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Change in lung function in never-smokers with nontuberculous mycobacterial lung disease: A retrospective study

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ABSTRACT

Purpose: Never-smokers account for a large proportion of subjects in general population studies on nontuberculous mycobacteria lung disease (NTM-LD). However, the influence of NTM infection on the lung function of never-smokers has not yet been evaluated. The aim of this study was to determine how NTM-LD impairs the lung function in never-smokers, and whether there are an association between successful NTM-LD treatment in radiologic outcomes and improvement in lung function of never-smokers with NTM-LD or not.
Methods: We performed a retrospective study of patients (1) who have never smoked during their lifetime; (2) with at least two respiratory specimens from sputum, one bronchial washing sample, or one lung tissue that were culture positive for the same NTM species; and (3) who underwent at least two pulmonary function tests. We enrolled healthy never-smokers as the control group.
Results: In 22 never-smokers with NTM-LD, the median forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) at baseline was lower than those in 9 healthy never-smokers [1800 vs 2080 ml ($p = 0.23$) and 2230 vs 2620 ml ($p = 0.06$)], respectively. The median change in FEV_1 in never-smokers with NTM-LD was lower than that in healthy never-smokers [−70 vs 20 ml per year ($p = 0.07$), respectively]. On univariate analysis, baseline %-predicted FEV_1 in never-smokers with NTM-LD was associated with changes in FVC ($p = 0.026$) and FEV_1 ($p = 0.013$). Anti-NTM treatment was administered for at least 1 year in 19 patients (86.4%). The relationship between worsening chest CT findings and rapid progressive decline in both FVC ($p = 0.66$) and FEV_1 ($p = 0.23$) were not significant.
Conclusion: Never-smokers with NTM-LD showed lung function decline. There was no association between successful NTM-LD treatment in radiologic outcomes and improvement in lung function of never-smokers.

Introduction

The prevalence and mortality rates of nontuberculous mycobacterial lung disease (NTM-LD) have been globally increasing [1–5]. Radiologic features of fibrocavitary disease, anemia, low body mass index (BMI), high C-reactive protein, and coexistence with chronic pulmonary aspergillosis have been known to be negative prognostic factors of NTM-LD [6,7].

Pulmonary function tests (PFTs) provide a convenient way to objectively assess lung function for the management of patients with chronic obstructive pulmonary disease (COPD) and interstitial pneumonia [8]. In these cases, the rapid decline in lung function is a negative prognostic factor [9,10]. Among never-smokers, prior pulmonary tuberculosis (PTB) infection and bronchial asthma are risk factors for lung function impairment [11].

Pulmonary infection with nontuberculous mycobacteria (NTM) leads to air trapping, distal to the small airways [12]. However, the effect of chronic inflammation caused by NTM on lung function decline in the long-term remains unclear. Never-smokers make up a large proportion of subjects in general population studies of NTM-LD. The influence of NTM infection on the long-term lung function of never-smokers has not yet been determined. We conducted a retrospective study to determine how NTM-LD may impair the lung function in never-smokers compared with that in healthy never-smokers, and whether

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there are an association with a substantial decline and response to anti-NTM treatment.

Materials and methods

Study participants

This study was conducted at the Kinki-Chuo Chest Medical Center, a 385-bed center in Southern Osaka that specializes on pulmonary disease. We performed a retrospective study of consecutive patients with at least two respiratory specimens from sputum, one bronchial washing/brushing samples, or one lung tissue that were culture-positive for the same NTM species between August 1, 2012 and August 31, 2015. Patients were enrolled if (1) they fulfilled the diagnostic criteria of the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) guidelines [13], (2) underwent at least two PFTs, and (3) had never smoked during their lifetime. We excluded patients with other comorbidities (e.g., PTB, bronchial asthma, and interstitial pneumonia, which impaired lung function). We also enrolled healthy never-smokers as the control group, (1) patients visited our hospital for medical checkups between August 1, 2012 and August 31, 2015, (2) had no respiratory symptoms, (3) had never smoked during their lifetime, and (4) showed no abnormal lesion on chest CT and underwent at least two PFTs. This study was approved by the institutional review board of National Hospital Organization Kinki-Chuo Chest Medical Center (No. 566, date of approval: December 22/2016). Informed consent was waived because of the retrospective nature of the study.

