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Epidemiologic Characteristics of Extrapulmonary Tuberculosis in Korea, 1995-2010: Microbiological Diagnosis versus Clinical Diagnosis

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Background: The aim of the present study was to investigate the epidemiologic characteristics of extrapulmonary tuberculosis (EPTB) in Korea. In addition, the results of culture-confirmed (CC) EPTB were compared with those of clinically-diagnosed (CD) EPTB.
Methods: We retrospectively reviewed non-duplicate data of tuberculosis from the Samsung Medical Center from 1995 to 2010. A total of 6,249 and 38,726 cases of tuberculosis were CC and CD EPTB cases, respectively. The cases were categorized according to the type of specimen or by the clinically-affected sites.
Results: The proportions of EPTB among all tuberculosis cases were 12% (745/6,249) and 22% (8,608/38,726) of the CC and CD cases, respectively. The distribution of both age and gender between pulmonary tuberculosis (PTB) and EPTB cases were significantly different ($P<0.001$). The most common types of EPTB were tuberculous lymphadenitis, pleural TB, and abdominal TB. Pleural involvement was more common in males, while lymph node involvement was observed more frequently in females in both the CC and CD cases (M/F ratio in regards to pleura were 1.63 and 2.08, while M/F ratio in regards to the lymph node were 0.46 and 0.54).
Conclusion: The dataset of EPTB cases in Korea was first evaluated over a 16-year period and compared the cases of CC EPTB to those of CD EPTB. The epidemiologic characteristics of EPTB were different from that of PTB as well as the EPTB of other countries. The present study might provide useful information regarding the epidemiology of EPTB in Korea and other countries. **(Korean J Clin Microbiol 2012;15:92-97)**

Key Words: Extrapulmonary tuberculosis, Korea, Tuberculosis

INTRODUCTION

Tuberculosis (TB) remains one of the major public health problems causing significant morbidity and mortality worldwide. The most commonly involved site of TB is the respiratory tract, which results in pulmonary tuberculosis (PTB). Additionally, it can affect any sites of the body including lymph nodes, pleura, the gastrointestinal tract, and the genitourinary tract, which results in extrapulmonary tuberculosis (EPTB). The incidence and prevalence rate of TB and EPTB vary from country to country. According to the notification rate of TB, there were reported cases of 36,305 TB (74.3 cases per 100,000 people) and 8,129 EPTB (16.6 cases per 100,000) in Korea in 2010 (http://www.knta.or.kr/) [1]. The reported proportion of EPTB among all TB in Korea from 2004 to 2010 was 11% (3,556/31,503), 15% (5,171/35,269), 14% (5,044/35,361), 14% (5,005/34,710), 17% (5,813/34,157), 19% (6,923/35,845), and 22% (8,129/36,305) during successive years [1]. However, considering lower voluntary reporting, diagnostic difficulty of EPTB, and missed cases, it is likely that actual proportion of EPTB was much higher than what was reported.

Studies have been conducted on EPTB epidemiology according to the region and the country. The proportion of EPTB in the United States (USA) was 18.7% (47,293/253,299) during 1993-2006 [2]. The most commonly affected sites of EPTB in the USA were lymph nodes (40%), pleura (20%), and bone and/or joint (11%) [2]. Another epidemiologic study showed that the proportion of EPTB in England and Wales increased from 48% in 1999 to 53% in 2006 [3]. A study in Turkey dem-

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onstrated that EPTB prevalence during 2001-2007 was 26% (103/397) of total TB, and the most common types of EPTB were genitourinary TB (27%) and meningeal TB (19%) [4]. Except for the last study performed in Turkey, several prior studies regarding EPTB have been performed using cases diagnosed clinically based on histological, radiological, and microbiological evidence (Table 1) [2,4-13]. Only some of these clinically-diagnosed (CD) cases were confirmed by microbiological culture. So far, there have been few studies regarding microbiologically-confirmed EPTB.

The aim of the present study was to investigate the characteristics of EPTB at a tertiary hospital in Seoul, Korea. In addition, the data of culture-confirmed (CC) EPTB were compared with those of CD EPTB.

