J Infect Chemother 21 (2015) 352–356

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original article

Increasing patients with pulmonary *Mycobacterium avium* complex disease and associated underlying diseases in Japan

Yutaka Ito [a, c, *], Toyohiro Hirai [a], Kohei Fujita [d], Koichi Maekawa [e], Akio Niimi [c], Satoshi Ichiyama [b], Michiaki Mishima [a]

[a] *Department of Respiratory Medicine, Kyoto University, Kyoto, Japan*
[b] *Clinical Laboratory of Medicine, Kyoto University, Kyoto, Japan*
[c] *Department of Respiratory Medicine, Allergy and Clinical Immunology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan*
[d] *Division of Respiratory Medicine, National Hospital Organization Kyoto Medical Center, Kyoto, Japan*
[e] *Division of Respiratory Medicine, Takeda General Hospital, Kyoto, Japan*

ARTICLE INFO

Article history:
Received 28 August 2014
Received in revised form
20 November 2014
Accepted 1 January 2015
Available online 9 January 2015

Keywords:
Nontuberculous mycobacteria
Mycobacterium avium complex
Collagen vascular disease
Rheumatoid arthritis

ABSTRACT

This study was conducted to evaluate trends in the isolation of strains of nontuberculous mycobacteria (NTM) and trends in the number of patients with pulmonary *Mycobacterium avium* complex (MAC) disease. We retrospectively reviewed microbiological results and clinical data to identify patients who were diagnosed with pulmonary MAC disease at Kyoto University Hospital in Japan between 2000 and 2013. NTM were isolated from 6327 of 80,285 samples (7.9%) for mycobacterial culture. The proportion of NTM isolates among all mycobacterial isolates increased from 355 of 792 samples (44.8%) in 2000 to 688 of 847 samples (81.2%) in 2013. MAC was most frequently observed (5436 isolates, 85.9%), followed by *Mycobacterium abscessus* (175 isolates, 2.8%) and *Mycobacterium kansasii* (74 isolates, 1.2%). A total of 592 patients with pulmonary MAC disease were identified (age, 66.0 ± 11.5 years; females, 61.1%). Compared with the early cohort (2000–2006, 236 patients), more patients in the late cohort (2007–2013, 356 patients) had an underlying disease (157 [66.5%] vs. 284 [79.8%], P = 0.0003), a Charlson comorbidity index score ≥1 (115 [48.7%] vs. 213 [59.8%], P = 0.008), collagen vascular disease (18 [7.6%] vs. 60 [16.9%], P = 0.001), rheumatoid arthritis (11 [4.7%] vs. 41 [11.5%], P = 0.004), and used immunosuppressive drugs (22 [9.3%] vs. 63 [17.7%], P = 0.004). The numbers of patients with lung disease, malignant disease and diabetes mellitus increased; however, their frequencies did not differ. The recovery rate of NTM and patients with pulmonary MAC disease increased, especially in patients with collagen vascular disease or rheumatoid arthritis or who used immunosuppressive drugs.

1. Introduction

The prevalence of nontuberculous mycobacteria (NTM) disease has increased in several countries. Previous population-based studies have demonstrated a 1.5- to 3-fold increase in the isolation of NTM and the prevalence of pulmonary NTM disease in Canada, the USA, England and Australia [1–5]. The annual incidence of pulmonary NTM disease increased 4-fold from 2000 to 2008 at a tertiary care center in Taiwan [6]. The rate of NTM recovery from respiratory specimens increased approximately 6-fold from 2000 to 2011 at a tertiary referral hospital in South Korea [7].

Mycobacterium avium complex (MAC) disease is the most frequently observed NTM disease [8–10]. Although pulmonary MAC disease had predominantly presented in a fibrocavitary form in elderly males with chronic lung disease and cavitary disease, the prevalence of a nodular bronchiectatic form that occurs mostly in elderly female patients with no apparent preexisting lung disease has increased [10]. Among the various underlying diseases in patients with pulmonary MAC disease, chronic obstructive pulmonary disease (COPD) was more common in the USA, Denmark and Germany [8,11,12], whereas previous tuberculosis (TB) is more common in Japan and Korea [13,14]. COPD and asthma patients

* Corresponding author. Department of Respiratory Medicine, Allergy and Clinical Immunology, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, Aichi 467-8601, Japan. Tel.: +81 52 853 8216; fax: +81 52 852 0849.
E-mail address: yutaka@med.nagoya-cu.ac.jp (Y. Ito).

http://dx.doi.org/10.1016/j.jiac.2015.01.004
1341-321X/

treated with inhaled corticosteroid (ICS) therapy and patients using immunosuppressive agents and tumor necrosis factor (TNF)-α antagonists have an increased risk of pulmonary NTM disease [15–17]. However, Al-Houqani et al. reported that COPD and use of a TNF-α antagonist resulted in a smaller increase in pulmonary MAC disease [18].

In Japan, the prevalence of NTM disease was estimated to be 33–65/100,000 [19]. Although more than half of patients with pulmonary MAC disease were male in the 1980s, the number of female patients increased after 1996 and accounted for 70% of patients [20]. Although the annual incidence of pulmonary MAC disease was nearly stable in one hospital in Japan between 1996 and 2002 [20], the trend after 2003 has not been previously reported.

The aim of this study was to evaluate trends in the isolation of NTM strains, trends in the number of patients with pulmonary MAC disease and trends in their underlying diseases over a 14-year period in a university hospital in Japan.