Data collection

Information on a patient history was obtained during an outpatient visit. Height and weight were measured. Data on use of inhaled medications and the course of anti-NTM treatment were collected from the medical records. The patients received combination antibiotic therapy, as recommended by the ATS and IDSA [13].

Pulmonary function test

A CHESTAC-800 spirometer from CHEST was used. A forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio (FEV_1/FVC) of <70% was considered to indicate airflow obstruction. The predicted FEV_1 (%) was calculated on the basis of age, sex, and height, according to the ATS/European Respiratory Society guideline [14]. Each machine was calibrated daily before use. Each patient performed at least three forced expiratory maneuvers that fulfilled the criteria of repeatability [14] from diagnosis day to the last available PFT. Baseline PFT was defined as PFT performed most closely after at the date of the diagnosing the NTM lung disease. In each patient, annual lung function change (ml/year) was calculated as [(the last FEV_1 or FVC)–(FEV_1 or FVC at baseline)/follow-up duration (years)]. Rapid progression of FEV_1 or FVC decline was defined as >40 ml loss per year [10,15].

Evaluation of radiologic findings

We classified chest radiography and computed tomography (CT) findings at the time of diagnosis as either fibrocavitary disease, nodular bronchiectatic disease, or mixed form [16]. Deterioration was defined as progressively increasing nodules, infiltration, or consolidation on follow-up chest CT findings. No deterioration was defined as stable disease without significant interval changes on both available chest CT images and PFTs. Lesions that demonstrated a waxing and waning pattern during follow-up were reevaluated by comparing the baseline and most recently available CT findings. Chest CT findings were independently evaluated by two pulmonary specialists (TK and TT). In case of disagreement of interpretations, consensus was reached by discussion.

Bacteriologic outcomes of treatment for NTM

We classified patients according to their treatment and outcomes, which were evaluated by comparing baseline and last follow-up PFT. Disease progression in terms of bacteriologic outcomes was determined by the interval between the date of diagnosis and the date on follow-up after one year. After 12 months of treatment, culture conversion or relapse was assessed periodically. Negative conversion was defined as two consecutive negative cultures within three months after chemotherapy for 12 months. Sputum samples were collected and assayed for mycobacterial cultures once every 2 months in clinical practice. If the patient could not expectorate even after sputum induction, sputum conversion was considered to be from positive to negative. Relapse was defined as sputum conversion to positive (at least one positive sputum culture) after a preceding conversion from positive to negative.

Statistical analysis

Statistical analyses were performed using the JMP statistical software (12th version, SAS Institute Inc., Cary, NC). Proportions and medians were used to describe the demographic, clinical, and radiographic characteristics. Linear regression analysis was used to identify factors associated with changes in FEV_1 and FVC on follow-up. The analyses included all never-smokers and excluded patients with other comorbidities (e.g., PTB, bronchial asthma, and interstitial pneumonia) that might strongly influence lung function impairment.

Results

The characteristics of the 22 never-smokers with NTM-LD and 9 asymptomatic never-smokers without any other respiratory comorbidity are summarized in Table 1. The median age and the proportion of men were similar between 9 asymptomatic never-smokers without any other respiratory comorbidity and 22 never-smokers with

Table 1
Never-smokers with nontuberculous mycobacterial lung disease vs those without.

