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CT Imaging Characteristics of Nontuberculous Mycobacteria Lung Disease, Active Tuberculosis and Multi-Drug Resistant Tuberculosis

Liang Xu[1], *Shuangmei Xu*[2]

[1]Department of Respiratory and Critical Care Medicine, Affiliated Hospital of Shaoxing University, Shaoxing 312000, Zhejiang Province, China; [2]Department of Radiology, Zhuji Affiliated Hospital of Shaoxing University, Zhuji 311800, Zhejiang Province, China

Abstract. *Background:* The differential diagnosis of nontuberculous mycobacteria (NTM) lung disease, active tuberculosis (ATB) and multi-drug resistant tuberculosis (MDR-TB) remains difficult. *Objectives:* To explore the CT imaging characteristics of NTM lung disease, ATB and MDR-TB for differential diagnosis. *Methods:* Patients with NTM lung disease (n=200), ATB (n=200) and MDR-TB (n=200) who were examined and treated from August 2013 to May 2021 were included. Their chest CT imaging results were retrospectively analyzed, and the imaging characteristics were compared. *Results:* The proportion of cases complicated with underlying lung disease, cough and hemoptysis was significantly higher in NTM group than those in ATB and MDR-TB groups (P<0.05). Compared with ATB and MDR-TB groups, NTM group had significantly more cases of nodule-bronchus dilation type, but significantly fewer cases of nodule-mass type and other types (P<0.05). In NTM group, the cases of thin-wall cavity, bronchiectasis and centrilobular nodules increased, but the detection rate of thick-wall cavity, lung consolidation, atelectasis, lung damage, lung volume reduction, intrapulmonary calcification, hilar and mediastinal lymph node calcification, acinar nodules, pleural thickening and pleural effusion declined compared with ATB and MDR-TB groups (P<0.05). The detection rates of lesions, cavities and bronchiectasis in the lingual lobe of left lung and middle lobe of right lung were significantly higher in NTM group than those in ATB and MDR-TB groups (P<0.05). *Conclusions:* The imaging characteristics of NTM lung disease are quite similar to those of ATB and MDR-TB, but they can be differentially diagnosed through the types of cavities and nodules, incidence rate of bronchiectasis, and differences in lung consolidation, lung damage, calcification, pleural thickening and pleural effusion.

Key words: nontuberculous mycobacteria lung disease, active pulmonary tuberculosis, multi-drug resistant tuberculosis, CT imaging

Introduction

The *Mycobacterium tuberculosis* (MTB) complex including *M. tuberculosis*, *M. microti*, *M. bovis* and *M. africanum*, as well as *Mycobacteriaceae* except for *M. leprae* is collectively referred to as nontuberculous mycobacteria (NTM) (1). In addition to severely invading the lungs, NTM also causes skin and soft tissue infections, lymphadenitis and musculoskeletal system lesions (2). Pulmonary tuberculosis (PTB) is a common chronic respiratory disease caused by MTB infection in the lungs (3). When the lesions are in the active stage with sputum smear-positive tuberculosis, the disease will develop rapidly and become highly infective, also known as active pulmonary tuberculosis (ATB). The main symptoms of ATB patients include cough, mild fever, poor appetite, fatigue and emaciation (4). MTB in patients

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Correspondence: Shuangmei Xu
Department of Radiology, Zhuji Affiliated Hospital of Shaoxing University, Zhuji 311800, Zhejiang Province, China
E-mail: jensenmcintoshaudd@yahoo.com; xushuangmei2021@126.com

is also resistant to two or more major first-line anti-tuberculosis drugs, including isoniazid and rifampin, so it is referred to as multi-drug resistant tuberculosis (MDR-TB) (5). In recent years, the lung disease is diagnosed mainly based on the clinical symptoms and signs of patients using MTB sputum examination, fiberoptic bronchoscopy, imaging examination and biopsy of lung and pleura, and imaging examination is still an important diagnostic method. In this study, the chest CT imaging results of NTM lung disease, ATB and MDR-TB were retrospectively analyzed, and the similarities and differences of CT imaging characteristics were explored, aiming to raise the accuracy of diagnosis and treatment of the three diseases, and to benefit early clinical diagnosis and treatment.

