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Clinical Characteristics of Genitourinary Tuberculosis during a Recent 10-Year Period in One Center

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Purpose: This study was conducted to analyze the clinical characteristics and treatments of patients with genitourinary tuberculosis (GUTB) over the past 10 years.
Materials and Methods: The study population comprised 101 patients who were diagnosed with GUTB and hospitalized from January 2000 to December 2009. Acid-fast bacilli (AFB) smear, urine tuberculosis culture, urine tuberculosis polymerase chain reaction (PCR), intravenous urography, cystoscopy, and histopathologic findings were used for patient selection. Yearly proportion, gender, patient distribution according to age, history of tuberculosis, and presence of other organ tuberculosis were analyzed.
Results: The patients hospitalized with GUTB counted for 0.9% of all patients admitted to the department of urology. The sex ratio was 1:1.53 (male:female), and the patients' mean age was 45.57±12.55 years (range, 19-81 years). Among the patients, there was one immunocompromised patient. A total of 22 patients (21.8%) had a medical history of tuberculosis, mostly pulmonary tuberculosis (90.9%). The sensitivity of AFB stain, tuberculosis culture, and PCR was 41.6%, 55.4%, 33.7%, respectively. A total of 54 patients required additional surgical treatment: 30 cases of nephrectomy, 8 cases of epididymectomy, 8 cases of ureteral stent, 5 cases of nephrostomy, 1 case of ureterectomy, 1 case of augmentation cystoplasty, and 1 case of transurethral resection of prostate.
Conclusions: The frequency of GUTB tended to decrease progressively. However, GUTB is still a threat to public health. There was no previous history of tuberculosis in two-thirds of the cases of GUTB and more than half of them required further surgical treatment.

Key Words: *Prevalence; Tuberculosis, urogenital; Urology*

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INTRODUCTION

A World Health Organization Report in 2007 showed that the number of new patients with tuberculosis was 927 in 100,000, of whom 132 died [1]. The number of new patients in Korea was 32,010 (67.2 in 100,000) in 2002 and 30,687 (64 in 100,000) in 2003 [2]. In 2008, the number of new patients with extrapulmonary tuberculosis (EPTB) was 5,813, which accounted for 17.0% of all new patients with tuberculosis. The number of new genitourinary tuberculosis (GUTB) patients was 123 (0.4%) in 2008 and 146 (0.4%) in 2009, which ranked lowest [2,3]. Although EPTB, including GUTB, is relatively rare compared with pulmonary tuberculosis, interest in EPTB has increased according to increases in the number of patients with human immunodeficiency virus (HIV) infection and those using immunodepressants as well as according to a shift toward an elderly-aged society [4].

GUTB requires long-term antituberculous chemotherapy like pulmonary tuberculosis and other types of tuberculosis. Unlike pulmonary tuberculosis, the diagnostic sensitivity and specificity of urine tuberculosis tests are not as high, and GUTB requires a variety of surgical treatments [5]. Although the number of new patients with GUTB has de-

creased, various treatment modalities have been performed in clinical settings. Therefore, this study was conducted to investigate morbidity, diagnostic methods, and treatment modalities over a recent 10-year period and to compare the results with those reported by previous studies published in Korea.

MATERIALS AND METHODS

1. Patients

This study retrospectively analyzed a total of 101 patients with GUTB who were admitted and treated between January 2000 and December 2009. The patients underwent urine acid-fast bacillus (AFB) smear, the urine *Mycobacterium tuberculosis* culture test, polymerase chain reaction (PCR) for urine *M. tuberculosis*, intravenous urography, computed tomography, cystoscopy, or histopathological examination.

2. Diagnostic methods

GUTB was diagnosed as the presence of one or more positivities in terms of histopathological findings, urine AFB smear, urine *M. tuberculosis* culture, and urine PCR for *M. tuberculosis*. PCR was conducted with urine specimens as follows. After centrifugation of the urine specimens, the supernatant was discarded and the precipitate was dissolved with a solvent. This process was repeated and yielded DNA extract by use of the COBAS amplicor MTB PCR (Roche Molecular System, Indianapolis, IN, USA) and AdvanSure TB/NTM real-time PCR (LG Life Science Diagnostic division, Daejeon, Korea) kits.

