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Original Article

Tree-in-bud pattern of chest CT images for diagnosis of Mycobacterium abscesses

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Abstract: Objectives: Changes of chest CT images in *Mycobacterium* and non-*Mycobacterium* abscesses in patients with lung disease were with a view to making an early diagnosis. Methods: 124 primary patients diagnosed with non-tuberculosis *Mycobacterium* infections with a positive sputum acid-fast smear were enrolled in this retrospective study. CT images and clinical data of these patients were analyzed. Results: The 52 *Mycobacterium* abscess lung disease cases included bronchiectasis 82.7% (43/52), which was more easily detected bilaterally than unilaterally (29/52 *vs.* 14/52), lung consolidation 44.2% (23/52), nodules 44.2% (22/52), cavities 32.7% (17/52), tree-in-bud pattern 42.3% (22/52) and patchy shadow 63.5% (33/52) in CT images. Tree-in-bud pattern was more common in *Mycobacterium* abscess compared with non-*Mycobacterium* abscess lung disease (42.3% *vs.* 18.1%, P = 0.004). A significant difference of the lung area involved by tree-in-bud in CT was found between non-*Mycobacteria* abscess and *Mycobacterium* abscess lung disease (17.0% *vs.* 7.2%, P < 0.001), and tree-in-bud occurred more readily unilaterally (21.2% vs. 6.9%, P = 0.029), and in the inferior lobe of the right lung (3.2% *vs.* 0.2%, P = 0.029) in *Mycobacterium* abscess lung disease. Patchy shadow was more common in non-*Mycobacterium* abscess lung disease (63.5% *vs.* 80.1%, P = 0.041). Further multi-factor analysis confirmed that tree-in-bud was an independent predictor of *Mycobacterium* abscess lung disease. Conclusions: Different CT results existed between non-*Mycobacterium* abscess and *Mycobacterium* abscess lung diseases. The tree-in-bud pattern might be helpful to choose a suitable therapy in patients, with an acid-fast bacilli smear-positive diagnosis of lung disease.

Keywords: *Mycobacterium* abscess, lung disease, acid-fast bacilli, smear positive lung disease, chest CT performance

Introduction

Non-tuberculosis *Mycobacterium* diseases are those caused by non-tuberculous *Mycobacterium* (NTM) except for *Mycobacterium tuberculosis* and *Mycobacterium leprae*, with the lungs being the most commonly involved organ. In recent years, the incidence of infection caused by NTM has been gradually rising, thus making it an important pathogenic bacterium in the clinic [1-3]. *Mycobacterium* abscess is a fast-growing NTM that produces lung infection. Research in the USA has shown that more than 80% of fast-growing NTM lung diseases are caused by *Mycobacterium*-induced abscesses [1]. 12% of *Mycobacterium* abscesses were isolated from 17,915 NTM strains in South Korea, which was only secondary to *Mycobacterium avium-intracellulare* composite group [4]. In addition, different therapy regimes were given due to different sensitivities of the bacteria to drugs, particularly *Mycobacterium* and non-*Mycobacterium* abscess; the *Mycobacterium* abscess was independently separated according to the American Thoracic Society guidelines. At present, more and more iatrogenic infections and outbreaks caused by *Mycobacterium* abscess have been reported, which have become one of the most common bacteria for iatrogenic infection, thus attracting the close attention of Chinese and other scholars [5-7]. However, effective treatment of *Mycobacterium* abscess pulmonary disease is still lacking, with broad-spectrum antibiotics being administered intravenously as the main treatment in hospitals. Unfortunately, these bacteria are resistant to most antibiotics and are naturally resistant to anti-tuberculosis drugs. Their low efficacy, high resistance rate, gastrointestinal toxicity are well known and found even for presently well-established effective antibiotics, including amikacin, cefoxitin or imipenem and others, thereby resulting in a worse prognosis for *Mycobacterium* abscesses infection compared to non-*Mycobacterium* infection [6, 8, 9].

