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NONTUBERCULOUS MYCOBACTERIA IN KOREA

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Since *M. smegmatis* was identified as a first identified nontuberculous mycobacteria (NTM) in 1885, 71 species of mycobacterium have been either recognized or proposed[1]. After the first report of disseminated NTM infection in an AIDS patient in 1982[2], the number of NTM patients has dramatically increased in the developed world, where the prevalence of TB is very low[3,4]. However, the prevalence of NTM in AIDS patients remains low in Africa where TB is endemic[5,6]. In Japan, NTM was reported to be increasing in-line with a reduction in TB[7]. In Korea, during the past 30 years, the prevalence of TB has dramatically reduced from 5.1% in 1965 to 1% in 1995[8]. In this context, we felt it important to review the epidemiology of NTM in Korea. The purpose of this presentation is to describe the epidemiology and clinical implications of NTM disease in Korea.

Epidemiology

In 1966, the first report of NTM isolation from soil was published[9]. Although attempts have been made to estimate the prevalence of NTM infection by skin testing[10], the real situation in Korea could only be estimated after the Korean Institute of Tuberculosis commenced mycobacteria species identification in 1981 according to the Runyon classification[11]. The institute used biochemical testing to identify individual NTM species from 1992[12] and PCR-RFLP of *rpoB* gene from 2001[13].

Thus, we reviewed the database of the Korean Institute of Tuberculosis, which is the national referral TB laboratory, and found that the number of NTMs isolated from clinical samples has increased, especially after 2000[14] (Table 1). As mentioned above, during the same period, the prevalence of active tuberculosis has decreased from 5.1% in 1965 to 1.0% in 1995[8]. The most commonly isolated NTM from 1992 to 2002 was *M. avium-intracellulare* complex (MAC), followed by *M. abscessus*, *M. fortuitum*, *M. gordonae* and *M. kansasii*. The observed increase in the number of NTM isolates may be attributed to increases in MAC, *M. chelonae* complex (especially *M. abscessus*), *M. gordonae*, and *M. kansasii*. Throughout the period 1992–2002, the number of MAC cases increased from 245 to 769, *M. chelonae* complex from 32 to 279, *M. gordonae* from 5 to 126, and *M. kansasii* from 1 to 62.

Nontuberculous mycobacteriosis in Korea

The first case of NTM disease in Korea was reported in 1981[15], and was a case of *M. avium-intracellulare* complex pulmonary disease. Although other sporadic reports of NTM diseases followed[16,17], the real incidence of NTM disease in Korea was documented for the first time by a national survey upon NTM diseases in 1995[18]. Cases of isolated NTM were collected at the Korean Institute of Tuberculosis from 1981 to 1994. Analysis was performed on 158 patients thought to have NTM disease. The number of patients with NTM diseases was very low, between 1 and 10, from 1981 to 1993 ; however, it increased dramatically in 1994 (96 cases). *M. avium-intracellure* complex was found to have been the major etiologic factor (65%), followed by *M. fortuitum* (13%), *M. chelonae* (10%) and *M. gordonae* (4%) (Table 2). Ninety patients (57%) were over 60 years and the male to female ratio was 2.6 : 1, and 98 patients (62%) lived in Seoul, the largest Korean city. One hundred and thirteen patients (72%) had a history of tuberculosis, 10 (6%) a history of COPD, 6 (4%) bronchiectasis, and 6 patients pulmonary fibrosis. The most common extra-pulmonary disease was diabetes (6%). The major patients complaints were cough (62%) or sputum (61%) ; dyspnea (30%), hemoptysis (21%), and weight loss (13%) were also common. Forty-two patients (27%) had cavitary lesions and 18 patients (11%) pleural effusion. One hundred and twenty nine (82%) out of 158 patients underwent

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Table 1 The number of NTM isolated in Korean Institute for Tuberculosis, 1997–2002[14]

Organism	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
M. avium-intracellulare	245	302	329	287	266	253	551	499	593	693	769
M. fortuitum	49	66	60	41	27	20	47	62	56	92	184
M. chelonae complex	32	34	43	55	23	28	63	92	88	166	279
M. chelonae	n-a	n-a	n-a	n-a	n-a	n-a	n-a	n-a	n-a	8	18
M. abscessus	n-a	n-a	n-a	n-a	n-a	n-a	n-a	n-a	n-a	158	261
M. scrofulaceum	1	3	15	2	3	0	4	0	0	0	2
M. terrae complex	14	25	43	27	8	5	32	25	35	3	52
M. szulgai	3	2	9	5	0	6	6	13	18	12	15
M. gordonae	5	12	21	10	15	9	22	39	18	31	126
M. kansasii	1	9	21	18	16	12	22	26	35	47	62
M. celatum	0	0	0	0	0	0	12	8	11	7	10
M. marinum	0	0	0	0	0	2	1	0	1	1	0
M. smegmatis	0	0	0	0	0	0	0	0	0	0	0
Unidentifiable	98	250	608	403	558	752	422	400	314	559	63
Total number	448	703	1149	848	916	1087	1182	1164	1169	1777	1841