METERIALS AND METHODS

1. Study design and study subjects

This study was performed using the data obtained at Samsung Medical Center, which is the second largest medical center located in Seoul, Korea, from January 1, 1995 to December 31, 2010. Samsung Medical Center is a tertiary care center with 2,005 beds and about 7,500 outpatients per year in Seoul, which has a population of about 10,039,000 (http://kostat.go.kr/portal/korea/index.action) [14]. For this study, the CC cases were defined as TB confirmed via the mycobacterial culture method, which is the gold standard for the diagnosis of TB. In contrast, the CD cases were defined as TB via the clinical judgment based on clinical, radiological, histological, as well as microbiological methods. By definition, the CD cases included the CC cases in the current study. We retrospectively reviewed the data regarding both cases with clinical diagnosis of TB and culture-positive TB. All the study subjects were non-duplicated during the study period, and the age was selected at the time of diagnosis of TB. The cases of EPTB with concurrent PTB were excluded, while the cases of EPTB involved simultaneously in the various sites were all included according to the sites. The subjects were categorized according to the type of culture-positive specimen or clinically-affected sites. The cases of EPTB were defined as TB diagnosed in any site other than the respiratory tract.

2. Culture of *Mycobacterium tuberculosis*

The culture of Mycobacterium from a clinical specimen was done in Ogawa medium using conventional solid egg-based

Table 1. Prior studies on extrapulmonary tuberculosis

	Clinically-diagnosed cases using clinical, radiological, histological, and microbiologic methods											CC* cases	
	Peto, 2009 [2]	Fiske, 2010 [5]	Garcia-Rodriguesz, 2011 [6]	te Beek, 2006 [7]	Sreeramareddy, 2008 [8]	Ilgazli, 2004 [9]	Fader, 2010 [10]	Al-Otaibi, 2010 [11]	Wiwatworapan, 2008 [12]	Kim, 2009 [13]	This study	Gunal, 2011 [4]	This study
Subjects	United States	Tennessee	Caucasian	Netherlands	Nepal	Turkey	Afghanistan	Saudi Arabia	Thailand	Korea	Korea	Turkey	Korea
Duration	1993-2006	2000-2006	1991-2008	1993-2001	2003-2006	1996-2000	2006-2008	2001-2007	2007	2004-2006	1995-2010	2001-2007	1995-2010
Number	47,293	564	705	5,042	230	636	118	248	398	40	8,608	103	745
Proportion	19%	26%	37%	38%	49%	31%	-	58%	47%	13%	22%	26%	12%
Male/female	24,624/22,660	348/216	227/306	2,610/2,432	119/111	345/291	39/79	120/128	228/170	198/122	4,020/4,588	55/48	370/375
Mean age (range)	44 (0-105)	43†	44 (11-95)	45-64‡	29.5†	23 (1-86)	32	20-29‡	47.6	45† (20-74)	43	33†	49
Distribution of affected sites													
Pleura	20%	27%	41%	21%	-	31%	9%	12%	27%	-	25	10.7%	26
Lymph node	40%	32%	31%	39%	43%	56%	37%	42%	30%	20	31	9.7%	20
Bone and joint	11%	11%	6%	9%	12%	4%	12%	14%	25%	10	9	10.7%	16
Abdominal§	5%	3%	5%	4%	15%	2.8	7%	13%	3%	20	13	9.7%	18
Genitourinary	7%	6%	7%	4%	3%	2%	5%	4%	1%	-	6	27%	10
CNS	5%	4%	4%	2%	7%	1%	20%	4%	5%	3%	6	19%	7
Others	12%	17%	7%	21%	20%	4%	10%	11%	9%	47%	10	13%	2

*Culture-confirmed; †Median age; ‡Most common age group in each study; §Gastrointestinal tract and peritoneum.
Abbreviation: CNS, central nervous system.

methods. The automated broth-based system, BACTEC MGIT 960 system (Becton Dickinson, Franklin Lakes, NJ, USA), was used, along with traditional solid-based methods since February 2009. The final culture interpretations were done after 8 weeks (in case of the solid-based method) or 6 weeks (in case of the broth-based method) of incubation at 37 degree Celsius. In addition to the culture, Ziehl-Neelsen staining was also performed to find acid-fast bacilli (AFB). The differentiation of *Mycobacterium tuberculosis* (MTB) from Nontuberculous Mycobacteria (NTM) was based on the presence of cord formation with AFB staining, an MPT-64 antigen test (SD, Yongin, Korea), a Gen-Probe MTD test (Gen-Probe, Inc., San Diego, CA, USA), or Multiplex-PCR (M&D, Wonju, Korea). Specimens of stool and homogenized tissue were treated before incubation with 4%, and 1% NaOH-N-acetyl-L-cysteine (NaOH-NALC), respectively. All other specimens were treated before incubation with 2% NaOH-NALC except for the sterile sample.