Because of the relatively higher incidence of *Mycobacterium* abscess in NTM infections, the risk of outbreak, spread of infection, drug resistance, and poor prognosis by these bacteria was increased, making them potentially more harmful to public health. Therefore, early diagnosis of *Mycobacterium* abscess infection, especially early differential diagnosis of non-*Mycobacterium* abscess, would be of important significance for the clinical diagnosis and treatment of *Mycobacterium* abscess infection.

Sputum acid-fast bacilli (AFB) smear microscopy is one of the most commonly used and effective methods for early clinical diagnosis of *Mycobacterium* lung disease [10]. Samples from patients who are AFB positive are cultured so that the infecting bacterial strain(s) can be identified, but clinicians often need other tests to provide a differential diagnosis of NTM (mainly due to the length of time required for strain identification). Imaging can provide important information to help identification of the disease and understand its potential severity e.g. lesion size. Thus, CT imaging before confirmed bacterial culture results is of great clinical interest for the early differential diagnosis and treatment of NTM related diseases.

Therefore, this study set out to compare chest CT imaging differences between *Mycobacterium* abscesses and non-*Mycobacterium* abscesses in patients with lung disease. The aims were to determine the characteristics of *Mycobacterium* abscess lung disease using imaging techniques and to assess the possibility of using imaging as a predictor of *Mycobacterium* abscess lung disease.

Patients and methods

Patients

AFB smear-positive patients (4,167 of 13,509 cases of sputum specimens analyzed) were diagnosed and treated in Shanghai Pulmonary Hospital, which is affiliated to Tongji University, from January 2011 to January 2014. Samples were collected at least twice from AFB smear-positive patients. To varying degrees, sputum specimens, bacterial culture and strain identification were performed for all AFB smear-positive patients. In total, 4,043 patients were diagnosed with tuberculosis by strain identification, 124 patients with a non-tuberculosis *Mycobacterium* infection (of which 52 were *Mycobacterium* abscesses) and 72 cases were non-*Mycobacterium* (NM) abscesses. All patients underwent CT imaging and the general clinical data from the primary diagnosis plus the chest CT examination results were compared between *Mycobacterium* abscesses and NM abscesses-lung disease (LD) infections. The Tongji University and the ethics committee of Shanghai Pulmonary Hospital, which is affiliated to Tongji University, approved the study. All of the patients enrolled in the study signed consent forms.

Diagnosis of pulmonary Mycobacterium abscesses-LD and NM abscesses-LD

An AFB smear was performed on all the sputum specimens. Polymerase chain reaction (PCR) was performed for Mycobacterium tuberculosis using the IS6110 probe (Life Technologies, Carlsbad, USA). Modified Roche medium (BaiHui, Wuxi, China) was employed for Mycobacterium cultivation. Confirmed diagnosis of Mycobacterium abscesses-LD and NM abscesses-LD was based on the results of Mycobacterium cultures and American Thoracic Society guidelines [1].

CT scanning methods

Computer tomography (CT) imaging was performed in the radiology department of the Shanghai Pulmonary Hospital within 3 months of AFB smear analysis. A conventional CT scan was performed using multi slice spiral CT (Brilliance CT 64-channel, Philips, Eindhoven, Netherlands), with a scanning layer thickness of 5 mm and an interval of 5 mm. HRCT scan was performed with a slice thickness of 1 mm and an interval of 10 mm. The scan range was from the apex pulmonis to the costophrenic angle position under maximal inspiratory amplitude. CT performance of *Mycobacterium abscesses*-LD and NM abscesses-LD was recorded according to the following description:

Table 1. Species identification result of NTM

Species	Quantity
Mycobacterium abscesses	52 (41.9)
Mycobacterium intracellulare	42 (34.7)
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)
Mycobacterium paraffinum	1 (0.8)

Table 2. Clinical characteristics of patients with *Mycobacterium* abscesses-LD and NM abscesses-LD

