

Genitourinary tuberculosis in a medical center in southern Taiwan: an eleven-year experience

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Background and Purpose: Genitourinary tuberculosis is the second most common disease form of extrapulmonary tuberculosis. This study analyzed the clinical characteristics and outcome in 31 patients with genitourinary tuberculosis treated between 1994 and 2004 at a tertiary medical center in southern Taiwan.

Methods: Data were collected by chart review. Diagnosis was based on microbiological or histological proof plus compatible radiographic findings and clinical presentation.

Results: This study included 14 men (45%) and 17 women (55%). Their ages ranged from 31 to 81 years (mean, 58.1 years). Genitourinary symptoms (83.9%) were more frequent than constitutional symptoms (35.5%). Pyuria plus hematuria with sterile culture (51.6%) was the most common finding. Only 25.8% of patients had a known history of pulmonary tuberculosis. Diagnosis was based on microbiological findings in 11 patients (35.5%), and by histological findings in 20 (64.5%) patients. Intravenous pyelography revealed abnormalities in 94% of patients and renal ultrasonography in 79.2%. Imaging studies were characteristic of advanced stage in most patients. Twenty-five percent of patients were classified as having treatment failure after at least 6 months of therapy. The treatment failure rate was higher in patients with positive microbiological findings (71.4%) than in those with histological findings alone (5.9%, $p=0.003$).

Conclusions: The high rate of treatment failure and advanced stage of disease at diagnosis are indicative of the challenge in the care of patients with genitourinary tuberculosis in Taiwan.

Key words: *Mycobacterium tuberculosis*, retrospective studies, treatment failure, urogenital tuberculosis

Introduction

Tuberculosis remains a major health problem worldwide. In 2001, the incidence of tuberculosis in Taiwan was higher than that in most developed countries at 64.84 per 100,000 [1]. Extrapulmonary involvement was found in about one-fifth of newly diagnosed tuberculosis cases in Taiwan, with genitourinary tuberculosis comprising 4% of extrapulmonary cases [1]. Genitourinary tuberculosis has an insidious course and nonspecific presentations, including dysuria, gross hematuria, and flank pain that result in difficulties in diagnosis and subsequent delay of treatment, and lead to serious urological complications, such as lithiasis, renal function damage, and infertility [2].

Although 6-month antituberculosis chemotherapy of genitourinary tuberculosis has been recommended [3-5], the outcome of this regimen in Taiwan has not been reported. To our knowledge, although many studies have investigated extrapulmonary tuberculosis [6-10], there is limited information on genitourinary tuberculosis in Taiwan. This study investigated the clinical characteristics and response to treatment in 31 patients with genitourinary tuberculosis diagnosed at a tertiary medical center in southern Taiwan between 1994 and 2004.

Methods

Patients

Patients diagnosed with genitourinary tuberculosis between 1994 and 2004 at a tertiary medical center in southern Taiwan were identified from a computerized database of records. Patients who had received treatment

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for less than 6 months ($n = 3$), had only one set of positive polymerase chain reaction (PCR) results from urine ($n = 3$), and women with tuberculosis involving the ovary, uterus, and peritoneum without any clinical urinary symptoms and signs ($n = 2$) were excluded. Surgical interventions (nephrectomy, ochiectomy/epididymectomy) were performed in patients when a mass-like lesion was found over the kidneys, testis, or epididymis by imaging studies (renal ultrasonography or intravenous pyelography). Basic characteristics, underlying diseases, treatment responses, and outcomes were also recorded and analyzed.

Diagnosis

The medical records of patients were retrospectively reviewed. All cases were diagnosed based on microbiological findings (positive *Mycobacterium tuberculosis* culture or at least one set of positive acid-fast staining from urine samples) or histological findings of granulomatous inflammation (granulomas composed of epithelioid cells and Langhans giant cells with or without caseous necrosis) plus compatible clinical and roentgenographic findings. All tissue specimens for histology were obtained through surgical intervention, cystoscopic bladder biopsy, or transurethral resection of the prostate. PCR for detection of *M. tuberculosis* in urine was performed as previously described [11] in 25 patients with high clinical suspicion but negative acid-fast bacilli in urine.

Urinary PCR detection of *M. tuberculosis*

In the laboratory, all the samples were processed in a class II biosafety cabinet. An entire first morning sample of voided urine was collected. The samples were decontaminated, concentrated, and centrifuged at 3000 rpm for 20 min. The pellet was washed once and resuspended in Tris-hydrochloride (Tris-HCl) buffer (pH 8.3).

Two oligonucleotide primers within the *IS 6110* insertion element, designated as Pt-8 (5'-GTGCGGATG GTCGCAGAGAT-3') and Pt-9 (5'-CTCGATGCCCTC ACGGTTCA-3'), were used for PCR, resulting in amplification of a 541-bp DNA fragment. This *IS 6110* insertion element is almost specific for *M. tuberculosis* complex. The composition of the PCR mix was 10 mM Tris-HCl (pH 8.3), 50 mM sodium chloride, 2.0 mM magnesium chloride, 0.01% (w/v) gelatin, 0.2 mM (each) deoxynucleoside triphosphate (dATP, dCTP, dGTP, and dTTP), and 0.2 μ M each of the primers Pt-8 and Pt-9, 1U of *Taq* polymerase (Perkin-Elmer Applied

Biosystems, Foster City, CA, USA) per 50 μ L reaction volume. The reaction included 40 cycles of 1.5 min of denaturation at 94°C, 2 min of annealing at 65°C, and 3 min of primer extension at 72°C, followed by a final extension for 10 min at 72°C. PCR products were analyzed by agarose electrophoresis and staining with ethidium bromide.