TABLE 1. Yearly proportion of patients with genitourinary tuberculosis among patients admitted to the department of urology and in Korea

Year	No. of in-patients in urology	No. of GUTB (%)	No. of new TB patients in Korea		No. of new GUTB patients in Korea (%)
			No.	/10^5 population	
2000	1,092	6 (0.55)	-[a]	-[a]	-[b]
2001	1,084	21 (1.94)	34,123	72.1	-[b]
2002	1,035	17 (1.64)	32,010	67.2	-[b]
2003	1,050	18 (1.71)	30,687	64.0	-[b]
2004	1,017	13 (1.28)	31,503	65.4	-[b]
2005	1,045	12 (1.15)	35,269	73.0	130 (0.36)
2006	1,184	5 (0.42)	35,361	73.2	120 (0.34)
2007	1,126	4 (0.36)	34,710	71.6	137 (0.39)
2008	1,196	2 (0.17)	34,157	70.3	123 (0.36)
2009	1,382	3 (0.22)	35,845	73.5	146 (0.41)
Total	11,211	101 (0.90)			

GUTB: genitourinary tuberculosis, [a]: The Korea Centers for Disease Control and Prevention has operated the Korean Tuberculosis Surveillance System since 2001, [b]: statistical data have not been reported

3. Analysis of previous studies

To compare our results with those of previous studies, we searched the KoreaMed (http://www.koreamed.org/), RISS (http://www.riss.kr/), and Korean Medical Database (http://kmbase.medric.or.kr/) by using the keywords "renal tuberculosis" and "genitourinary tuberculosis." Thirty-four articles were retrieved. Of the 34 articles retrieved, 10 with similar study objectives and designs were selected.

4. Statistical analysis

Statistical analysis was performed in terms of age at diagnosis, clinical symptoms, past history of tuberculosis, and involvement of other organs and findings of urinalysis. The changing patterns of tuberculosis patients were included in the analysis items. Chi-square test and Mann-Whitney u-test were performed. All statistical analyses were performed by using Open Office.org Calc ver. 3.2.1 (Open Office.org®, Oracle Corp., Redwood Shores, CA, USA) and MedCalc ver. 11.2.1.0 (MedCalc®, MedCalc Software, Mariakerke, Belgium). A p-value of < 0.05 was considered statistically significant.

RESULTS

Of a total of 11,211 patients who were admitted to our department during a recent 10-year period, 101 patients were admitted to our hospital owing to GUTB. Chronologically, the number of patients with GUTB was the highest in 2001 (21, 1.9%), and after 2005 it decreased to less than 0.5% (Table 1). The mean age of the patients was 45.57±12.55 years (range, 19-81 years), and most patients were in their 40s (73.2%). The male to female ratio was 1:1.53. There was only one Mongolian foreigner. The mean number of admitted patients during the period of 2000-2004 was 15; the corresponding number was 5.2 during the period of 2005-2009 (p=0.016).

The most common symptom on admission was frequency (n=41, 40.6%), followed by hematuria (n=34, 33.7%), dysuria (n=17, 16.8%), flank pain (n=17, 16.8%), scrotal swelling (n=3, 3.0%), fever and chills (n=3, 3.0%), and perineal discomfort (n=2, 2.0%) (Table 2). Renal or ureteral tuberculosis occurred in 81 (80.2%) patients, and bladder tuberculosis occurred in 4 (4.0%). Genital tuberculosis occurred in 16 (15.8%) patients, epididymal or testis tuberculosis occurred in 15 (14.9%), and prostate tuberculosis occurred in

TABLE 2. Chief complaints observed in patients with genitourinary tuberculosis

Symptoms	No. of patients	Frequency (%)
Frequency	41	40.6
Hematuria	34	33.7
Dysuria	17	16.8
Flank pain	17	16.8
Fever	3	3.0
Scrotal swelling	3	3.0

TABLE 3. Location and origin of genitourinary tuberculosis

Location	No. of patients (%)
Urinary	
Kidney and/or ureter	81 (80.20)
Bladder	4 (3.96)
Genital	
Epididymis and/or testis	15 (14.85)
Prostate	1 (0.99)
Origin	
Primary	67 (66.34)
Secondary	34 (33.66)
Lung	22
Intestine	1
Spine	1

