	12	53	0	12	3	3	3	9	8	8	34
Mediastinal lymphadenopathy	41	40	0	0	0	0	0	0	81	10	4	0	0	0	0	0	0	14
Hilar lymphadenopathy	29	10	0	0	0	0	0	0	39	10	1	0	0	0	0	0	0	11
Calcified lymph nodes	11	30	0	0	0	0	0	0	41	3	2	0	0	0	0	0	0	5
Cystic changes	1	0	1	0	0	1	0	0	2	1	3	0	0	1	1	1	2	5
Pleural effusion	10	42	0	0	0	0	0	0	138	1	16	0	0	0	0	0	0	30
Interstitial fibrosis	8	4	5	5	9	3	4	9	35	5	0	4	3	5	3	2	5	22
Pneumothorax	0	2	1	1	1	1	1	1	6	0	1	1	1	1	1	1	1	6
Pleural thickening	0	1	0	0	0	0	0	0	1	1	1	2	2	2	1	1	1	9

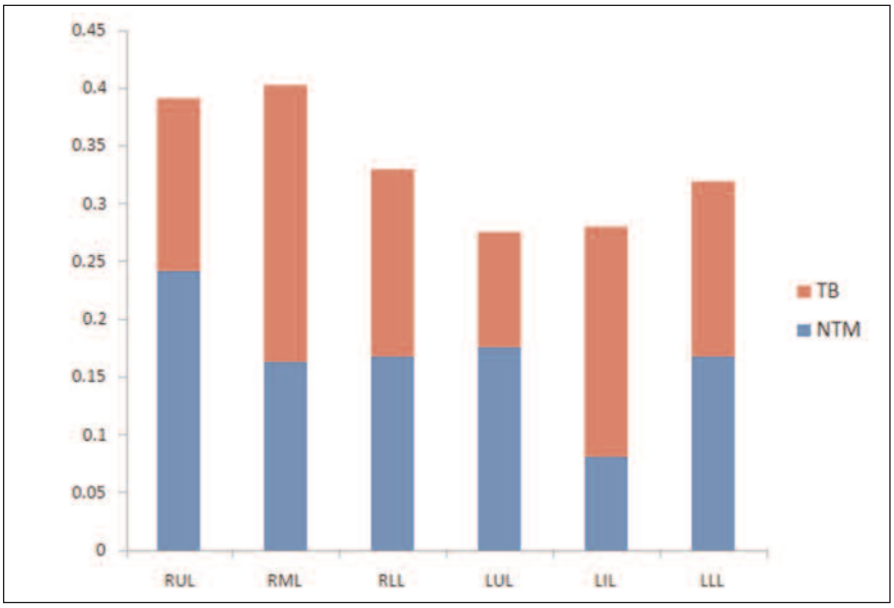

Figure 2. The right middle lobe and the left lingual segment bronchiectasis are more commonly seen in NTM lung disease ($p < 0.001$).

nificantly higher in NTM-LD patients as shown by CT scan. In addition, involvement of lung segments is significantly different between NTM-LD and PTB. Bilateral bronchiectasis (Figure 1), the right middle lobe (23.9% *vs.* 16.3%) and the left lingual segment bronchiectasis (19.9% *vs.* 8.2%) ($p < 0.001$) (Figure 2 and Table IV) are more prominent in NTM-LD.

Table IV. Comparative chest CT findings of non-tuberculous mycobacterial lung diseases and pulmonary tuberculosis.