3. Statistical analysis

Data were expressed as mean±SD. We compared the categorical data, such as age and gender, according to the type of specimen or involved sites using the chi-square test. *P* values less than 0.05 were considered statistically significant. All analyses were performed with the PASW version 19.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Clinically-diagnosed cases

Clinical diagnosis of TB consisted of 30,118 cases (78%) of PTB and 8,608 cases (22%) of EPTB during the study period (Table 2). In addition, the proportions of EPTB per year during 16 years ranged from 19-22% with a CV of 2.4%. Of the 8,608 EPTB cases, the most commonly involved types were tuberculous lymphadenitis (N=2,655, 31%), followed by pleural TB (N=2,147, 25%), abdominal TB (gastrointestinal tract and peritoneum; N=1,146, 13%), skeletal TB (N=737, 9%), genitourinary TB (N=504, 6%), CNS TB (N=494, 6%), others (N=548, 6%) and miliary TB (N=377, 4%) (Table 2).

The mean ages of patients with EPTB and PTB were 43 years and 47 years, respectively. The male to female (M/F) ratio was 0.88 (4,020/4,588) in EPTB, while it was 1.31 (17,058/13,060) in PTB. The distribution of both age and gender between PTB and EPTB cases were significantly different ($P<0.001$ for both,

Table 2. Characteristics of tuberculosis from 1995 to 2010

	Number	Proportion (%)	Age (years)*				Gender (M/F)
			<20	20-39	40-59	≥60	
I. Clinically-diagnosed cases							
Total PTB	30,118	78	1,926	8,816	9,979	9,397	1.31 (17,058/13,060)†
Total EPTB	8,608	22	712	3,326	2,669	1,901	0.88 (4,020/4,588)†
Tuberculous pleurisy	2,147	25	127	799	591	630	1.63 (1,332/815)
Tuberculous lymphadenitis	2,655	31	299	1,253	775	328	0.46 (839/1,816)
Skeletal tuberculosis	737	9	58	205	226	248	0.99 (367/370)
Abdominal tuberculosis	1,146	13	73	436	420	217	0.92 (549/597)
Genitourinary tuberculosis	504	6	16	168	221	99	1.07 (260/244)
CNS tuberculosis	494	6	51	190	154	99	1.19 (268/226)
Others (skin, ear, gland etc.)	548	6	53	157	176	162	0.73 (231/317)
Unclassified (miliary etc.)	377	4	35	118	106	118	0.86 (174/203)
II. Culture-confirmed cases							
Total PTB	5,504	88	145	1,792	1,626	1,941	1.45 (3,253/2,251)‡
Total EPTB	745	12	32	245	253	215	0.99 (370/375)‡
Pleura	197	26	9	80	54	54	2.08 (133/64)
Lymph node	148	20	2	67	22	24	0.54 (52/96)
Bone & joint	118	16	11	27	36	44	0.84 (54/64)
Gastrointestinal tract & periteneum	137	18	3	28	52	51	0.96 (67/70)
Genitourinary	77	10	2	21	31	23	0.97 (38/39)
CNS	51	7	5	18	8	20	0.55 (18/33)
Cardiac	9	1	0	1	1	7	2.00 (6/3)
Others (skin, ear, gland etc.)	8	1	2	3	1	2	0.33 (2/6)

*P value<0.001; †P value<0.001; ‡P value<0.001.
Abbreviations: PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis; CNS, central nervous system.

