Imaging characteristics of nontuberculous mycobacterial pulmonary nodules

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Introduction. Nontuberculous mycobacteriosis (NTM) of the lungs can develop nodules. In order to clarify some of the characteristics of lung NTM nodules, we examined volume doubling time (VDT) and maximum standardized uptake value (SUVmax) in positron emission tomography (PET) of pathologically diagnosed NTM nodules.

Methods. From November 2012 to August 2018, clinical and radiological information were retrospectively investigated in eight patients who were surgically resected and diagnosed as NTM. These eight patients were followed up until November 2020 and were confirmed to have no appearance of lung cancer or reappearance of lung NTM nodules. The VDT was calculated using the Schwartz formula.

Results. The median maximum diameter of the nodule at the time of the first CT scan was 16.0 (range: 9.9–20.0) mm. The median maximum diameter of the nodule on CT performed before the surgical biopsy was 18.8 (range: 10.4–32.8) mm. The median doubling time calculated from these results was 203 (range: 20–568) days. Caseous granulomas and acid-fast bacilli were histologically confirmed in all eight patients. Culture of excised nodules revealed *Mycobacterium intracellulare* in five patients and *Mycobacterium avium* in three patients. Six patients received PET, and median SUVmax was: 7.0 (range: 3.3–21.0). Median VDT was around 200 days. Some patients had irregular-shaped nodules.

Conclusions. CT/PET-CT characteristics of lung nodules are not reliable in differentiating lung NTM nodules from malignant ones. To avoid unnecessary resection, it may be better to collect various information on imaging findings in the nodule itself and in opacities other than the nodule.

Key words: lung mycobacterium infections nontuberculous; X-Ray computed tomography.

What is new? What is important?

Nontuberculous mycobacteriosis of the lungs can develop nodules. The median doubling time of the nodules was 203 days. Some of them had high maximum standardized uptake value in positron emission tomography. To avoid unnecessary resection, it may be better to collect various information on imaging findings in the nodule itself and in opacities other than the nodule.

INTRODUCTION

The commonly observed CT findings in patients with lung nontuberculous mycobacteriosis (NTM) are centrilobular, peribronchovascular multiple small nodules, bronchiectasis, consolidation, tree-in-bud in the middle lobe and/or lingual lobe [1–4]. Although not common, in some patients lung NTM manifests as a solitary nodule, mass, or mass-like consolidation mimicking malignancy [5–13]. These lung NTM nodules might be accompanied by these commonly observed parenchymal findings. In order to complicate this aspect, patients

with coexisting lung NTM and lung cancer have also been reported [9–13]. It might be particularly difficult to distinguish NTM nodule from lung cancer in patients with NTM nodule without these lung parenchymal findings. The usefulness of FDG-PET/CT has been investigated for the purpose of differentiating pulmonary NTM nodules from lung cancer. However, it is known that some patients of NTM nodules have FDG uptake [5, 14, 15].

In order to clarify some of the characteristics of lung NTM nodule, we examined volume doubling time (VDT) and maximum standardized uptake value (SUVmax) in positron

emission tomography (PET) of patients whose pathological diagnosis was confirmed by surgical biopsy.

MATERIAL AND METHODS

From November 2012 to August 2018, clinical information and chest CT and FDG-PET images were retrospectively investigated in all the 8 patients with NTM nodule who were surgically resected for the purpose of differentiating lung cancer. These 8 patients were followed up until November 2020 and were confirmed to have no appearance of lung cancer or reappearance of lung NTM nodules. We used multi-slice CT scan: Canon Aquilion Prime SP (0.5 mm × 80 PUREVISION (160 slices)(CANON, Tokyo, Japan), and PET-CT: SIEMENS PET-CT (Biograph Horizon, Siemens Healthcare, Tokyo, Japan).

VDT was calculated using the Schwartz formula [19]. The maximum diameter of the nodule on the CT image was measured by pulmonologists. For lung lesions other than nodules, pulmonologists investigated the presence of opacities in the same lobe as nodule existed, and middle lobe, and lingular lobe. The actual calculation method was as follows: VDT was calculated using the chest CT scans that were recorded several times during the clinical course. The VDT was calculated using a modification of the following Schwartz formula of exponential growth (Nakamura): $VDT = (t \times \log 2) / (3 \times \log (V2/V1))$; where V1 and V2 were the largest diameters on the CT scan measured at 2 different times, and t was the time interval between 2 measurements.

This study conformed to the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labor and Welfare of Japan. Written comprehensive consent for a non-interventional retrospective study was obtained from each patient. Analysis of the medical records of lung cancer patients was approved by the Ethics Committee in our institute (NO-16-66).

RESULTS

Table 1 shows the patient backgrounds of the eight patients investigated. The median age was 76 (55–79) years. There were 5 males and 3 females. No patients had diabetes, HIV infection. No patient had corticosteroid treatment. One had a history of smoking, but none had a history of inhalation of industrial substances. No patient had a history of pneumonia, including in childhood.