CT findings	Number of patients involved			Number of involved lobes		
	TB (n=210)	NTM (n=124)	*p*-value	TB (n=1260)	NTM (n=744)	*p*-value
Tree-in-bud pattern	76	35	0.150	207	84	0.002
Nodules (D ≥ 1 cm)	75	50	0.415	129	93	0.122
Bronchiectasis	96	106	< 0.001	244	322	<0.001
Thin-walled cavity (D ≥ 3 cm)	36	25	0.558	48	30	0.812
Thin-walled cavity (D ≥ 3 cm)	16	21	0.011	20	27	0.005
Thick-walled cavity (D ≥ 3 cm)	131	39	< 0.001	241	66	<0.001
Thick-walled cavity (D ≥ 3 cm)	98	50	0.305	161	83	0.290
Consolidation	128	52	0.001	210	95	0.020
Patches	178	91	0.015	518	241	<0.001
Nodules (D < 1 cm)	140	59	0.001	339	154	0.002
Atelectasis	20	1	0.001	22	1	0.01
Ground-glass opacity	25	10	0.355	47	17	0.087
Reticular opacities	14	1	0.012	32	1	<0.001
Volume reduction	18	12	0.843	53	34	0.734
Mediastinal lymphadenopathy	81	14	< 0.001			
Hilar lymphadenopathy	39	11	0.017			
Calcified lymph nodes	41	5	< 0.001	41	5	<0.001
Cystic changes	1	4	0.065	2	5	0.109
Pleural effusion	52	17	0.017	138	30	<0.001
Interstitial fibrosis	12	5	0.611	35	22	0.890
Pneumothorax	2	1	1.0			
Pleural thickening	1	2	0.558			

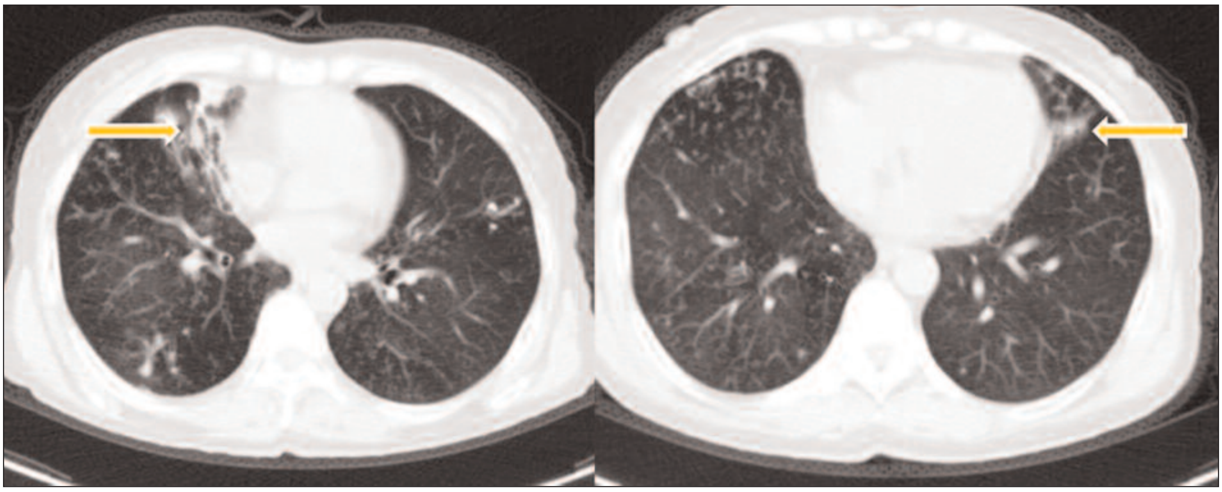

Figure 3. Chest CT scan demonstrates right middle, left lingual segment bronchiectasis in the 49-year old women with *Mycobacterium intracellulare* induced lung infections.

The following CT imaging features have higher prevalence in PTB patients: the thick-walled cavity (D < 3 cm) (62.4% *vs.* 31.5%, $p <$ 0.001), pulmonary consolidation (61.0% *vs.* 41.9%, $p = 0.001$), patchy (84.8% *vs.* 73.4%, $p = 0.015$), D < 1 cm nodules (66.7% *vs.* 47.6%, $p = 0.001$), atelectasis (9.5% *vs.* 0.8%, $p = 0.001$), reticular opacities (6.7% *vs.* 0.8%, $p = 0.012$), mediastinal lymph nodes (38.6% *vs.* 11.3%, $p < 0.001$), hilar lymph nodes (18.6% *vs.* 8.9%, $p = 0.017$), lymph node calcification (19.5% *vs.* 4.0%, $p < 0.001$) and pleural effusion (24.8% *vs.* 13.7%, $p = 0.017$).