2. Materials and methods

We retrospectively reviewed microbiological results from the electronic laboratory record system at Kyoto University Hospital (1121 beds) between January 2000 and December 2013 and identified patients who met the 2007 American Thoracic Society microbiological criteria for pulmonary NTM disease [10]. Culture was performed using the BACTEC Mycobacteria Growth Indicator Tube 960 system (BD, Franklin Lakes, NJ, USA). Identification of *Mycobacterium tuberculosis, M. avium* and *Mycobacterium intracellulare* strains was performed using the COBAS Amplicor polymerase chain reaction (PCR) assay or the COBAS TaqMan MAI test (Roche Diagnostics, Basel, Switzerland). Because PCR primers used before 2001 could not discriminate between *M. avium* and *M. intracellulare*, unspecified isolates were designated as MAC isolates. DNA–DNA hybridization was performed with the DDH Mycobacteria Kit (Kyokuto Pharmaceutical Industrial Co., Tokyo, Japan) to identify other mycobacterial species than *M. tuberculosis, M. avium* and *M. intracellular*. The medical records of each patient with pulmonary MAC disease were reviewed, and clinical data, including demographic characteristics, microbiological results and the presence of underlying diseases at diagnosis of pulmonary MAC disease, were collected. The Charlson comorbidity index (CCI) score at the time of diagnosis was calculated for each patient. Patients with chronic lung disease included those who were dyspneic with moderate activity and without treatment or those who were dyspneic only and experienced asthma attacks. Patients with active malignant disease included those who were initially treated in the last five years [21]. The cohort was divided into the early cohort (2000–2006) and the late cohort (2007–2013). The institutional review board of Kyoto University approved the research protocol.

JMP version 10.0 (SAS Institute, Cary, NC, USA) was used for all statistical analyses. The variables were compared between the early cohort and the late cohort using the chi-square test, Fisher's exact test and the Wilcoxon test. Comparisons of more than two groups were performed using analysis of variance. A P value of <0.05 was considered statistically significant.

3. Results

3.1. Annual incidence of mycobacterial isolates

From 2000 to 2013, the laboratory at Kyoto University Hospital received 80,285 clinical samples for mycobacterial culture. *M. tuberculosis* and NTM were isolated from 3777 samples (4.7%) and 6327 samples (7.9%), respectively. *M. tuberculosis* and NTM, respectively, were isolated from 2143 samples (5.3%) and 2473 samples (6.2%) of 40,205 samples in the early cohort and 1634 samples (4.1%) and 3854 samples (9.6%) of 40,080 samples in the late cohort. The proportion of NTM isolates among all isolates of acid-fast bacilli increased from 355 of 792 samples (44.8%) in 2000 to 688 of 847 samples (81.2%) in 2013 and from 2473 of 4614 samples (53.6%) in the early cohort to 3854 of 5488 samples (70.2%) in the late cohort. In the 6327 NTM isolates, MAC was most frequently observed (5436 isolates, 85.9%), followed by *Mycobacterium abscessus* (175 isolates, 2.8%) and *Mycobacterium kansasii* (74 isolates, 1.2%). Among the 4899 MAC isolates for which the species were specified, 3415 isolates (69.7%) were *M. avium*, and 1484 isolates (30.3%) were *M. intracellulare* (Fig. 1).

When the numbers of isolates were counted as one isolate from one patient each year, *M. tuberculosis* and NTM, respectively, were isolated from 877 samples (3.0%) and 2807 samples (10.0%) among 28,208 clinical samples. *M. tuberculosis* and NTM, respectively, were isolated from 464 samples (3.5%) and 1043 (7.8%) samples of 13,363 clinical samples in the early cohort and 413 samples (2.8%) and 1764 (11.9%) samples of 14,845 clinical samples in the late cohort.

3.2. Characteristics of patients with pulmonary MAC disease

During the study period, 592 patients with pulmonary MAC disease were identified. Diagnostic sources were sputum in 440 patients, specimen obtained through bronchoscopy in 128 patients and lung tissue in 24 patients. The mean age was 66.0 ± 11.5 years at diagnosis, and females predominated (362 patients, 61.1%). Lung disease, malignant disease and collagen vascular disease were the most frequent conditions. Male patients had more underlying diseases, including lung diseases, previous TB, interstitial pneumonia, COPD, asthma, malignant disease, diabetes mellitus and chronic heart disease, compared with female patients, whereas female patients had more collagen vascular diseases, including rheumatoid arthritis (RA), compared with male patients (Table 1).

3.3. Trends in the underlying diseases that significantly increased

The annual frequency of newly diagnosed patients increased from 24 patients in 2000 to 54 patients in 2013, which is an approximate 2-fold change (Fig. 2). A 1.5-fold increase was observed from the early cohort (236 patients, 39.9%) to the late cohort (356 patients, 60.1%). Diagnostic sources in the early cohort and in the late cohort, respectively, were sputum in 180 patients (40.9%) and 260 patients (59.1%), specimen obtained through bronchoscopy in 45 patients (35.2%) and 83 patients (64.8%), and lung tissue in 11 patents (45.8%) and 13 patients (54.2%). The mean

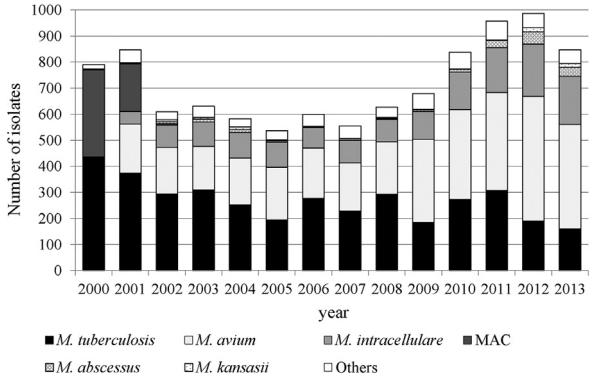

Fig. 1. Number of mycobacterial species isolated each year from 2000 to 2013. MAC, *Mycobacterium avium* complex.