	Mycobacterium abscesses (*n* = 52)	NM abscesses (*n* = 72)	P
Age	58	59	0.994
Male	31	39	0.585
Ever smoker	20	24	0.574
Diabetes mellitus	10	13	1.0
Malignancy	1	0	0.419
Autoimmune disease	1	0	0.419
COPD	11	12	0.641
Pneumoconiosis	0	1	1.0

tree-in-bud (centrilobular nodules with a linear branching pattern), nodules (d ≥ 1 cm), bronchiectasis, thin walled cavity (d < 3 cm), thin walled cavity (d ≥ 3 cm), thick wall cavity (d < 3 cm), thick wall cavity (d ≥ 3 cm), lung consolidation, patchy shadow, nodules (d < 1 cm), atelectasis, ground glass nodules, reticular opacity, decrease of lung volume, mediastinal lymphadenectasis, hilar lymphadenopathy, calcified lymph nodes, bronchial cystic expansion, pleural effusion, interstitial fibrosis, pneumothorax and pleural thickening. All the CT images were analyzed and confirmed by two radiological and lung disease experts, who were blinded to the microbiology results. The sensitivity and specificity for the identification of *Mycobacterium* abscess lung disease by CT imaging were calculated as: sensitivity = true positive/cases group and specificity = true negative/cases group

Statistical analysis

All statistical analysis was performed using SPSS for Windows (Version 16.0, Chicago, SPSS Inc). The chi-square test or Fisher's exact test were employed for comparison of classification variables and an independent sample *t*-test was employed for comparison of continuous variables. Differences of CT performance characteristics were evaluated using single factor analysis. Multi-factor analysis using a logistic regression model was performed to determine the independent predictor of *Mycobacterium* abscesses-LD and NM *abscesses*-LD. P < 0.05 was considered to be statistically significance.

Results

Among the NTM strains detected in our study, 52 (41.9%) were *Mycobacterium* abscesses in 21 males and 31 women, who had a median age of 58 years (range 23~80 years). Intracellular *Mycobacteria* (42/72, 58%) was the most common strain in the 72 non-*Mycobacteria* abscesses patients (**Table 1**), among who were 39 males and 33 women, with a median age of 59 years (range 18-78). No significant differences of gender, age, smoking history, malignant tumor or other basic diseases were found between the two groups (**Table 2**).

Based on the CT findings on laterality and the distribution of *Mycobacterium abscesses* and NM *abscesses*-LD (Supplementary Table 1), the most common CT manifestations in the 124 cases of NTM lung disease was bronchiectasis (85.5%, 106/124) and patchy shadow (73.4%, 91/124), followed by nodules (47.6%, 59/124), lung consolidation (41.1%, 51/124), cavity (27.4%, 34/124) and tree-in-bud (28.2%, 35/124).

The most common CT manifestations in the 52 cases of *Mycobacterium* abscesses-LD was also bronchiectasis (82.7%, 43/52), which was easier to detect bilaterally rather than unilaterally (29/52 *vs.* 14/52), and tended to be present more in the middle lobe of right lung and left lingual (35/146 *vs.* 26/146) (Supplementary Table 1; **Figure 1A**), followed by patchy shadow (63.5%, 33/52), lung consolidation (44.2%, 23/52) and nodules (44.2%, 23/52). No obvious laterality and distribution differences were found for lung consolidation and nodules. Cavities were found in 17 patients (32.7%, 17/52), which were mainly located in the upper lobe (9/17) (Supplementary Table 1; **Figure 1B**),