In multivariate analysis, CT scan findings of bronchiectasis (Figure 3) (OR = 8.521, 95% CI = 4.209-17.250, $p < 0.001$) and thin-walled cavity formation (Figure 4) (D ≥ 3 cm) (OR = 3.561, 95% CI = 1.394-9.097, $p = 0.008$) were independently associated with patients diagnosed as NTM-LD. While the CT scan presence of thick cavities (D < 3 cm) (Figure 5) ($p < 0.001$, OR = 0.212, 95% CI = 0.113-0.398), D < 1 cm nodule (Figure 6) ($p = 0.003$, OR = 0.367, 95% CI = 0.189-0.713), atelectasis (Figure 7) ($p = 0.004$, OR = 0.039, 95% CI = 0.004-0.356), mediastinal lymph nodes (Figure 8) ($p = 0.006$, OR = 0.182, 95% CI = 0.054-0.615) and lymph node calcification ($p = 0.018$, OR = 0.247, 95% CI = 0.078-0.784) was strongly associated with PTB patients.

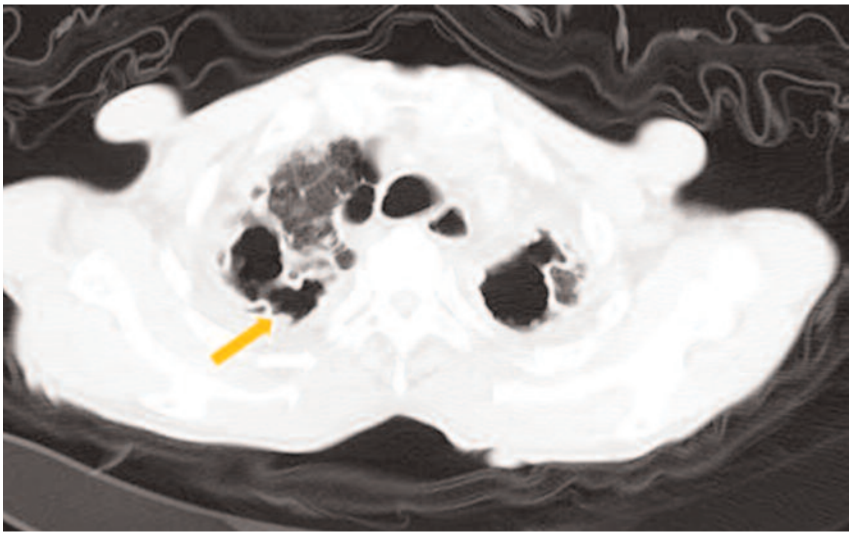

Figure 4. Chest CT scan shows bilateral large cavities in the 53-year old man with Mycobacterium kansasii induced lung infection.

Figure 5. Chest CT scan shows left dorsal segment small thick-walled cavity in the 35-year old man with pulmonary tuberculosis.

Discussion

This is the first study in China that analyzed CT imaging features in patients with sputum AFB-positive NTM-LD and PTB. Our study is so far with largest sample size of NTM-LD accompanying with all species identification data. We found that bronchiectasis in the right middle lobe or left lingual segment and thin-walled cavity with a diameter more than 3 cm are the frequently chest CT features in patients with NTM-LD.

Definite diagnosis of NTM-LD cannot simply rely on isolated and cultured NTM from the respiratory tract. Patients positive for NTM culture do not always mean to have NTM-LD. Such infection may indicate colonization or transient infection. Therefore, for NTM-LD diagnosis, etiology, clinical symptoms and the imaging findings are indispensable[17]. Previous studies demonstrated that the main imaging features of NTM-LD were bronchiectasis, pulmonary nodules, centrilobular nodules and cavities involving both lobes of the lungs, etc. The imaging features in our study are mostly identical to previously reported radiological findings. Similarly, PTB diagnosis is also based on mycobacterial culture from lower respiratory tract specimens and PCR results, but in the diagnosis of PTB, clinical symptoms and chest imaging also play an important role[18]. Typical CT features in PTB patients include cavity formation, lung consolidation, patchy lung nodules, mediastinal lymph node enlargement, lymph node calcification, and pleural effusions. In our paper, the main imaging results in PTB patients were also mostly consistent with the previously reported radiological findings.