Methods

Baseline clinical data

Patients with NTM (n=200, NTM group), ATB (n=200, ATB group) and MDR-TB (n=200, MDR-TB group) who were examined and treated in our hospital from August 2013 to May 2021 were collected. In NTM group, there were 150 males and 50 females aged 18-74 years, with an average of (50.6 ± 12.1) years old. The duration of disease was 2-55 months, with an average of (26.8 ± 9.2) months. In ATB group, there were 148 males and 52 females aged 17-74 years old, with an average of (50.3 ± 11.8) years old. The duration of disease was 3-54 months, with an average of (26.9 ± 10.3) months. In MDR-TB group, there were 152 males and 48 females aged 18-74 years old, with an average of (50.6 ± 12.3) years old. The duration of disease was 3-55 months, with an average of (27.1 ± 9.3) months.

Diagnostic criteria

According to the "Guideline for the Diagnosis and Treatment of Nontuberculous Mycobacteria Lung Disease" developed by the Society of Tuberculosis, Chinese Medical Association in 2000, NTM lung disease can be diagnosed combined with radiological imaging and clinical examination if one of the following criteria is met under the premise that the patients have respiratory and/or systemic symptoms, intrapulmonary lesions can be detected in imaging examination, other diseases have being excluded and there is no exogenous pollution on specimens. 1) The same pathogen is confirmed by 3 times of sputum NTM culture. 2) The same pathogen is confirmed by sputum NTM culture twice, and the acid-fast bacillus (AFB) smear is positive once. 3) The bronchial lavage fluid NTM culture is positive (above 2+) once. 4) The bronchial lavage fluid NTM culture is positive, and the AFB smear is positive (above 2+). 5) The positive NTM culture is confirmed by bronchopulmonary tissue biopsy. 6) Granuloma similar to NTM lesions is found via lung tissue biopsy, and the sputum or bronchial lavage fluid NTM culture is positive. Besides, ATB can be diagnosed if one of the following criteria is met: 1) The sputum MTB test is positive. 2) The tuberculin test is positive. 3) The lesions cannot be absorbed after anti-inflammatory treatment for 7-10 d, and the imaging examination shows obviously absorbed lesions after treatment with anti-tuberculosis drugs. In addition, MDR-TB is diagnosed if MTB is found to be positive in sputum culture or fiberoptic bronchoscopy, and also resistant to two or more drugs including isoniazid and rifampin according to drug susceptibility test.

Inclusion and exclusion criteria

Inclusion criteria: 1) patients who met diagnostic criteria in each group, 2) those without undergoing any treatment recently, 3) those with complete and searchable clinical medical records and imaging data, and 4) those who were informed and signed the consent. Exclusion criteria: 1) patients with bacterial, fungal or viral infection, or autoimmune diseases, 2) those who took immunomodulators or glucocorticoids recently, 3) those complicated with diseases of heart, liver, kidney, thyroid or other systems or diabetes, 4) those who had alcohol or morphine abuse or dependence, 5) pregnant women, or 6) those with mental illness. This study was reviewed and approved by the Medical Ethics Committee of our hospital.

Examination methods

Routine chest scan was performed for patients using a Toshiba Aquilion 16-slice full-body spiral CT machine (slice thickness: 5 mm, slice gap: 5 mm, 2 mm high resolution for local lesions, screw pitch: 0.2-0.24, tube current: 100 mA, tube

voltage: 120 kV). Before the examination, the patients received the inspiration and breath-holding training. During the examination, the head of patient entered into the machines first in a supine position, and the axial plain scan was conducted for the whole lung along the direction from apex of lung to diaphragmatic dome at the time of deep inspiration breath holding. After the examination, two experienced radiologists read the images in a double-blind way. In the case of inconsistent diagnosis results, the diagnosis was confirmed after discussion between the two radiologists. The lesion site, characteristics and diagnosis results were recorded in detail. The CT imaging features of NTM lung disease, ATB and MDR-TB were analyzed.

Statistical analysis

All data were statistically analyzed by SPSS17.0 software. The quantitative data were expressed as mean ± standard deviation. Multigroup comparisons were performed by one-way analysis of variance. In the case of significant difference, intergroup comparisons were conducted with the independent t test. The numerical data were represented as percentage, and intergroup comparisons were carried out by the Chi-square test. P<0.05 was considered statistically significant.

Results

Baseline clinical data

There were no statistically significant differences in gender, age, course of disease, fever, expectoration, decrease rate of Hb and ALB, and increase rate of WBC among the three groups (P>0.05). The proportion of cases complicated with underlying lung disease, cough and hemoptysis was higher in NTM group than that in ATB group and MDR-TB group, and the differences were statistically significant (P<0.05) (Table 1).