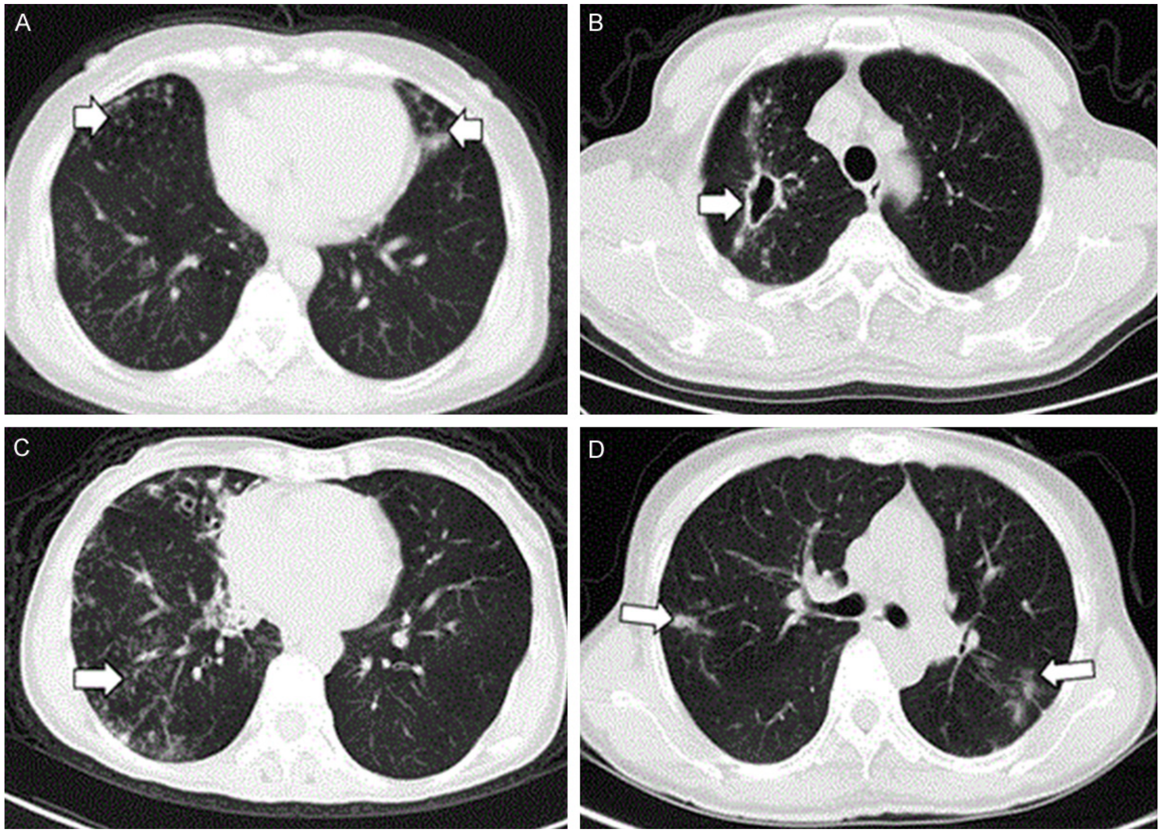

Figure 1. Different CT results in different patients with *Mycobacterium* abscesses and intracellular mycobacteria. A. Chest thin layer CT in a 59-year-old female with mycobacterial abscess lung disease indicated bronchiectasis in the middle lobe of the right lung and left lingula. B. Chest thin layer CT in a 49-year-old male with mycobacterial abscess lung disease revealed a cavity in the upper lobe of the right lung. C. Chest thin layer CT in a 61 year-old female with mycobacterial abscess lung disease showed small centrilobular nodules in the right lower lung and bronchiectasis in the middle lobe of the right lung. D. Chest CT in a 49 year-old male with non-myobacterial abscess lung disease shows a patchy shadow in the bilateral upper lobe.

without obvious laterality. However, a tree-in-bud pattern was detected in 42.3% (22/52) of *Mycobacterium* abscesses-LD patients, which was 2.3 times (42.3% *vs.* 18.1%, P = 0.004) higher than that found in the NM abscesses-LD patients (**Table 3** and **Figure 1C**).

A significant difference was found by CT in amount of lung area lesions between non-*Mycobacterium* abscess and *Mycobacterium* abscess lung disease patients (17.0% (53/312) *vs.* 7.2% (31/432), P < 0.001). The lesions were more prominent unilaterally (21.2% *vs.* 6.9%, P = 0.029) (Supplementary Table 1; **Figure 2A**) and in the inferior lobe of the right lung (3.2% *vs.* 0.2%, P = 0.029) (**Figure 2B**), while patchy shadow was more common in NM abscess lung disease (63.5% *vs.* 80.1%, P = 0.041) (**Figure 1D**). The sensitivity and specificity of tree-in-bud and patchy shadows for the diagnosis of *Mycobacterium* abscess lung disease was further analyzed, and we found that the sensitivity and specificity of patchy shadows was 63.5% (33/52) and 18.1% (13/72) respectively, and was 42.3% (22/52) and 81.9% (59/72) for small centrilobular tree-in-bud development. A further multi-factor analysis confirmed that tree-in-bud was an independent predictor for *Mycobacterium*-LD diagnosis (P = 0.004, OR = 3.662, 95% CI = 1.524-8.798) (**Table 4**).