Our study found that CT imaging showing bronchiectasis, thin-walled cavity ($D \geq 3$ cm) were independently associated with the diagnosis of NTM-LD; meanwhile, thick-walled cavity ($D < 3$ cm), $D < 1$ cm nodules, atelectasis, mediastinal lymph nodes enlargement and lymph node calcification are strongly associated with PTB. A correlation between bronchiectasis and NTM has been previously reported; especially the relationship between bronchiectasis and *Mycobacterium avium*, *Mycobacterium intracellulare complex* (MAC) induced pulmonary infection. Our CT scan findings of bilateral bronchiectasis, right middle lobe, and left lingual lobe bronchiectasis being related to NTM-LD are also similar to other reports[19]. However, other CT findings to distinguish the significance between NTM and PTB are rarely reported. Yuan et al[20] compared chest CT findings in 75 PTB and 20 NTM-LD patients and found that bronchiectasis, pleural effusion, and pulmonary nodules could be used to distinguish PTB from NTM with statistically significance. Conversely, we found that the type of cavity and the nodule's size were not classified and sample size was relatively smaller in term of atelectasis, mediastinal lymph node enlargement and calcification, which may have caused a certain deviation while performing data analysis.

Cavity is the most typical radiological feature in pulmonary tuberculosis. Kim et al[21] reported that cavitary AFB smear-positive PTB and NTM-

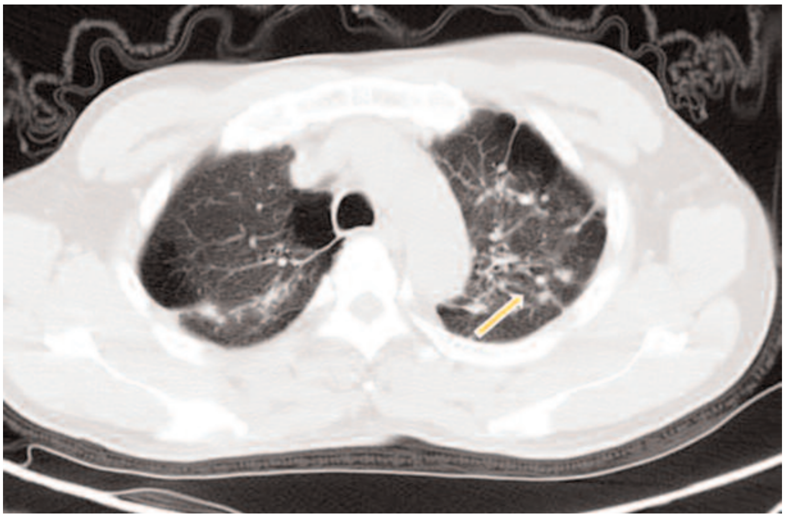

Figure 6. Chest CT scan shows bilateral upper segments small nodules in the 53-year old man with pulmonary tuberculosis.

LD have quite similar clinical features. This makes it more difficult for cavitary pulmonary mycobacterial infection patients to get empiric treatment. Thus, more detailed imaging description on cavity is very crucial. Kahkouee et al[22] referred that thick-walled cavities and lymph node calcification may indicate TB, while bronchiectasis and small nodules in the same lung segment or the adjacent one was an independent predictor for NTM-LD, which is very similar to our findings, but laterality and distribution of cavities showed no difference in PTB and NTM-LD in our study) (Figure 1, Figure 9). Since their research focused on the CT finding differences between multi-drug resistant tuberculosis (MDR-TB) and NTM-LD, and their sample size was relatively small (43 MDR-TB *vs.* 23 NTM), their conclusion about decreased lung volume and pleural thickening was different from ours. Even though we believe that atelectasis and mediastinal lymph node enlargement can help differentiate NTM-LD from PTB, it should be emphasized that if lymph node enlargement was noted, acid-fast staining microscopic examination on lymph node aspirate will increase diagnostic sensitivity and specificity[23]. Thus, if needle biopsies can be performed on enlarged lymph nodes, endobronchial ultrasound (EBUS) and other tests may be more helpful for differential diagnosis.

