IDENTIFYING NON-TUBERCULOUS MYCOBACTERIUM LUNG DISEASES IN ACID-FAST BACILLI POSITIVE PATIENTS

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Abstract. We conducted a case-control study by comparing the clinical and radiographic features of acid-fast bacilli positive patients with pulmonary tuberculosis (PTB) to those with non-tuberculous mycobacterium (NTM) lung diseases diagnosed according to American Thoracic Society (ATS) criteria. The occurrence of NTM lung disease was associated with persistence in symptoms after the fifth month of treatment (p=0.018), middle lobe involvement (p<0.01), lower lobe involvement (p=0.004), multiple lobe involvement (p=0.001) and reticulo-nodular infiltration (p=0.041). On logistic regression analysis, persistence of symptoms after 5 months of treatment (p<0.001), middle lobe involvement (p<0.001) and lower lobe involvement (p<0.05) were significant predictors of NTM lung disease. These findings suggest physicians should consider NTM lung disease if there is involvement of the middle lobe or lower lobes on chest radiography or the persistence of symptoms at the fifth month of treatment.

Key words: non-tuberculous mycobacterium, acid-fast bacilli, identification

INTRODUCTION

The rate of recovery of non-tuberculous mycobacterium (NTM) from sputum specimens with a positive acid-fast bacilli (AFB) smear varies by studied populations. It accounted for 1 to 2% of suspected tuberculosis (TB) cases in the 1950s and 1960s (Crow *et al*, 1957). A report from the Centers for Disease Control and Prevention (CDC) during 1979-1980 (Good and Snider, 1982) found NTM consisted of approximately one-third of mycobacteria isolated. Data from Philadelphia during the 1980s (Prince *et al*, 1989) showed a decrease in the prevalence of TB and an increase in the prevalence of NTM disease. The ratio of NTM to TB isolated increased from 1:3.2 to 1.6:1 during 1980s and 1990s at a South Carolina Community Hospital (Cox *et al*, 1994). NTM recovery rates are also high in Korea and Spain, at 10.6% (Jeon *et al*, 2005; Koh *et al*, 2005) and 21.1% (Coll *et al*, 2003), respectively.

Pulmonary disease can be caused by several NTM species (Dailloux *et al*, 2006; Shitrit *et al*, 2007; Park *et al*, 2007, 2008). NTM can be categorized into two distinct types: cavitary lesions of the upper lung lobes and nodular and bronchiectatic changes in the lungs (ATS, 1997). As a

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result of this, it is difficult for physicians to differentiate the active pulmonary tuberculosis (PTB) from NTM lung disease (Christensen *et al*, 1979, 1981).

Since culture results are required to confirm infection, the diagnosis of NTM may be delayed, especially in developing countries where sputum cultures are not routinely performed. The similarity in the clinical presentation of TB and NTM infection causes difficulty in making a diagnosis (Koh *et al*, 2002).

There are few current studies evaluating the differences in clinical and radiographic findings between the two diseases (Al Jarad *et al*, 1996; Koh *et al*, 2006). We evaluated the characteristics of patients infected with NTM to assist physician differentiating NTM lung disease from TB in acid-fast bacilli (AFB) smear positive patients.

MATERIALS AND METHODS

We enrolled patients over age 15 in our hospital with positive AFB sputum smears and cultures for mycobacterium during 2005-2006. TB patients were categorized as controls and NTM patients were categorized as cases. The diagnosis of NTM was made using American Thoracic Society (ATS) Guidelines for the Diagnosis of Non-tuberculous Mycobacterium, issued in 1997 (Anonymous, 2007). This study received approval from the ethics committee of Ramathibodi Hospital, Mahidol University, Thailand; no consent was obtained due to its retrospective design.

Review of clinical and radiographic findings

The medical records of all eligible patients were reviewed; sex, age, underlying disease, history of immunosuppressive drug use, family history of pulmonary tuberculosis (PTB), history of previous tuberculosis treatment, chief complaint, initial sputum AFB results, and the results of sputum for AFB after the second, fifth and sixth months of treatment were recorded.

Radiographic findings were reviewed to determine the presence and distribution of patchy infiltrations, reticulonodular infiltrations, reticular infiltrations, nodular infiltrations, cavitary lesions, bronchiectasis, military patterns, pleural effusions, lymphadenopathy, and volume loss. We also reviewed follow-up chest radiography results after the second, fifth and sixth month of treatment.

Statistical analysis

We used the unpaired *t*-test to evaluate for differences in continuous variables between the two groups. All categorical data were analyzed by the Pearson chi-square or Fisher's exact test. A logistic regression model was used to determine independent variables as predictors. A p-value <0.05 was considered statistically significance. We used STATA statistical software version 10 for all analyses.