	Never-smokers with NTM lung disease (*n* = 22)	Healthy group (*n* = 9)	*p*-value
Age, years	70 (48–85)	64 (45–80)	0.50
Male, *n* (%)	6 (27.3)	3 (33.3)	1.00
Body mass index (kg/m$^{2)}$	19.2 (13.9–23.9)	20.5 (15.7–41.7)	0.30
Comorbidity			
Aspergillosis, *n* (%)	2 (9.1)	0 (0.0)	1.00
DM, *n* (%)	0 (0.0)	1 (1.1)	0.29
LC, *n* (%)	2 (9.1)	0 (0.0)	1.00
GERD, *n* (%)	2 (9.1)	0 (0.0)	1.00
CKD, *n* (%)	2 (9.1)	0 (0.0)	1.00
HTN, *n* (%)	0 (0.0)	1 (1.1)	0.29
Baseline spirometry			
FVC, mL	2230 (1270–3570)	2620 (2080–4490)	0.06
FVC, % predicted	92.5 (55.7–142.8)	108.3 (76.4–125.8)	0.15
FEV_1, mL	1800 (860–3130)	2080 (1460–3450)	0.23
FEV_1, % predicted	87.6 (45.3–139.5)	94.8 (68.5–117.3)	0.74
FEV_1/FVC	78.5 (67.7–97.5)	76.1 (62.4–94.1)	0.24
Interval days between baseline and last spirometry	2.76 (0.58, 5.83)	1.80 (0.31, 6.43)	0.05
Changes in lung function			
FVC change, mL/year	−80 (−440.0–0.0)	−140 (−390–80)	0.76
FEV_1 change, mL/year	−70 (−340–50)	20 (−0.4–0.16)	0.07

NTM, nontuberculous mycobacteriosis; FVC, vital capacity FEV_1, forced expiratory volume in 1 s; DM, diabetes mellitus; LC, lung cancer; CKD, chronic kidney disease

Table 3
Initial treatment of nontuberculous mycobacterial lung disease in never-smokers.

Use of chemotherapy	19 (86.4)
RFP + EB + CAM	12 (54.5)
RFP + EB	1 (4.5)
RFP + CAM	2 (9.1)
RFP + EB + CAM + SM	1 (4.5)
EM + LVFX	1 (4.5)
RFP + CAM + STFX	1 (4.5)

CAM, clarithromycin; EB, ethambutol; RFP, rifampicin; STFX, sitafloxacin hydrate; LVFX, levofloxacin

NTM-LD. The most common NTM species isolated alone was *Mycobacterium avium* complex (MAC) in 90.9% never-smokers with NTM-LD. All never-smokers with NTM-LD had nodular bronchiectasis pattern on radiography. No patients showed emphysema on their CT findings. Anti-NTM treatment was administered for at least 1 year in 19 patients (86.4%) (Table 3).

In all 22 never-smokers with NTM-LD, the median values of FEV_1 and FVC at baseline were lower than those in the control group (healthy never-smokers) [1800 vs 2080 ml ($p = 0.23$) and 2230 vs 2620 ml ($p = 0.06$), respectively]. The median change in FEV_1 in never-smokers with NTM-LD was lower than that in healthy never-smokers [−70.0 vs 20 ml ($p = 0.07$)] (Table 1, Fig. 1). In univariate analysis, baseline %-predicted FEV_1 was associated with changes in FVC (β coefficient = − 0.361; $p = 0.026$) and FEV_1 (β coefficient = − 0.519; $p = 0.013$; Table 2). The relationships between worsening chest CT findings and rapid progressive decline in both FVC ($p = 0.66$) and FEV_1 ($p = 0.23$) were not significant. Among 10 patients who received successful treatment based on bacteriologic outcome, rapid progressive decline was seen in FVC in 9 patients and in FEV_1 in 4 patients (Table 4).

Table 2
Nontuberculous *Mycobacterium* species in never-smokers with nontuberculous mycobacterial lung disease (n = 22).