1 (0.9%). A past history of pulmonary tuberculosis was detected in 22 (21.8%) patients, intestinal tuberculosis in 1, and spine tuberculosis in 1. On chest X-rays taken after the diagnosis of GUTB, inactive pulmonary tuberculosis was detected in 12 patients and secondary GUTB was detected in 34 (33.7%) patients (Table 3). Urinalysis revealed proteinuria in 58 (57.4%) patients, hematuria in 51 (51.5%), and pyuria in 42 (42.4%). All but 4 patients underwent at least one of the following tests: the urine AFB test, the urine culture test, and PCR. Of these patients, 86 (86.9%) were positive for at least 1 test; the positivity rate was 41.6% for the urine AFB test, 55.4% for the urine *M. tuberculosis* culture test, and 33.7% for PCR.

Of the total patients, 1 was on medication with immunodepressants and 1 was positive for HIV. Although all patients were scheduled to receive 6- or 9-month chemotherapy with isoniazid, rifampicin, and ethambutol or pyrazinamide according to Gow or the Centers for Disease Control and American Thoracic Society protocol, chemotherapy was instituted for a mean duration of 7.9 months (range, 5-16 months) due to low patient compliance and adverse reactions. As for adverse reactions, abnormal liver function was observed in 4, pruritus in 3, and skin eruption in 1. The urine culture test was positive in 86 patients before the start of chemotherapy, but it became negative within 3 months of chemotherapy. Surgical treatments were performed in 54 (53.4%) patients: nephrectomy in 30, epididymectomy in 8, ureteral stent insertion in 8, nephrostomy in 5, augmentation cystoplasty in 1, ureterectomy in 1, and transurethral resection of the prostate (TURP) in 1 patient who was confirmed as having tuberculosis by tissue biopsy. Surgical treatment was performed on 38 (50.5%) of 75 patients between 2000 and 2004 and on 16 (61.5%) of 26 patients between 2005 and 2009, but the difference was not statistically significant (p=0.154).

DISCUSSION

In Korea, tuberculosis has been relatively well controlled so far. However, ≥35,000 new patients with tuberculosis develop every year, of whom ≥2,300 die. Furthermore, as the number of patients with tuberculosis that is multidrug-resistant has increased, tuberculosis has seriously threatened national health [6]. In 2007, the prevalence of tuberculosis was 34 per 100,000 in the United States, 21 in Japan, and 6 in Australia. However, in 2009, its prevalence was 73.5 per 100,000 in Korea, which was relatively high compared with other developed countries [1]. During the past 10 years, the number of new patients with tuberculosis was 34,123 in 2001, 32,010 in 2002, and 30,687 in 2003, which showed a decreasing tendency; however, it was 31,503 in 2004, 25,269 in 2005, 35,361 in 2006, 34,710 in 2007, 34,157 in 2008, and 35,845 in 2009, which showed that the mean number of new patients was maintained at approximately 35,000 during the period after 2005 but has increased since then [3]. The reasons for this increase may be aging of the general population and the increasingly frequent use of immunodepressants. Another reason for this increase may be the increase in the number of foreign immigrants. The number of reported new foreign immigrants with tuberculosis was 736 (1.7%) in 2008 and 637 (1.3%) in 2009. In 2009, the number of Chinese patients was the highest (54.6%) [2,3]. In our study, tuberculosis developed in one Mongolian patient. Immigrants with tuberculosis might play a key role in controlling tuberculosis in Korea.

The term GUTB was first introduced by Willbolz et al, and it represents tuberculosis that occurs in the kidney, ureter, testis, and epididymis through blood-borne infection [7]. Although GUTB was the most common subtype of EPTB in the past [8], it was recently reported to account for <0.5% of all patients with EPTB and 1.5% of all patients with pulmonary tuberculosis [9]. Becker reported that GUTB patients associated with pulmonary tuberculosis accounted for <5% of all GUTB patients, approximately 50% of whom had a past history of pulmonary tuberculosis [10]. Tuberculosis of the ureter and bladder was directly transmitted from the kidney. Tuberculosis occurs in the seminal vesicle and prostate in males and in the uterus and ovarian tube in females through the hematogenous or lymphatic route [11]. The clinical symptoms of GUTB vary according to interactions between the host and *M. tuberculosis*. Dysuria, hesitancy, and frequency commonly occur in renal and prostatic tuberculosis, and some cases of renal tuberculosis present with dysuria and flank pain [12].