RESULTS

This study was comprised of 63 patients with PTB and 17 patients with NTM lung disease. Of the 17 NTM patients, 35% of patients had *Mycobacterium* abscesses and 29% had *Mycobacterium avium* complex (MAC). The mean ages of the patients with NTM and PTB were 51.2 and 46.9 years old, respectively. Underlying diseases in both groups included diabetes mellitus (DM), cirrhosis, HIV and chronic obstructive pulmonary disease (COPD).

On univariate analysis, there were no significant differences between patients with PTB and NTM lung disease in terms of sex, age, underlying disease, immuno-

Table 1
The clinical characteristics of patients with PTB and NTM lung disease.

Variables	NTM	PTB	*p*-value
Total cases	17	61	
Sex			
Male	7 (41%)	39 (61%)	0.16
Female	10 (58%)	24 (38%)	
Ages	51	47	
Underlying disease			
DM	1 (6%)	6 (10%)	0.67
HIV	2 (12%)	7 (11%)	0.94
None	13 (71%)	43 (68%)	0.33
Symptoms			
Dyspnea	1 (6%)	7 (11%)	0.524
Cough	10 (59%)	37 (59%)	0.994
Fever	3 (18%)	8 (13%)	0.559
Weight loss	1 (6%)	1 (2%)	0.314
Hemopthysis	2 (12%)	10 (16%)	0.674
Immunosuppressive drug use	2 (12%)	4 (6%)	0.6
Previous TB treatment	5 (29%)	9 (14%)	0.18
History of smoking	5 (29%)	17 (27%)	0.53

suppressive drug use, family history of PTB, previous TB treatment, smoking status or presenting symptoms (Table1).

The radiographic characteristics of NTM and TB are shown in Table 2. This study demonstrated reticulo-nodular infiltration is associated with the presence of NTM lung disease (p=0.041). There were no significant associations seen with patchy or reticular infiltrates and the type of mycobacterial infection.

A middle lobe infiltrate was observed in 59% of in NTM patients and 6% of PTB patients (p<0.01). A lower lobe infiltrate was seen in 71% of NTM patients and 30% of PTB patients (p=0.004). Multiple lobe lung involvement was seen in 94% of NTM patients and 46% of PTB patients (p=0.001). Upper lobe involvement, bronchiectasis and cavities were found in the majorities of PTB patients.

PTB patients were more likely to have symptom improvements by the fifth month than NTM patients (p=0.018). Symptom improvement was similar between the two groups by the second month of treatment. No association was seen with change in chest radiography during follow-up period and the presence of the NTM lung disease (Table 3).

On logistic regression analysis, the variables associated with NTM lung disease were right middle lobe infiltrates (p<0.01), lower lobe infiltrates (p=0.041) and the persistence of symptoms after the fifth month of treatment (p<0.01).

DISCUSSION

The earliest recognized pattern of NTM lung disease was cavitary lesions, predominantly involving the upper lobes, similar to that of the PTB (Koh *et al*, 2005).

Table 2
Univariate analysis of radiographic characteristics and distribution of pulmonary lesions in patients with PTB and NTM lung disease.

Variables	NTM, *n* (%)	PTB, *n* (%)	*p*-value
Radiographic findings			
Cavity	3 (18)	21 (33)	0.249
Patchy lesions	8 (47)	31 (49)	1.000
Reticulonodular lesions	9 (53)	16 (25)	0.041
Reticular lesions	2 (12)	9 (14)	1.000
Nodule	1 (6)	13 (21)	0.280
Bronchiectasis	4 (24)	8 (13)	0.271
Radiographic distribution			
Multi-lobar	15 (94)	25 (46)	0.001
Upper lobe	8 (47)	38 (60)	0.410
Middle lobe	10 (59)	4 (6)	<0.010
Lower lobe	12 (71)	19 (30)	0.004

Table 3
Clinical characteristics during follow-up of NTM and TB patients.

Variables	NTM, *n* (%)	PTB, *n* (%)	*p*-value
Follow-up information			
Persistence of symptoms			
At 2 months	5 (29)	7 (13)	0.103
At 5 months	4 (29)	2 (4)	0.018
At 6 months	2 (14)	2 (4)	0.206
Persistence of CXR findings			
At 2 months	6 (35)	14 (16)	0.104
At 5 months	0	7 (11)	0.329
At 6 months	2 (13)	3 (5)	0.278

Christensen *et al* (1981) reported 12% of patients with MAC demonstrated fibronodular bronchiectasis radiographic pattern rather than a cavitary lesion. Unlike the previous report, this study did not demonstrate an association between the presence of bronchiectasis or cavity on chest radiography and the presence of NTM lung disease. Such a difference might be caused by our study design, which found the radiographic characteristics of PTB patients of cavities and bronchiectasis were more commonly seen. As a result, it was difficult to exhibit the association.

Our study demonstrated results in terms of the location of radiographic abnormalities similar to those found by Koh *et al* (2005): infiltrations of the middle and lower lobes were associated with NTM lung disease. Reticulo-nodular infiltrations

and multi-lobar involvement were more likely associated with NTM lung disease.