Chest CT imaging results

In NTM group, the two lungs showed multiple spotted patchy nodules and shadows, especially in the lower lobes, which were scattered in smooth thin-walled cavities with various shapes and sizes (Figure 1A). In ATB group, multiple micronodules in the middle and lower lobe of the right lung were clustered together, accompanied by thickened interlobular septum. There were micro-nodules in the center of the lobules and tree buds in the upper lobes of both lungs (Figure 1B). In MDR-TB group, there were nodular and patchy high-density shadows in the upper lobes of both lungs. The upper right lobe exhibited contractile changes, thickening

Table 1. Baseline clinical data

Index	NTM group (n=200)	ATB group (n=200)	MDR-TB group (n=200)
Gender			
Male	150	148	152
Female	50	52	48
Age (year)	50.6±12.1	50.3±11.8	50.6±12.3
Disease course (month)	26.8±9.2	26.9±10.3	27.1±9.3
Complication with underlying lung disease	141	65*	61*
Fever	55	57	59
Cough	143	100*	104*
Expectoration	155	163	161
Hemoptysis	88	43*	46*
Hb reduction	69	65	66
ALB reduction	92	89	90
WBC increase	86	82	84

WBC: White blood cell; Hb: hemoglobin; ALB: albumin.

of the pleura on both sides, and a small amount of pleural effusion (Figure 1C).

Lesion types in chest CT imaging

There was no statistically significant difference in the distribution of cavity-based and mixed lesions among the three groups (P>0.05). NTM group had more nodular-bronchiectasis type than ATB group and MDR-TB group, and ATB group and MDR-TB group had more nodule-mass type and other types than NTM group, showing statistically significant differences (P<0.05). There was no statistically significant difference in the lesion types between ATB group and MDR-TB group (P>0.05) (Table 2).

Chest CT imaging characteristics

No statistically significant differences were found in the number of lung lobes involved, and single or multiple cavities among the three groups (P>0.05). Compared with those in ATB group and MDR-TB group, the thin-wall cavities, bronchiectasis and lobular central nodules were increased, while the detection rates of thick-wall cavities, lung consolidation, atelectasis, lung damage, decline in lung volume, intra-pulmonary calcification, hilar and mediastinal lymph node calcification, acinar nodules, pleural thickening and pleural effusion were decreased in NTM group, and the differences were statistically significant (P<0.05). There was no significant difference in the lesions between ATB group and MDR-TB group (P>0.05) (Table 3).

Detection rates of lesions, cavities, bronchiectasis and nodules

The detection rate of bronchiectasis significantly rose in the lingular segment of left lung and middle lobe of right lung (P<0.05), but had no significant difference in other parts (P>0.05). There was no statistically significant difference in the detection rate between ATB group and MDR-TB group (P>0.05).

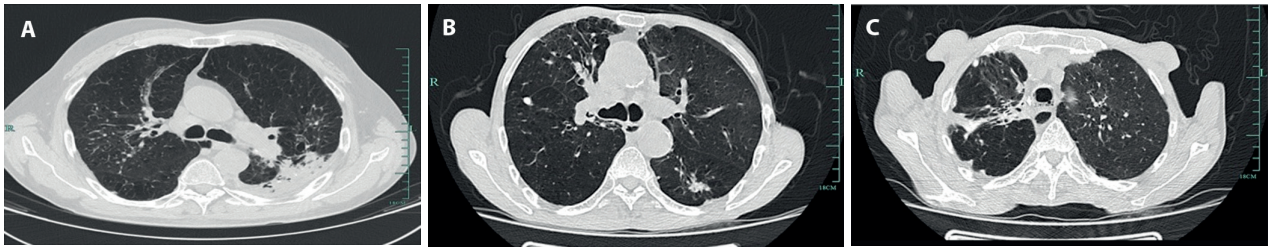

Fig. 1. Chest CT imaging results. A: Chest CT image in NTM group. The two lungs showed multiple spotted patchy nodules and shadows, especially in the lower lobes, which were scattered in smooth thin-walled cavities with various shapes and sizes. B: Chest CT image in ATB group. Multiple micronodules in the middle and lower lobe of the right lung were clustered together, accompanied by thickened interlobular septum. There were micro-nodules in the center of the lobules and tree buds in the upper lobes of both lungs. C: Chest CT image in MDR-TB group. There were nodular and patchy high-density shadows in the upper lobes of both lungs. The upper right lobe exhibited contractile changes, thickening of the pleura on both sides, and a small amount of pleural effusion.