Diseases attributable to NTM infection have a rising trend in many developed and developing countries[24-26]. In endemic areas, generally the im-

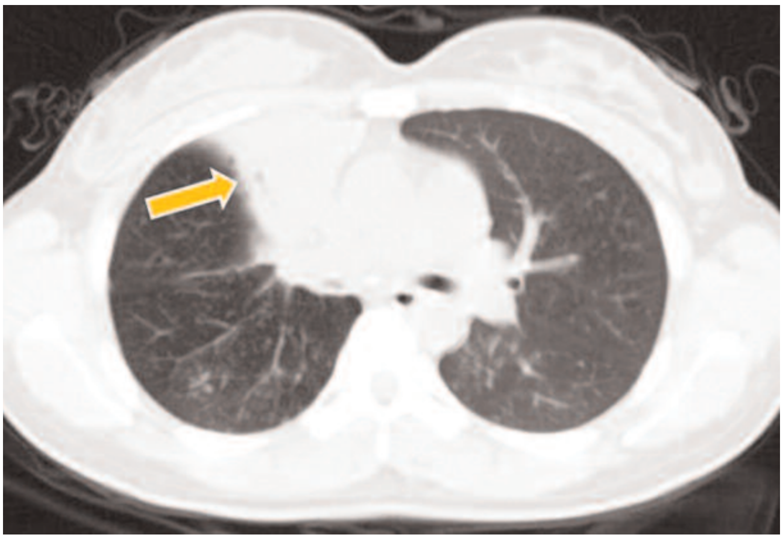

Figure 7. Chest CT scan shows right upper lobe atelectasis in the 39-year old woman with pulmonary tuberculosis.

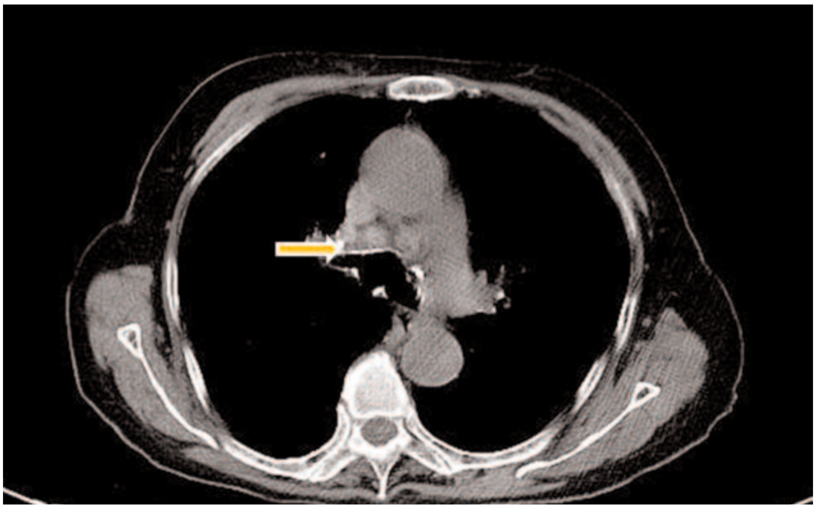

Figure 8. Chest CT scan shows mediastinal lymphadenopathy in the 43-year old man with pulmonary tuberculosis.

mediate and empirical treatment of mycobacterial diseases based on the result of AFB sputum smear is the first choice for a clinician and has an important impact on disease transmission control. However, this will cause an increase of unnecessary empiric anti-TB therapy and consequently increased adverse effects by such treatment and public health cost.