Field *et al* (2006) found HIV infection was associated with NTM lung disease. Our results differ from those of Field *et al* (2006) possibly because we had far fewer HIV patients in our study, making it less likely to demonstrate differences between cases and controls.

The small number of TB cases in the present study was due to enrolling only patients with positive results on both sputum smear and culture, representing approximately one-third of total cases of tuberculosis per year. As a result of this, this study was less powerful. However, the finding of an association between middle lobe and the lower lobe infiltrations on initial chest x-ray should be beneficial to physicians to consider obtaining sputum cultures for mycobacterium, especially in physicians working in developing countries. Physicians should also be aware the persistence of symptoms beyond the fifth month of treatment may indicate NTM lung disease or MDR TB.

REFERENCES

Al Jarad N, Demertzis P, Jones DJ, *et al*. Comparison of characteristics of patients and treatment outcome for pulmonary non-tuberculous mycobacterial infection and pulmonary tuberculosis.*Thorax* 1996; 51: 137-9.

American Thoracic Society (ATS). Diagnosis and treatment of disease caused by nontuberculous mycobacteria. *Am J Respir Crit Care Med* 1997; 156 (suppl): 1-25.

Anonymous. An official ATS/IDSA statement: diagnosis,treatment, and prevention of nontuberculous mycobacterial diseases **s** *Am J Respir Crit Care Med* 2007; 175: 367-416.

Christensen EE, Dietz GW, Ahn CH, *et al*. Initial roentgenographic manifestations of pulmonary *Mycobacterium tuberculosis*, *M. kansasii*, and *M. intracellularis* infections. *Chest* 1981; 80: 132-6.

Christensen EE, Dietz GW, Ahn CH, *et al*. Pulmonary manifestations of *Mycobacterium intracellularis*. *AJR Am J Roentgenol* 1979; 133: 59-66.

Coll P, Garrigo M, Moreno C, Marti N. Routine use of Gen-Probe Amplified Mycobacterium Tuberculosis Direct (MTD) test for detection of *Mycobacterium tuberculosis* with smear-positive and smear-negative specimens. *Int J Tuberc Lung Dis* 2003; 7: 886-91.

Cox JN, Brenner ER, Bryan CS. Changing patterns of mycobacterial disease at a teaching community hospital. *Infect Control Hosp Epidemiol* 1994; 15: 513-5.

Crow HE, King CT, Smith CE, Corpe RF, Stergus I. A limited clinical, pathologic, and epidemiologic study of patients with pulmonary lesions associated with atypical acid-fast bacilli in the sputum. *Am Rev Tuberc* 1957; 75: 199-222.

Dailloux M, Abalain ML, Laurain C, *et al*. Respiratory infections associated with nontuberculous mycobacteria in non-HIV patients. *Eur Respir J* 2006; 28: 1211-5.

Field SK, Cowie RL. Lung disease due to the more common nontuberculous mycobacteria. *Chest* 2006; 129: 1653-72.

Good RC, Snider DE. Isolation of nontuberculous mycobacteria in the United States. *J Infect Dis* 1982; 146: 829-33.

Jeon K, Koh WJ, Kwon OJ, *et al*. Recovery rate of NTM from AFB smear-positive sputum specimens at a medical centre in South Korea. *Int J Tuberc Lung Dis* 2005; 9: 1046-51.

Koh WJ, Kwon OJ, Lee KS. Diagnosis and treatment of nontuberculous mycobacterial pulmonary diseases: a Korean perspective. *J Korean Med Sci* 2005; 20: 913-25.

Koh WJ, Kwon OJ, Lee KS. Nontuberculous mycobacterial pulmonary diseases in

immunocompetent patients. *Korean J Radiol* 2002; 3: 145-57.

Koh WJ, Yu CM, Suh GY, *et al*. Pulmonary TB and NTM lung disease: comparison of characteristics in patients with AFB smear-positive sputum *Int J Tuberc Lung Dis* 2006; 10: 1001-7.

Park S, Suh GY, Chung MP, *et al*. Clinical significance of *Mycobacterium fortuitum* isolated from respiratory specimens. *Respir Med* 2008; 102: 437-42.

Park HY, Koh WJ, Kwon OJ, *et al*. Pulmonary disease caused by *Mycobacterium xenopi*: the first case in Korea. *Yonsei Med J* 2007; 48: 871-5.

Prince DS, Peterson DD, Steiner RM, *et al*. Infection with *Mycobacterium avium* complex in patients without predisposing conditions. *N Engl J Med* 1989; 321: 863-8.

Shitrit D, Priess R, Peled N, Bishara G, Shlomi D, Kramer MR. Differentiation of *Mycobacterium kansasii* infection from *Mycobacterium tuberculosis* infection: comparison of clinical features, radiological appearance, and outcome. *Eur J Clin Microbiol Infect Dis* 2007; 26: 679-84.