Table 2. Lesion types in chest CT imaging

Type	NTM group (n=200)	ATB group (n=200)	MDR-TB group (n=200)
Cavity-based	59	61	63
Nodular-bronchiectasis	102	29*	27*
Nodule-mass	17	40*	44*
Mixed	7	21	24
Others	17	52*	45*

Mixed type: nodular-bronchiectasis and cavity-based; others: interstitial changes, branch-like and undetermined. *P<0.05, with significant difference with NTM group.

Table 3. Chest CT imaging characteristics

Index	NTM group (n=200)	ATB group (n=200)	MDR-TB group (n=200)
Involved lung lobes			
1~2	57	61	60
3~4	67	65	63
5~6	75	73	78
Thin-wall cavity	101	23*	24*
Thick-wall cavity	37	79*	81*
Single cavity	13	15	12
Multiple cavities	93	87	85
Bronchiectasis	126	83*	90*
Lung consolidation	55	129*	125*
Atelectasis	0	20*	23*
Lung damage	0	25*	19*
Lung volume reduction	19	63*	57*
Intra-pulmonary calcification	57	131*	127*
Hilar and mediastinal lymph node calcification	35	99*	101*
Lobular central nodule	99	62*	57*
Acinar nodule	47	85*	83*
Pleural thickening	81	128*	132*
Pleural effusion	23	77*	75*

*P<0.05, with significant difference with NTM group.

The detection rate in each part had no significant difference among the three groups (P>0.05) (Table 4).

Discussion

NTM lung disease mostly occurs in patients with pre-existing chronic lung diseases such as pneumoconiosis, bronchiectasis and tuberculosis, whose clinical manifestations are similar to tuberculosis. The diagnosis of tuberculosis is mainly based on bacteriological examination, but its detection rate in bacteriology has not reached 100%. Currently, imaging has become one of the commonly-used diagnostic methods. In addition, NTM and MTB have much in common in bacterial composition and antigen. It is not easy to distinguish NTM lung disease from tuberculosis through pathological changes and chest imaging, so it is necessary to pay attention to differential diagnosis (6). It has previously been reported that there was no significant difference in the incidence rate of cough and hemoptysis between NTM group and MDR-TB group (7). In this study, the proportion of cases with cough and hemoptysis in NTM group was higher than that in ATB group and MDR-TB group, and the differences were statistically significant (P<0.05), being consistent with previous results (8). Cough and hemoptysis are important clinical symptoms of bronchiectasis. NTM lung disease mostly shows pulmonary granuloma, and caseous necrosis rarely occurs. Granulomatous lesions are nodular lesions formed by the aggregation of lymphocytes and epithelioid cells, which can easily involve the large airway and bronchiole and induce bronchiectasis, thereby leading to cough and hemoptysis (9). In this study, the proportion of cases complicated with underlying lung disease in NTM group was significantly increased compared with that in ATB group and MDR-TB group, consistent with earlier research reports (10). The reason is that NTM is an opportunistic pathogen and has weaker virulence than MTB. In addition, congenital or secondary immunodeficiency is a predisposing factor for NTM, so patients with chronic underlying lung disease are more prone to NTM.

Table 4. Detection rates of lesions, cavities, bronchiectasis and nodules

Index	NTM group (n=200)	ATB group (n=200)	MDR-TB group (n=200)
Lesion			
Left upper lobe	125	135	141
Left lingular lobe	161	51*	51*
Left lower lobe	107	114	110
Right upper lobe	165	171	171
Right middle lobe	156	55*	60*
Right lower lobe	123	127	123
Cavity			
Left upper lobe	23	27	25
Left lingular lobe	35	9*	11*
Left lower lobe	17	21	20
Right upper lobe	21	24	31
Right middle lobe	32	7*	7*
Right lower lobe	14	19	18
Bronchiectasis			
Left upper lobe	19	22	23
Left lingular lobe	32	9*	7*
Left lower lobe	15	17	21
Right upper lobe	16	21	18
Right middle lobe	31	7*	7*
Right lower lobe	15	15	17
Nodule			
Left upper lobe	29	25	23
Left lingular lobe	23	22	18
Left lower lobe	25	27	25
Right upper lobe	19	21	17
Right middle lobe	31	29	33
Right lower lobe	23	28	27

Lesions included bronchiectasis, cavities, lung consolidation, atelectasis, lung volume reduction, nodules and calcification. *P<0.05, with significant difference with NTM group.