Table 2 The frequency of each mycobacteria causing diseases from 1981–1994 in Korea[18]

Species	N (%)
M. avium-intracellulare	103 (65.2)
M. fortuitum	20 (12.7)
M. chelonae	15 (9.5)
M. gordonae	7 (4.4)
M. terrae	5 (3.2)
M. scrofulaceum	3 (1.9)
M. kansasii	2 (1.3)
M. szulgai	2 (1.3)
M. avium intracellulare and *M. terrae*	1 (0.6)
Total	158 (100)

treatment, 86 patients (67%) were treated with an isoniazid and rifampicin based regimen and 30 patients (23%) with isoniazid or rifampicin based regimens. Thirty-six patients (28%) improved clinically with treatment, 65 (50%) showed no change and 8 patients deteriorated or died. Data on the other 49 patients were insufficient.

NTM diseases in Seoul National University Hospital (SNUH)

From Jan. 1998 to Jun. 2002, NTM was isolated at least once in sputum, bronchial washing or excised tissue from 154 patients at SNUH. Of these, 55 patients met the diagnostic criteria of NTM disease as proposed by the American Thoracic Society[19]. The number of NTM disease cases annually at SNUH increased from 8 cases in 1998 to 22 in 2001. Sixty percent (33 patients) of these cases were caused by *M. avium-intracellulare*, 13% (7 patients) by *M. chelonae* complex, 9% by *M. fortuitum*, and 4% by *M. gordonae*. Interestingly, among 99 patients with NTM colonization without clinical disease, *M. avium-intracellulare* occurred in only 32% (32 patients), and *M. fortuitum* in 22% (22 patients). Thirty patients (56%) among these 54 had a history of tuberculosis. The other 24 patients were previously diagnosed to have bronchiectasis (40%), COPD (13%) or idiopathic pulmonary fibrosis (4%). Chest-CT was performed in 50 patients of 55 with NTM diseases. The most common findings by chest CT were bronchiectasis (68%) and nodules (56%). Other common findings included cavitary lesion (24%), atelectasis (24%), focal fibrosis (24%), emphysematous features (20%), and consolidative lesion (20%). NTM causing clinical diseases showed a high level of resistance (>70%) to isoniazid, rifampicin, streptomycin and to ethambutol.

M. kansasii disease in Korea[14]

The number of isolated *M. kansasii* rapidly increased from only 1 in 1992 to 62 in 2002. During the period Jan. 1997 to Dec. 2002, *M. kansasii* was isolated 204 times from 150 patients. Among these, the number of patients positive for *M. kansasii* by culture more than twice was 30. Among these 30 patients, we excluded 7 from analysis because of insufficient clinical data and another 2 due to a positive *M. tuberculosis* culture in same period. Of the other 21 patients, 6 patients were excluded because their pulmonary lesion in chest radiographs didn't improve after at least 6 months of isoniazid and rifampicin-based treatment. Even though *M. kansasii* was isolated more than twice from the sputum of these 6 patients, we decided that in these patients *M. kansasii* might be a colonizer rather than a true pathogen.

We reviewed the clinical characteristics of the remaining 15 patients with probable *M. kansasii* lung diseases. Twelve were males of mean age 42.9 years, and all lived in urban areas. Nine patients (60%) had a history of TB. The frequent symptoms were cough (53%), hemoptysis (13%), dyspnea (7%) and fatigue (7%). By chest radiography, half of the patients (47%) had a cavitary lesion and the right upper lobe was the most commonly involved site (52%). Twelve patients

were treated with an isoniazid and rifampicin based regimen. The other three were treated with rifampicin/cycloserine/prothionamide/ofloxacin, rifampicin/ethambutol/pyrazinamide/prothionamide or rifampicin/cycloserine/pyrazinamide/prothionamide. With treatment, culture-conversion occurred in 10 patients, and smear-conversion was identified in three. In these 3 patients no follow-up culture was done after smear-conversion. In another 2 patients, follow-up culture was not done after diagnosis. Lesions in chest radiographs completely disappeared in two, and improved with some residual lesion in 13. These clinical characteristics of *M. kansasii* lung diseases, such as, male dominance, predilection for urban residents and cavitary lesion in RUL well match other reports on *M. kansasii* lung diseases [20)~23)].

Conclusion

In concert with a reduction of TB prevalence in Korea, the number of NTM isolations has dramatically increased, particularly from the 1990's. *M. avium-intracellulare* complex (MAC), *M. abscessus*, *M. fortuitum*, *M. gordonae* and *M. kansasii* are common species. As has been confirmed by national survey of NTM diseases by the Korean Academy of Tuberculosis and Respiratory Diseases, NTM diseases are increasing rapidly in Korea commensurate with the decreasing prevalence of TB. Moreover, *M. kansasii* pulmonary disease, usually found in urban areas, is also increasing.

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