Nodules were found in 6 cases of the right lung and in 2 cases of the left lung. In 4 patients, the nodule was found in the upper lobe, 3 were in the lower lobe, and 1 was in the middle lobe.

The characteristics of the nodules are shown in Table 2. The median interval between the first CT scan and CT scan taken at prior to surgical biopsy was 133 (range 15–983) days. The median maximum diameter of the nodule at the time of the first CT scan was 16.0 (range: 9.0–20.0) mm. The median maximum diameter of the nodule on CT performed before the surgical biopsy was 18.8 (range: 10.4–32.8) mm. The median VDT calculated from these results was 203 (range: 20–568) days. FDG-PET was performed in 6 of the 8 cases. The median SUVmax of those patients was 7.0 (range: 3.3–21.0).

Table 1
Characteristics of 8 patients with lung NTM nodule

No. of patient	age, gender	Lesion site	Lesion shape	Opacities in the same robe
1	55, male	right upper lobe	Serrated nodule	Emphysematous cyst, scars
2	63, male	left upper lobe	Irregular nodule	Scattered, linear opacities
3	68, female	right upper lobe	Irregular nodule	Scattered, linear opacities
4	78, male	right lower lobe	Oval	Scattered, linear opacities
5	76, female	right lower lobe	Irregular nodule	Scattered, linear opacities
6	79, female	right upper lobe	Irregular nodule	None
7	78, male	left lower lobe	Oval	Scattered, linear opacities
8	75, male	right middle lobe	Elliptical nodule	Linear opacities

Table 2
Doubling time and PET SUVmax in 8 patients with lung NTM nodule

No. of patient	Diameter (mm)*	Interval between CTs (day)	VDT (day)	SUVmax	Cultured NTM	Caseous granuloma	
(at the first time at preoperative)							
1	9.0	10.4	352	549	3.4	<i>M. avium</i>	present
2	12.1	13.4	133	300	nd	<i>M. intracellulare</i>	present
3	17.2	20.5	15	20	9.3	<i>M. intracellulare</i>	present
4	16.5	19.3	49	73	4.6	<i>M. intracellulare</i>	present
5	20.0	29.8	983	568	11.8	<i>M. intracellulare</i>	present
6	16.2	32.8	522	181	21.0	<i>M. avium</i>	present
7	15.8	18.4	84	128	nd	<i>M. avium</i>	present
8	14.7	16.8	132	224	3.3	<i>M. avium</i>	present

PET: positron emission tomography, SUVmax: maximum standardized uptake value, NTM: non-tuberculous *Mycobacterium*, nd: not done

In 7 patients, scattered nodular and linear opacities were confirmed in the same lung lobe and in the middle lobe/lingular lobe. Changes in shape of NTM nodules were seen in 3 patients: 1 from an oblong elliptical nodule to a circular nodule, 1 from an oblong irregular nodule to a longitudinal irregular nodule, and 1 case from a longitudinal irregular nodule to a horizontal irregular nodule. Caseous granulomas and acid-fast bacilli were histologically confirmed in all 8

patients. Culture of excised nodules revealed *Mycobacterium intracellulare* in 5 patients and *Mycobacterium avium* in 3 patients.

We present nodules in two patients (Figure 1: patient number 3 and Figure 2: patient number 6 in Table 1). The nodule in case 3 was nearly spherical and the nodules in case 6 were irregular. Both nodules had irregular margins, but there were no findings of entrainment in the surrounding structure.

Figure 1. Chest CT and FDG-PET/CT of lung NTM nodule in a patient (Patient number 3 in Table 1). A: a maximum diameter 17.23 mm nodule in the upper right lobe taken on the first chest CT scan, B: the same nodule increased up to 20.46 mm taken at prior to surgical biopsy, C: FDG-PET/CT scan showing the SUV max of the nodule was 9.33.

Figure 2. Chest CT and FDG-PET/CT of lung NTM nodule in a patient (Patient number 6 in Table 1). A: a maximum diameter 16.18 mm nodule in the upper right lobe taken on the first chest CT scan, B: the same nodule increased up to 32.79 mm taken at prior to surgical biopsy, C: FDG-PET/CT scan showing the SUV max of the nodule was 20.

DISCUSSION

To the best of our knowledge, there has been no report on investigating VDT in lung NTM nodules. Therefore, this was the first study on this evaluation. Schwartz formula is a method of calculating VDT assuming that the nodule is spherical or has a shape similar to a spherical shape. The advantage of this method is that it is cheap and easy to calculate. Although nodule cannot be assumed to be spherical, VDT can be difficult to interpret, the median VDT in our eight patients with lung NTM nodules was 203 (range: 20–568) days. VDT was 100 days or less in 2 patients (No. 3 and 4), who's two CT scan interval of 50 days or less. On the other hand, VDT was the longest in patient No. 5 whose two CT scan interval close to 1,000 days. Due to the variability among nodules, VDT of them could not be exactly determined from the results of this study because of number of patients. Regarding VDT using chest CT, there have been some reports in lung cancer patients [16–18]. The median VDT of lung cancer using CT have been reported to be 227–348 days in lung adenocarcinoma and 88–131 days in lung squamous cell carcinoma [16–18]. VDT of lung cancer was not examined in this study, so comparison in VDT of lung NTM nodules and that of lung cancer cannot be possible. However, it was suggested that VDT of lung NTM nodules was not so different from those with these two histopathological types of lung cancer. Judging from the results of this study, therefore, it may be difficult to distinguish between lung NTM nodules and lung cancer using VDT alone.