A research from Taiwan[27] showed that about 40.4% AFB smear-positive patients approved to be caused by NTM. Among them, 25.8% received empiric anti-TB treatment, which caused about 44% patients to suffer from drug related adverse effects of anti-TB treatment.

It will be very significant to reduce or avoid, if possible, unnecessary empiric anti-TB treatment and consequently increased drug-related adverse effects and public health cost owing to the treatment of this kind of drug-induced complications. Our study demonstrated that the CT imaging showing bronchiectasis and thin-walled cavities (D ≥ 3 cm) were independent predictors for the diagnosis of sputum smear-positive acid-fast staining NTM-LD. Therefore, based on results of the current work, for patients who have suspected clinical presentations and sputum smear-positive acid-fast staining, clinicians can make more precise decisions about whether or not they should initiate empiric anti-TB treatment and avoid unnecessary adverse effects in patients with NTM lung diseases.

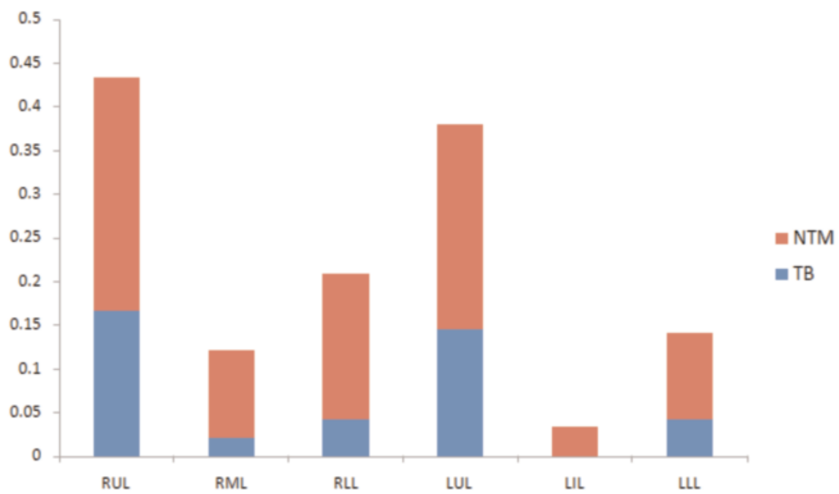

Figure 9. There is no significant difference between TB and NTM in the distribution of thin-walled cavity (p=0.777).

Table V. Multivariate analysis of predictors.

CT findings	p-value	Odds ratio	95% CI	Favor
Bronchiectasis	**< 0.001**	8.521	4.209-17.250	NTM
Thin-walled cavity (D ≥ 3 cm)	0.008	3.561	1.394-9.097	NTM
Thick-walled cavity (D < 3 cm)	**< 0.001**	0.212	0.113-0.398	TB
Consolidation	**0.218**	0.675	0.362-1.261	
Patches	0.744	0.866	0.364-2.057	
Nodules (D < 1 cm)	**0.003**	0.367	0.189-0.713	TB
Atelectasis	**0.004**	0.039	0.004-0.356	TB
Reticular opacities	0.133	0.168	0.016-1.725	
Mediastinal lymphadenopathy	**0.006**	0.182	0.054-0.615	TB
Hilar lymphadenopathy	0.351	1.915	0.489-7.495	
Calcified lymph nodes	**0.018**	0.247	0.078-0.784	TB
Pleural effusion	0.659	0.838	0.382-1.837	

Conclusions

The right middle lobe and left lingual segment bronchiectasis and thin-walled cavity with a dimension more than 3 cm are the frequently chest CT features in patients with NTM-LD, which might be helpful for early diagnosis in patients with AFB-smear positive. The CT scan distinction between NTM-LD and PTB may help clinicians recognize what is the most likely diagnosis in AFB-smear positive patients and avoid unnecessary adverse effects and the related health care costs of empirical anti-TB medication.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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