Discussion

The present study analyzed the CT imaging characteristics of *Mycobacterium* abscesses-LD patients with positive sputum AFB in China. It represents the largest sample size of *Mycobacterium* abscesses of any similar reports on NTM. Since all the collected samples were characterized by bacteria identification,

Table 3. Comparative chest CT findings of *Mycobacterium* abscesses and NM abscesses

CT findings	Number of patients involved			Number of involved lobes		
	Mycobacterium abscesses (*n* = 52)	NM abscesses (*n* = 72)	P	*Mycobacterium* abscesses (*n* = 312)	NM abscesses (*n* = 432)	P
Tree-in-bud pattern	22	13	0.004	53	31	< 0.001
Nodules (d ≥ 1 cm)	23	27	0.465	47	46	0.092
Bronchiectasis	43	63	0.606	146	176	0.115
Thin-walled cavity (d < 3 cm)	11	14	0.824	14	16	0.706
Thin-walled cavity (d ≥ 3 cm)	12	9	0.148	17	10	0.029
Thick-walled cavity (d < 3 cm)	21	18	0.080	38	28	0.009
Thick-walled cavity (d ≥ 3 cm)	25	25	0.143	43	40	0.059
Consolidation	23	29	0.714	43	56	0.744
Patches	33	58	0.041	94	147	0.268
Nodules (d < 1 cm)	22	37	0.365	63	91	0.784
Atelectasis	1	0	0.419	1	0	0.419
Ground-glass opacity	2	8	0.190	2	15	0.011
Reticular opacities	1	0	0.419	1	0	0.419
Volume reduction	6	6	0.556	16	18	0.595
Mediastinal lymphadenopathy	4	10	0.391	0	0	
Hilar lymphadenopathy	3	8	0.356	0	0	
Calcified lymph nodes	0	5	0.074	0	0	
Cystic changes	3	1	0.308	3	2	0.655
Pleural effusion	8	9	0.792	12	18	0.853
Interstitial fibrosis	1	4	0.398	5	17	0.079
Pneumothorax	0	1	1.0	3	3	0.699
Pleural thickening	0	2	0.509	0	9	0.012

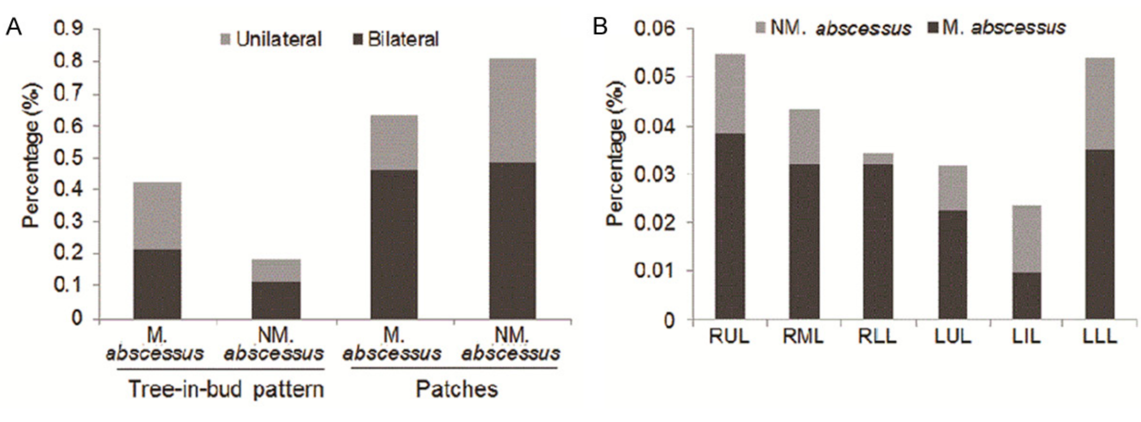

Figure 2. Percentage of tree-in-bud and patchy shadow in bilaterally and unilaterally locations, and the proportion of involved lobes in *Mycobacterium* abscesses-LD and NM abscesses LD. A. Higher percentage of tree-in-bud was found unilaterally in *Mycobacterium* abscesses LD (P = 0.029), but no significant difference for patchy shadows. B. A Higher proportion of small centrilobular nodules in the right lower lung (RRL) were found in *Mycobacterium* abscesses-LD than in NM abscesses-LD.

the finding that tree-in-bud is an independent predictor of *Mycobacterium* abscesses-LD is potentially of great interest.