M. avium	11 (50.0)
M. intracellular	9 (40.9)
M. avium + *M. abscessus* complex	1 (4.5)
M. avium + *M. kansasii*	1 (4.5)
Other bacterial infectious disease	
Pseudomonas aeruginosa	2 (9.1)

Discussion

The present study underscored two notable clinically relevant issues. First, patients with NTM-LD showed a decline in lung function even without tobacco exposure. Second, the success of NTM-LD treatment in never-smokers was not associated with an improvement in lung function.

The present study revealed that the tendency of decline in lung function of never-smokers with NTM-LD was a little greater than that of healthy never-smokers (FVC, $p = 0.76$; FEV_1, $p = 0.07$) In healthy Japanese individuals who had never smoked, the mean annual FEV_1 and FVC decline were 19.6 ml and 22.2 ml, respectively [17–20]. A retrospective study by Lee et al reported a decline in lung function in patients with NTM-LD, 38% of whom were never-smokers [21]; however, the population of this previous study was collected from a mycobacterial laboratory registry database of a single medical center.

The other highlight of our study was the absence of an association between successful NTM-LD treatment in radiologic/bacteriologic outcomes and improvement in lung function of never-smokers. We considered that chronic inflammation due to NTM might have affected lung function decline even after successful treatment with anti-NTM chemotherapy.

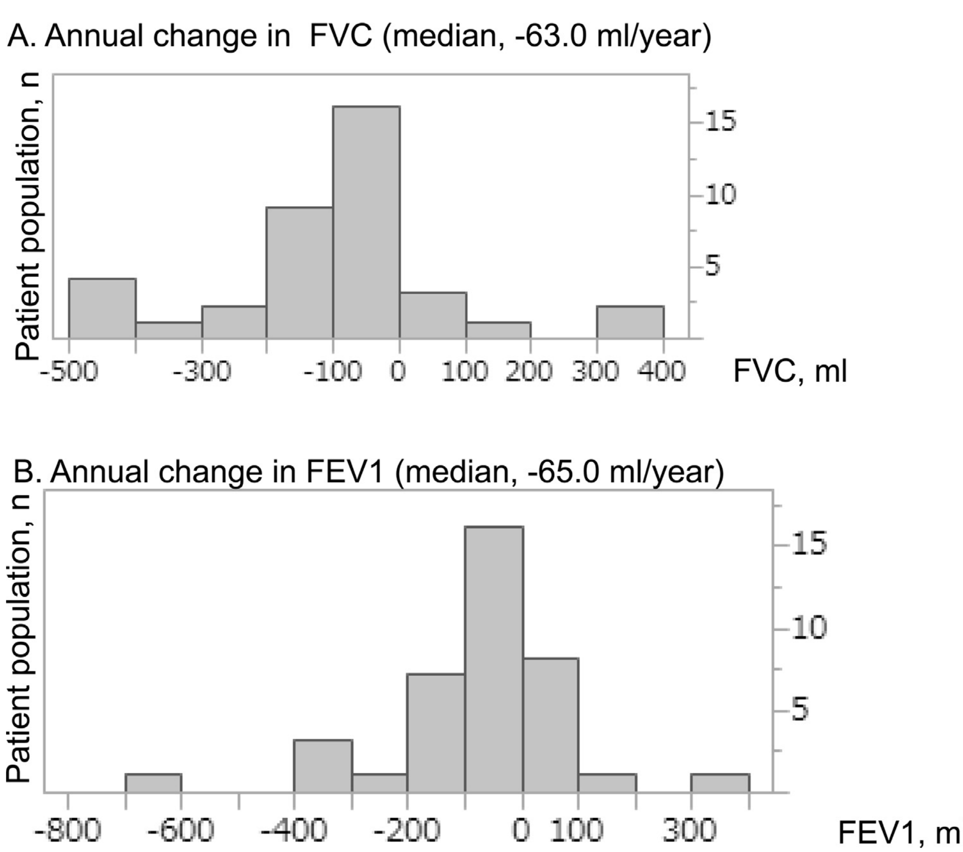

Fig. 1. Annual change in FVC and FEV_1.