Table 2). In addition, pleural TB and CNS tuberculosis were seen more in males than females (The M/F ratios in pleural TB and CNS tuberculosis were 1.6 and 1.2, respectively). While tuberculous lymphadenitis and miliary tuberculosis were more frequent in females than males (The M/F ratios of tuberculous lymphadenitis and miliary tuberculosis were 0.5 and 0.9, respectively)

2. Culture-confirmed cases

The PTB and EPTB among the culture-positive cases were composed of 5,504 (88%) and 745 (12%) cases, respectively (Table 2). In addition, the proportions of EPTB per year during 16 years ranged from 5.3-21% with a CV of 3.4%. The distribution of EPTB in 745 culture-positive specimens were in the pleura (N=197, 26%), lymph nodes (N=148, 20%), bone and joint (N=118, 16%), gastrointestinal tract (N=80, 11%), peritoneum (N=57, 7%), genitourinary area (N=77, 10%), the CNS (N=51, 7%), cardiac region (N=9, 1%), and others (N=8, 1%) (Table 2).

The mean ages of patients with EPTB and PTB were 49 years and 50 years, respectively. The M/F ratio was 0.99 (370/375) in EPTB, while it was 1.45 (3,253/2,251) in PTB. The age and gender distributions were significantly different between PTB and EPTB ($P<0.001$ for both, Table 2). In addition, pleura and cardiac involvement were more common in males (The M/F ratio in pleura and cardiac EPTB were 2.1 and 2.0, respectively, Table 2). Lymph node and CNS involvement was observed more often in females (The M/F ratio was 0.5 for both, Table 2).

DISCUSSION

Although a national surveillance program has continuously decreased the incidence of PTB, the incidence of EPTB has significantly increased in Korea since 2007 [1]. These contrasting increases of EPTB were also previously reported in the U.S., in addition to the Caucasian population [2,6]. According to the National Tuberculosis Surveillance System from 50 states in the U.S., the proportion of EPTB was reported to be increased from 15.7% in 1993 to 21.0% in 2006 [2] That study revealed an association between EPTB and female gender, nonwhite race, foreign birth, and a disproportionately slower decrease in EPTB prevalence, compared with the decrease in PTB cases [2]. In addition, the Caucasian population also showed a proportional increase of EPTB, along with a decreased incidence of TB [6]. The causes of the proportional increase of EPTB in the Caucasian population were reported to be an increase of life expectancy and the female-predominant distribution, in addition to the decline of BCG-vaccinated patients. Based on these previous studies, the epidemiology of EPTB might be different from those of PTB. For effective TB control in Korea, an epidemiologic study of EPTB in the Korean population is also needed. However, little studies regarding EPTB have been conducted in Korea [13]. Herein, we investigated the proportion and distribution of EPTB in a large Korean population. In addition, we were the first to compare the cases of CC EPTB to those of CD EPTB in Korean patients.

The current study revealed that the overall proportions of EPTB cases during the 16 years examined were 22% and 12% among the CD and CC cases, respectively. The CC cases consisted of only culture-positive cases of all EPTB; thus, the number of actual CC cases might be underestimated. Indeed, the diagnosis of EPTB may be difficult due to nonspecific clinical manifestations, lower sensitivity of AFB staining and mycobacterial culture, and difficulties in obtaining direct specimens from the extrapulmonary sites compared to those of PTB. Among a total of 745 CC cases of EPTB, the pleura, lymph nodes, and gastrointestinal tract with peritoneum were the most commonly affected sites in the Korean population. In the same manner, tuberculous lymphadenitis, pleural TB, and abdominal TB were the most common types among 8,608 cases with clinical diagnoses of EPTB. There was no difference in distributions of EPTB in both CC and CD cases in the current study. However, according to previous studies, the results analyzed using the cases with clinical diagnosis of EPTB were significantly different from the results evaluated using culture-proven EPTB (Table 1) [4,9]. The one epidemiologic study revealed that EPTB was common in early adulthood (mean age 23 years) and lymph nodes was the most common sites in the Turkish city of Kocaeli during 1996-2000 (Table 1) [9]. However, the other study demonstrated that genitourinary TB and meningeal TB were most common two types in Malatya, Turkey, during 2001-2007 (Table 1) [4]. The former study was performed using the cases with diagnoses based on the clinical evidence of EPTB, while the latter study was done using only culture-confirmed cases of EPTB [4,9]. Indeed, the epidemiologic results might be different according to study design, as well as country, region, city, and time, such as the results from two different studies in Turkey. The current study firstly demonstrated that there was no difference in the distributions of EPTB when the cases of CC were compared to those of CD in Korean pop-

ulation during the same 16 years.