Most research has considered nodules, tree-in-bud, patchy shadow (consolidation, ground glass), cavities, bronchiectasis and fibrous

Table 4. Multivariate analyses of predictors for *Mycobacterium* and NM abscesses

CT findings	P	Odds ratio	95% CI	
Tree-in-bud pattern	0.004	3.662	1.524-8.798	*Mycobacterium* abscesses
Thick-walled cavity (d < 3 cm)	0.126	1.930	0.831-4.482	
Patches	0.014	0.326	0.133-0.799	NM abscesses
Calcified lymph nodes	0.223	0.343	0.062-1.916	

stripes to be the major CT manifestations of NTM lung diseases [11, 12], and indeed similar results were found in the present study. In research on the CT characteristics of *Mycobacterium* abscesses-LD carried out by Han et al. and Jeong et al. the main findings were that tree-in-bud, bronchiectasis, fibrous cavities and nodules, were present, mainly in the upper lung, findings partly consistent with our research, since bronchiectasis was the most common CT result in our study (43/52), with cavity being detected relatively less frequently (17/52). Other CT imaging characteristics (e.g., patchy shadows, interstitial fibrosis, lymph nodes) also appeared, and patchy shadows as well as lung consolidations were common detected in patients with *Mycobacterium* abscesses-LD.

Although the CT manifestations of *Mycobacterium* abscesses-LD were comparatively recognized, to our knowledge, no reports on a comparison of the CT characteristics between *Mycobacterium* abscesses and NM abscesses-LD have been published. Chung et al. compared CT characteristics between *Mycobacterium* abscesses and *Mycobacterium avium* intracellular-LD, and found no differences between nodules and bronchiectasis between the two groups [13], findings which were certainly similar to our results; however, it is noteworthy that tree-in-bud was more common in *Mycobacterium* abscesses-LD. Tree-in-bud refers to small airway (at the bronchiole level) involvement of lesions, resulting in expansion of the airway and infiltration of pathological substances into the tube cavities, which manifests as nodular shadows of diameter of 2~4 mm and branch line shadows connected with these nodules in thin layer CT, which look like tree-in-buds. In a report on 50 cases of NTM lung diseases by Jun et al. the occurrence rate of tree-in-bud was 50% (25/50), which was similar to our results (42.3%).

Based on the studies of Chung et al. and Han et al. the CT characteristics of *Mycobacterium* abscesses-LD mainly occurred bilaterally and without a preferred lung lobe distribution, which was different from our findings. In the present study we also found that patchy shadows were more common in NM abscesses-LD, but the proportion of the lung lobe affected by patchy shadow, laterality and preferred location showed no significant differences compared to *Mycobacterium* abscesses-LD, which has not previously been reported. The reason might be that patchy shadow was not included in the CT imaging analysis of previous reports. Complications such as emphysema or pulmonary bullae, pleural effusion or pleural thickening adhesions, atelectasis or destroyed lung and mediastinal lymphadenectasis may exist and affect the multiple lung lobe CT results. For the differential diagnosis of NTM-LD, both microbiological analysis and clinical imaging data are considered to be indispensable [14]. Microbial analysis is highly specific but necessarily takes a longer time to complete, and therefore early differential diagnosis of *Mycobacterium* abscesses-LD by CT appearances before confirmed microbiological diagnosis is important clinically so that appropriate treatment can be initiated.

Above all, common characteristics of NTM-LD can be found in both *Mycobacterium* abscesses and NM abscesses-LD, such as bronchiectasis, tree-in-bud, cavity, lung consolidation and nodule shadows. However, bronchiectasis, a higher proportion of lung lobes involved by tree-in-bud, preferred unilateral, and inferior lobe lesions of the right lung was more common in *Mycobacterium* abscesses-LD, but patchy shadow was more common in NM abscesses-LD.