In this study, in terms of CT imaging characteristics, compared with ATB group and MDR-TB group, NTM group had obviously increased thin-wall cavities, bronchiectasis and lobular central nodules, and evidently decreased thick-wall cavities and acinar nodules. After NTM infection, the formation of granuloma is first induced in the terminal bronchiole, and then spreads through the bronchus, damaging the airway muscle layer, and leading to airway stenosis or even obstruction and increased pressure in the bronchial cavity, so that thin-wall cavities, nodules and bronchiectasis are caused (11,12). Bronchiectasis is a common complication of NTM lung disease. Clustered lobular central nodules are commonly seen in patients with NTM lung disease, and they are presumably formed by scattered granulomas in the bronchiole. The specific signs of bronchogenic dissemination of tuberculosis are acinar nodules, namely disseminated foci in the surrounding and other lung fields (13). Caseous lesions are a common feature of tuberculosis. Due to liquefaction and emptying after tissue necrosis in lesions, thick-wall cavities are

formed and acinar nodules appear in the surrounding and other lung fields (14). According to the main clinical symptoms and pathological changes, the lesions are classified into nodular-bronchiectasis type, cavity-based type, nodule-mass type, mixed type of nodular-bronchiectasis and cavity, and other types that cannot be judged including tree-in-bud sign and interstitial changes (15). According to CT classification results, NTM group had significantly more nodular-bronchiectasis type and significantly fewer nodule-mass type and other types than ATB group and MDR-TB group, and the possible reason is that nodules and tree-in-bud sign of NTM lung disease are less typical than those of tuberculosis.

In this study, no statistically significant differences were found in the number of lung lobes involved, and single or multiple cavities among the three groups ($P>0.05$), and the possible reason is that patients with NTM lung disease are often complicated with underlying lung disease with a long duration. MDR-TB strains are more pathogenic and can significantly damage lung tissues, leading to repeated lesion infiltration and dissemination, so the lesion activity is significant. Therefore, extensive lesion involvement can be observed in multiple lung fields in imaging, and the morphology of lesions is diverse (16). The duration of MDR-TB is often longer, and new lesions have emerged at another site before local lesions are improved, so that lung lesions continuously progress in a larger scope, calcification occurs, and cavities are formed and difficult to be closed, thereby aggravating lung injury and ultimately causing lung consolidation, lung damage, atelectasis, decline in lung volume and so on. Lung consolidation and atelectasis in NTM lung disease are more common in the case of large airway involvement, and it will cause lung damage if not treated promptly, but it rarely occurs. Herein, the detection rates of lung consolidation, atelectasis, lung damage, decline in lung volume, intra-pulmonary calcification, hilar and mediastinal lymph node calcification, pleural thickening and pleural effusion were significantly lower in NTM group than those in ATB group and MDR-TB group, being consistent with the above description. MTB causes early pleurisy via eroding the visceral pleura of the patient, thus triggering pleural thickening and pleural effusion. After penetrating the pleura, it can infect the pleural cavity to induce tuberculous empyema. Due to the prolonged course of disease, pleural adhesions and calcification occur in patients with MDR-TB. Pleural thickening and pleural effusion adjacent to the lesions can be seen occasionally in patients with NTM lung disease. In this study, the results revealed that the detection rates of pleural thickening and pleural effusion significantly declined in NTM group compared with those in ATB group and MDR-TB group, basically consistent with the research reports of Kahkouee et al. Bronchiectasis in the lingular segment and middle lobe is the characteristic manifestation of NTM lung disease (17). In this study, the detection rates of lesions, cavities and bronchiectasis in the lingular segment of left lung and middle lobe of right lung were markedly higher in NTM group than those in ATB group and MDR-TB group, basically consistent with previous studies. Besides, there was no statistically significant difference in these detection rates between ATB group and MDR-TB group, presumably because ATB and MDR-TB have no clear difference in definition, and there is a cross-inclusion relationship between them. NTM includes a variety of bacteria, and no detailed typing study was conducted in this paper. In addition, due to the small sample size, the characteristic differences in ATB and MDR-TB imaging were not found for differential diagnosis. Therefore, it is needed to further analyze the correlation between NTM of different types and imaging findings in the future, and expand the sample size, so as to study the characteristic differences in ATB and MDR-TB imaging for differential diagnosis.

In summary, NTM lung disease has many similarities with ATB and MDR-TB in the imaging characteristics, but they can be differentially diagnosed through the differences in the type of cavities and nodules, the incidence rate of bronchiectasis, lung consolidation, lung damage, calcification, pleural thickening and pleural effusion.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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