Interestingly, the proportions of EPTB per year were much more variable in CC cases than CD cases (The coefficient of variation from CC cases was 3.4%, while that from CD cases was 2.4%). There were some possible reasons for the variability in proportions of EPTB in the study duration. First, the national program for control of TB has been focused on PTB rather than EPTB, which results in the contrasting increase of EPTB. Second, the EPTB detection rate might be increased due to the improvement of diagnostic tests, including introduction of the broth-based culture method and interferon-gamma releasing assay, as well as the genotype-based assay. In the present study, the broth-based culture system was introduced in February 2009. Indeed, the proportion of culture-positive cases of EPTB was 12% (99/835) in 2007-2008, increasing to 20% (183/932) in 2009-2010 ($P<0.001$). Also, the proportions of CD cases of EPTB were 23% (1,027/4,449) and 25% (933/3716) in 2007-2008 and 2009-2010, respectively ($P=0.0352$).

The present study showed that the female gender and younger age were more prevalent in cases with EPTB compared with PTB cases. Pleural TB was more commonly found in males, while tuberculous lymphadenitis was more commonly observed in females in both CC and CD cases. However, there was a discrepancy in the M/F ratio of CNS TB between CC cases and CD cases (The M/F ratios of CNS TB were 1.19 and 0.55 in CD and CC cases, respectively). The previous study in Malatya, Turkey, showed that meningeal and bone and/or joint TB were commonly found in males, while lymphatic, genitourinary, and peritoneal TB were observed more in females [4].

In conclusion, the proportion and number of EPTB cases in Korea were increased during the study period, which was more significant in CC cases during 2007-2010. The epidemiologic characteristics of EPTB were different from those of PTB as well as EPTB from other countries. The most common types of EPTB were tuberculous lymphadenitis, pleural TB, and abdominal TB. Further study would be needed to find the causes of the increase in EPTB and to investigate the differences of radiologic and histologic findings among the cases.

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=국문초록=

국내 폐외결핵의 역학적 특성, 1995-2010: 미생물학적 진단과 임상진단의 비교

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배경: 본 연구에서는 국내 폐외결핵의 발생률과 역학적 특징을 조사하고자 하였다. 또한 배양을 통해 확진된 폐외결핵(culture confirmed-extrapulmonary tuberculosis, CC EPTB) 결과와 임상적 판단에 의해 진단된 폐외결핵(clinically diagnosed-extrapulmonary tuberculosis, CD EPTB) 결과를 비교하였다.

방법: 삼성서울병원에서 1995-2010 기간 동안 임상적으로 진단된 결핵 총 38,726예, 배양으로 확진된 총 6,249예를 대상으로 후향적으로 분석하였다. 폐결핵과 폐외결핵을 동시에 갖는 경우와 중복 검체는 제외하였으며, 여러 부위를 동시에 침범한 폐외결핵은 모두 포함하였다.

결과: 결핵 중에서 폐외결핵의 비율은 CC EPTB 12%, CD EPTB 22%로 확인되었다. CC EPTB와 CD EPTB 모두에서 폐외결핵은 나이와 성별 분포에 있어 폐결핵과 통계적으로 유의한 차이를 보였다($P<0.001$). 흔한 폐외결핵 형태는 결핵성 흉막염, 결핵성 림프절염, 복부 결핵이었다. 결핵성 흉막염은 남자에서 더 흔히 관찰되었고, 결핵성 림프절염은 여자에서 더 흔히 관찰되었다(남녀 비율; 결핵성 흉막염 1.63과 2.08, 결핵성 림프절염 0.46과 0.54).

결론: 본 연구를 통해 16년 동안의 국내 폐외결핵의 역학적 특징을 조사하였을 뿐만 아니라, 처음으로 폐외결핵의 임상진단과 미생물학적 진단의 결과를 비교하였다. CC EPTB의 발생률은 CD EPTB보다 낮았으나, 흔한 폐외결핵의 종류는 일치하였다. 국내 폐외결핵의 역학적 특성은 폐결핵과 달랐고, 다른 나라의 폐외결핵과도 다른 양상을 보였다. **[대한임상미생물학회지 2012;15:92-97]**

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