Due to some similar imaging findings between the two types of NTM-LD and certain imaging similarity with secondary pulmonary tuberculosis in some patients, the differential diagnosis of the two types of NTM lung disease should be considered closely with the clinical manifestations. NTM lung disease should be considered for those patients with positive clinical respiratory secretions AFB but ineffective anti-tuberculosis treatment.

In summary, if lesions were mainly bronchiectasis and accompanied by cavity, lung consolidation, tree-in-bud and nodule shadows, NTM-LD infection should be strongly suspected. If a higher proportion of the lung lobe is involved by tree-in-bud, and with preferred unilateral occurrence in the inferior lobe of the right lung, *Mycobacterium* abscesses-LD is likely indicated. For those with a higher percentage of patchy shadows, but without preferred unilateral tree-in-bud occurrence in the inferior lobe of the right lung, NM abscesses-LD may be indicated. CT imaging results may facilitate the early diagnosis and differentiation of NTM-LD before confirmed microbiological diagnosis reports are available.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Laterality and distribution of parenchymal lesions in patients with *Mycobacterium* abscesses and NM abscesses

CT findings	*Mycobacterium* abscesses									NM abscesses								
	Laterality		RUL	RML	RLL	LUL	LL	LLL	SUM	Laterality		RUL	RML	RLL	LUL	LL	LLL	SUM
	Bi	Uni								Bi	Uni							
Tree-in-bud pattern	11	11	12	10	10	7	3	11	53	8	5	7	5	1	4	6	8	31
Nodules (d ≥ 1 cm)	12	11	12	5	8	8	2	12	47	9	18	11	5	13	6	0	11	46
Bronchiectasis	29	14	25	35	22	17	26	21	146	45	18	23	42	30	15	38	28	176
Thin-walled cavity (d < 3 cm)	1	10	3	2	0	5	1	3	14	0	14	9	1	3	2	0	1	16
Thin-walled cavity (d ≥ 3 cm)	3	9	4	2	3	4	1	3	17	0	9	4	1	2	3	0	0	10
Thick-walled cavity (d < 3 cm)	8	13	13	1	2	12	2	8	38	5	13	9	1	3	6	3	6	28
Thick-walled cavity (d ≥ 3 cm)	9	16	19	2	7	12	0	3	43	6	19	17	3	5	13	1	1	40
Consolidation	9	14	10	8	6	11	6	2	43	10	19	12	11	5	9	6	9	56
Patches	24	9	25	11	12	16	13	17	94	35	23	36	25	25	24	16	21	147
Nodules (d < 1 cm)	11	11	13	6	14	9	10	11	63	17	20	22	14	17	11	11	16	91
Atelectasis	0	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Ground-glass opacity	0	2	1	0	0	1	0	0	2	1	7	4	3	4	1	2	1	15
Reticular opacities	0	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0
Volume reduction	0	6	2	2	2	4	3	3	16	0	6	1	1	1	5	5	5	18
Mediastinal Lymphadenopathy	2	2	0	0	0	0	0	0	0	8	2	0	0	0	0	0	0	0
Hilar lymphadenopathy	2	1	0	0	0	0	0	0	0	8	0	0	0	0	0	0	0	0
Calcified lymph nodes	0	0	0	0	0	0	0	0	0	3	2	0	0	0	0	0	0	0
Cystic changes	0	3	0	0	0	1	1	1	3	1	0	0	0	1	0	0	1	2
Pleural effusion	0	8	2	2	5	0	0	3	12	1	8	2	2	4	2	2	6	18
Interstitial fibrosis	1	0	1	1	1	1	0	1	5	4	0	3	2	4	2	2	4	17
Pneumothorax	0	0	0	0	0	1	1	1	3	0	1	1	1	1	0	0	0	3
Pleural thickening	0	0	0	0	0	0	0	0	0	1	1	2	2	2	1	1	1	9

Note: RUL-Right upper lobe; RML-Right middle lobe; RLL-Right lower lobe; LUL-Left upper lobe; LL-Left lingula; LLL-Left lower lobe.