In this study, GUTB was diagnosed by using the urine AFB test and the urine *M. tuberculosis* culture test. Although the urine AFB test is simple, economical, and rapid, it has low sensitivity and specificity for *M. tuberculosis*. The urine *M. tuberculosis* culture test has a higher specificity compared with the urine AFB test but requires at least 8 weeks before the results are obtained. Urine PCR can detect the presence of *M. tuberculosis* even when the urine AFB test and the urine *M. tuberculosis* culture test are negative, and it allows for earlier treatment by detecting *M. tuberculosis* in its early stages. However, some cases of GUTB are asymptomatic, and tuberculosis of the kidney

and ureter can progress to long-term infection [13]. In long-term latent infection such as renal tuberculosis, amounts of *M. tuberculosis* are relatively small, and weak humoral responses are observed in the serological test [14]. Kim et al have demonstrated that nontuberculous mycobacteria (NTM) or hemoglobin in hematuria can lead to false PCR negativity [15]. Jung et al reported that PCR sensitivity in urine was relatively low (60%) and the detection rate of NTM was also low compared with sputum specimens [16]. These reasons may explain the low PCR positivity in our study. There are several methods for decreasing false PCR negativity, such as multiple collections of urine samples, collection of high-quality samples such as the first morning urine, removal of inhibitors of PCR, and increasing urine concentration by centrifugation before analysis.

The primary treatment of GUTB is antituberculous chemotherapy. In the era when antituberculous chemotherapy was not used, GUTB treatment was restricted to transurethral ultraviolet radiation, urinary diversion, epididymectomy, orchiectomy, and prostatectomy [17]. Clinicians have recently instituted a 6- to 9-month combination of isoniazid, rifampicin and pyrazinamide, and ethambutol [18]. Short-term antituberculous chemotherapy shows better therapeutic effects and less adverse reactions than does long-term chemotherapy by decreasing excessive treatment fees and restriction of social activities [19]. Indications for surgical treatment of GUTB are complicated and various. Surgical treatments of GUTB accounted for about 0.5% of all urological surgeries [20]. Nephrectomy is performed in nonfunctioning kidneys, renal tuberculosis with involvement of the entire renal parenchyma due to hypertension and ureteropelvic obstruction, and cases accompanied by renal cell carcinoma. Partial nephrectomy is conducted in localized renal lesions that do not respond to antituberculous chemotherapy and renal tuberculosis with calcification. Various surgical techniques, including ureter stent insertion, ureteral dilation, nephrostomy, and ureteroureterostomy, can be performed in patients with ureteral stricture. Augmented cystoplasty should be considered in cases of contracted bladders. Surgical treatment should also be considered in tuberculosis of the testis or epididymis that shows persistent symptoms after administration of antituberculous agents [21].

In a review of the literature, the prevalence of GUTB was 2.3% to 8.5% before 2000, and it decreased to $<0.1\%$ since then; however, the percentage of surgical treatment was not significantly different between the 2 aforementioned categories. The frequency of surgical treatment for patients with GUTB was on average 49.4% during the period before 2000, and it was 58.1% since then, but the difference was not statistically significant (p=0.257). The prevalence of secondary GUTB was 37.1% during the period before 2000, and it was 34.8% since then, but the difference was not statistically significant (p=0.883). In the literature, the clinical manifestations varied among reported cases, and hematuria and frequency were the most common (Table 4) [21-30]. In 1970, Hur reported 165 patients with renal tuberculosis among soldiers during a study period of 3.5 years, 43 (26.1%) of whom underwent surgical treatments [22]. Chung and Ahn reported 43 patients with GUTB during a study period of 6 years, 27 (62.8%) of whom underwent

TABLE 4. Review of published articles on renal or genitourinary tuberculosis in Korea