Table 4
Relationship between radiologic/bacteriologic outcomes and rapid decline in lung function in never-smokers with nontuberculous mycobacterial lung disease.

	Total (n = 22)	Rapid FVC decline (n = 16)	Non rapid FVC decline (n = 6)	p-value	Rapid FEV_1 decline (n = 11)	No FEV_1 decline (n = 11)	p-value
Change in chest CT findings							
No deterioration	13	10	3	0.66	8	5	0.23
Deterioration	9	6	3		3	6	
Mycobacterial outcome							
Negative conversion	10	9	1	0.16	4	6	0.39
Relapse/persistent positive culture	12	7	5		7	5	

The impact of NTM-LD treatment on lung function change is controversial. With regard to antibiotic treatment, Khan et al. reported an improvement in FEV_1 in patients with MAC-LD [22], and Park et al. found that treatment failure of NTM-LD was an important predictor of lung function decline [15]. In contrast, Mehta et al. observed no substantial changes in lung function [23].

The present study focused on lung function decline in NTM-LD without the effect of tobacco exposure in never-smokers alone. However, it remains unclear whether pulmonary function declined at the time of negative conversion due to the retrospective nature of the study. All patients with NTM-LD in this study had nodular bronchiectatic disease. In bronchiectasis, there is excessive airway inflammatory response secondary to bacterial stimulation; this airway hyper-reactivity correlates with bacterial burden and may persist even after the infection is controlled [24]. For patients with persistent decrease in lung function even after successful treatment of NTM-LD, effective management of bronchiectasis should be considered [25,26]. Henkle et al. reported that 55% of patients had a history of inhaled corticosteroid use in the US Bronchiectasis and NTM Research Registry, with relatively few patients taking suppressive antibiotic therapies (e.g., macrolide therapy) [27].Further studies are needed to assess whether the therapeutic intervention for NTM-LD would contribute the rate of improvement in lung function in the long term.

Our study did not clarify whether the impact on lung function decline in NTM-LD was caused by inflammation due to the NTM itself, regardless of tobacco exposure. Nevertheless, we suggest that NTM-LD in never-smokers is a progressive disease with heterogeneity in lung function changes. Low baseline lung function was associated with poor prognosis of NTM-LD [6]. Kim et al. reported that in the natural course of MAC disease, even in the presence of nodular bronchiectasis, low FEV_1 at baseline was associated with an increased risk of worsening chest CT findings [28]. In the present study, %-predicted FEV_1 at baseline was associated with FVC and FEV_1 decline. However, there are other confounding variables in the background of the patients with NTM-LD. The lung function in patients with NTM-LD could be affected by the exposure to ambient pollution [29] and passive smoking [30]. It could also be affected by the inflammation of other pathogens (e.g. *Pseudomonas aeruginosa*) and the heterogeneity of treatment regimens (including macrolide vs not including macrolide).

The present study had several limitations. First, its retrospective nature has resulted in a small sample size and selection bias.Second, it could also be affected by the inflammation of other pathogens and the heterogeneity of treatment regimens. Third, we performed PFTs without evaluating residual volume (RV) routinely. Mehta et al. reported that RV may be improved in asthmatic patients with NTM-LD [23], and a recent study suggested that RV reversibility would be a good indicator of small airway dysfunction in bronchiectasis [31]. A prospective observational study of patients with NTM-LD should examine the association between therapeutic response and change in lung function based on PFTs at regular intervals.

Conclusion

In never-smokers with NTM-LD, lung function can decline. There was no association between successful NTM-LD treatment in radiologic outcomes and improvement in lung function of never-smokers.

Ethics approval and consent to participate

This study was approved by the institutional review board of National Hospital Organization Kinki-Chuo Chest Medical Center (No. 566, date of approval: December 22, 2016). Informed consent was waived because of the retrospective nature of the study.

Disclosure

Not applicable.

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Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

Not applicable.

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