In patients with lung NTM, centrilobular, peribronchovascular multiple small nodules, bronchiectasis, consolidation, tree-in-bud in the middle lobe and/or lingual lobe are commonly observed findings in chest CT scan. In 7 of our 8 patients, such findings were observed in the same lobe as NTM nodule existed and in middle/lingular lobes. In fact, there have been a few case reports of lung cancer coexisting with lung NTM [9–13]. Taking these condition into consideration, at present, both information on lung field in the same or other lobes than lung NTM nodules exist must be comprehensively evaluated. In addition to information on lung field conditions other than these nodules, another interesting result of this study was that noticeable changes in the shape of the nodules were confirmed over time in 3 of 8 patients. Usually, in lung cancer, they often remain spherical growth unless special mechanical

conditions are added, but this was not the case in these 3 patients. It was unclear whether this observation was useful for differentiating from lung cancer, but it was considered to be a noteworthy finding.

In this study, FDG-PET was performed in 6 of 8 patients. In FDG-PET, it has been reported that the SUVmax value of lung NTM nodules is not necessarily low [5, 14, 15]. Kawate *et al.* reported two lung NTM nodules with the SUVmax values 4.8 and 13.2, respectively [14]. In a lung NTM nodule reported by Min *et al.*, the SUVmax value was 12.5 [15]. The average SUVmax value of 4 NTM nodules in a report by Hong *et al* was 4.9 (range: 3.6–7.8) [5]. FDG-PET in our 6 patients showed the median value 7.0, which was consistent with the results of these previous studies [5, 14, 15]. The SUVmax for lung cancer has been reported to be 10 or higher [20, 21]. Budak *et al.* reported that it was 16.8 for lung adenocarcinoma and 17.9 for squamous cell lung cancer [20]. Al-Sarraf *et al.* reported that it was 15 for squamous cell lung cancer [21]. On the other hand, there have been many reports that SUVmax was less than 10 [22–24]. Usuda *et al.* report that it was 7.5 for malignant nodules and 3.9 for benign nodules [22]. Chrysikos *et al.* recommended a cutoff value of 5.0, and Zhou *et al.* reported a cutoff value of 3.9 [23, 24]. Based on these results, CT/PET-CT characteristics of lung nodules are not reliable in differentiating lung NTM nodules from malignant ones.

The limitations of this study were the small number of patients, the inconsistent CT imaging intervals, and the inclusion of patients with short imaging intervals. In fact, lung NTM nodules in this study evaluated were small nodules, and nodules with a low probability of obtaining appropriate samples by bronchoscopy or percutaneous biopsy. Therefore, CT imaging was performed at intervals according to the watch and wait policy. We thoroughly examined the indications for surgical biopsy. It is desirable to develop methods other than surgical biopsy that can obtain sufficient biopsy materials.

CONCLUSION

This was the first study to investigate VDT of nodule due to NTM. To avoid unnecessary resection, it may be better to collect various information on imaging findings in the nodule itself and in opacities other than the nodule.

Introducere. *Micobacterioza nontuberculoasă (NTM) a plămânului se poate dezvolta sub formă de noduli. Am examinat timpul de dublare al volumului (VDT) și valoarea SUVmax (maximum standardized uptake value) la analiza PET.*

Metode. *Au fost investigați retrospectiv 8 pacienți internați în perioada noiembrie 2012 – august 2018. Aceștia au fost urmăriți până în noiembrie 2020 și nu au dezvoltat cancer pulmonar sau reapariția nodulilor NTM. VDT a fost estimat folosind formula Schwartz.*

Rezultate. *Diametrul median al nodulului la momentul primei evaluări radiologice a fost de 16,0 mm (9,9–20,0 mm). Diametrul median al nodulului înainte de biopsia chirurgicală a fost de 18,8 mm (10,4–32,8 mm). Timpul median de dublare estimat a fost de 203 zile (20–568 zile). La biopsie au fost identificați bacil acid alcoolo-rezistenți și granuloame cazeoase la toți cei 8 pacienți. La 5 pacienți s-a evidențiat Mycobacterium intracellulare și la 3 pacienți s-a evidențiat Mycobacterium avium. 6 pacienți au avut analiza PET CT și SUVmax median a fost de 7,0 (3,3–21,0). VDT median a fost de 200 zile.*

Concluzii. *Caracteristicile PET-CT/CT ale nodulilor pulmonari nu diferențiază între nodulii NTM și cei maligni. Pentru a evita rezeecțiile inutile este mai bine a prelua cât mai multe informații asupra caracteristicilor imagistice.*

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