References	Year	Duration (yr)	Population (/duration)	Adm ratio[a]	Sex ratio	Seconday GUTB (%)	Symptoms (%)					Surgical treatment (%)
							Flank pain	Gross hematuria	Dysuria	Frequency	Fever	
Hur [22]	1970	3.5	165 (47.1)	-	1:0.12	43 (26.1)	-	52.8	8.5	18.8	-	43 (26.1)
Woo and Kim [27]	1977	7	50 (7.1)	3.7	1:0.67	28 (56.0)	40.0	38.0	40.0	54.0	6.0	23 (46.0)
Chung and Park [28]	1980	5	54 (10.8)	8.5	1:0.63	15 (27.8)	18.5	53.7	9.3	75.9	5.6	13 (24.1)
Kim and Kim [24]	1982	8	121 (15.1)	5.7	1:0.59	18 (14.9)	9.1	7.4	-	-	-	46 (38.0)
Park and Lee [29]	1982	6	47 (7.8)	5.7	1:0.67	21 (44.7)	19.1	40.2	29.8	55.3	-	21 (44.7)
Kim and Min [30]	1983	6	72 (12.0)	4.0	1:0.71	27 (37.5)	20.8	29.2	27.8	52.8	8.0	60 (83.3)
Won and Park [25]	1983	4	46 (11.5)	5.1	1:0.71	14 (30.4)	32.6	43.5	21.7	47.8	6.5	24 (52.2)
Chung and Ahn [23]	1989	6	43 (7.2)	2.3	1:0.5	14 (32.2)	32.6	37.2	-	53.5	-	27 (62.8)
Baeg et al [26]	1991	4	70 (17.5)	-	1:0.56	45 (64.3)	45.7	42.9	38.6	38.6	18.6	-[b]
Yi et al [21]	2005	15	142 (9.5)	0.8	1:0.71	51 (35.9)	19.0	25.3	19.2	41.1	5.0	89 (62.7)
Present	2010	10	101 (10.1)	0.9	1:1.53	34 (33.7)	16.8	33.7	16.8	40.6	3.0	54 (53.5)

GUTB: genitourinary tuberculosis, [a]: The ratio on GUTB patients of all patients administrated in the department, [b]: Baeg et al did not analyze surgical treatment in their article

surgical treatments and only 16 of whom received antituberculous chemotherapy [23]. Yi et al performed surgical treatments in 89 (62.7%) of 142 patients with GUTB during a period of 15 years [21]. In our literature review, the percentage of surgical treatments was 49.4% before 2000 and 58.1% since then, but the difference was not statistically significant. The prevalence of secondary GUTB has been reported to be ≤50%. Hur reported that the prevalence of secondary GUTB was 26.1% in Korea [22]. Kim and Kim reported that secondary GUTB occurred in 14.9% of the 121 inpatients with renal tuberculosis during a period of 8 years [24]. Won and Park reported that secondary GUTB occurred in 30.4% of the 46 patients with renal tuberculosis [25]. Baeg et al reported a relatively high prevalence of secondary GUTB (64.3%) [26]. In our review of the literature, the prevalence of secondary GUTB was 37.1% before 2000 and 34.8% since then, and the difference was not statistically significant.

This study analyzed the medical records of patients with GUTB during the past 10 years. With the reference year of 2000, the prevalence of tuberculosis was investigated in the literature, and the clinical features and treatment methods for patients with renal tuberculosis and GUTB reported in Korea were compared. Our study found that GUTB required antituberculous chemotherapy as well as urological surgeries and that at the time of diagnosis, renal function was considerably deteriorated because the onset of symptoms was delayed. The results of this study are subject to at least 2 limitations. First, this study was conducted only with inpatients. We selected only inpatients considering that the analysis of inpatients would have more clinical implications than an analysis of outpatients because patients with GUTB almost always need antituberculous chemotherapy and surgical treatment in approximately 50% cases. This might have resulted in selection bias. Second, comparisons between overall GUTB patients in the Korean population and ours were not made. We obtained accurate information on the prevalence of GUTB from the Korea Centers for Disease Control and Prevention, but we could not make comparisons between the 2 study populations. Further studies are needed to confirm our results.

CONCLUSIONS

Taken together, our results show that the prevalence of GUTB tended to decrease progressively. GUTB occurred slightly more frequently in females and mainly in subjects in their 40s. The prevalence of GUTB was relatively high (33.7%), which suggests that urological diagnostic methods performed at the department of urology may be important in the early diagnosis of GUTB. Short-term antituberculous chemotherapy showed good treatment outcome with less adverse drug reactions. Unlike tuberculosis of other organs, ≥50% of the patients with GUTB needed surgical treatments. Surgical treatments should be considered along with antituberculous chemotherapy in patients with GUTB.

Conflicts of Interest
The authors have nothing to disclose.

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