Definitions

Duration of treatment was defined as the number of days from the prescription of the first regimen to the last day on which prescribed medication could have been taken. Patients who were lost to follow-up or who refused further treatment were classified as having defaulted from treatment [12]. Patients who had received antituberculosis chemotherapy for 6 months and had positive microbiological findings in urine or persistent clinical urinary symptoms/signs associated with worsening image findings were classified as having failed treatment, according to the findings of previous studies indicating that genitourinary tuberculosis can respond to a 6-month intensive course of chemotherapy [3,4]. Therefore, cultures of *M. tuberculosis*, smears of acid-fast stain from urine, and intravenous pyelography were performed in all patients after 6 months of chemotherapy. Patients classified as having failed treatment received continued chemotherapy with or without the addition of quinolone until 12 or 18 months after the start of treatment, depending on microbiologic findings, clinical symptoms/signs, and/or image findings. The data collection period was defined as the start of the initial 6-month chemotherapy and included follow-up for 12 months with or without continued treatment and regardless of the response to treatment. Active pulmonary tuberculosis was defined as the presence of pulmonary tuberculosis lesions concurrently with positive result for acid-fast bacilli in sputum specimens or positive *M. tuberculosis* culture in sputum.

Statistical analysis

Fisher's exact test for small sample sizes was used for categorical variables. The threshold for significant difference was defined at $p < 0.05$. The test was two-tailed.

Results

During the 11-year study period, 31 cases of genitourinary tuberculosis were identified, including 11 (23.5%) with diagnosis based on microbiologic findings

(5 cases with positive culture of *M. tuberculosis* from urine, 4 cases with positive acid-fast bacilli in urine, and 2 cases with both) and 20 cases (64.5%) with diagnosis based on histological findings alone. Among the 11 cases with microbiologic findings, 3 also had histological evidence. The study included 14 males (45.2%) and 17 females (54.8%). The mean age of male patients was 54.4 years (range, 32-75 years), while that of females was 61.8 years (range, 31-81 years). Eight cases (25.8%) had pulmonary tuberculosis, and two of them had active disease at the time of diagnosis. The distribution of cases according to age group and underlying diseases is shown in Table 1.

Frequency/urgency and dysuria were the most common symptoms. Fever (29%), night sweating (3.2%), and body weight loss (3.2%) were infrequent presentations. Pyuria plus hematuria with sterile urine culture was the most common urinary finding (Table 2). However, concurrent pathogens were cultured from urine in 5 cases (*Escherichia coli* in 3 cases, *Proteus mirabilis* in 1 case, and *Enterobacter aerogenes* in 1 case). Intravenous pyelography was performed in 17 patients and revealed abnormalities in 16 (94.1%), including hydronephrosis in 10 (58.8%), ureter stenosis/stricture in 9 (52.9%), poor kidney function in 8 (47.1%), and

Table 1. Characteristics of 31 patients with genitourinary tuberculosis

Variable	No. of patients (%)
Gender	
Male	14 (45.2)
Female	17 (54.8)
Age (years)	
30-39	3 (9.7)
40-49	6 (19.4)
50-59	5 (16.1)
60-69	9 (29)
70-79	7 (22.6)
80-89	1 (3.2)
Local symptoms	
Frequency/urgency	19 (61.3)
Dysuria	18 (58.1)
Flank pain	11 (35.5)
Gross hematuria	10 (32.2)
Scrotal mass/pain	5 (16.1)
Total	26 (83.9)
Constitutional symptoms	
Fever	9 (29)
Malaise/fatigue	4 (12.9)
Night sweating	1 (3.2)
Body weight loss	1 (3.2)
Total	11 (35.5)

Table 2. Laboratory characteristics in patients with genitourinary tuberculosis

Characteristic	No. of patients (%)
Laboratory abnormalities	
Anemia (Hb <12 g/dL)	8 (25.8)
Poor renal function (Cr >1.5 mg/dL)	18 (58.1)
Poor liver function (ALT >40 IU/L)	5 (16.1)
Hyperkalemia (K ⁺ >5.5 meq/L)	1 (3.2)
Urinary abnormalities	
Pyuria (WBC >10/HPF; 400×)	8 (25.8)
Hematuria (RBC >5/HPF; 400×)	4 (12.9)
Pyuria + hematuria	16 (51.6)
Total	28 (90.3)
Systemic abnormalities	
Leukocytosis (WBC >10,000/μL)	8 (25.8)
Leukopenia (WBC <4000/μL)	0

Abbreviations: Hb = hemoglobin; Cr = creatinine; ALT = alanine aminotransferase; K⁺ = potassium; WBC = white blood cell; HPF = high power field; RBC = red blood cell

Table 3. Findings of imaging studies in patients with genitourinary tuberculosis

Roentgenographic finding	No. of patients with positive finding/ no. of patients (%)
Abnormalities on IVP	16/17 (94.1)
Hydronephrosis + ureter stenosis/stricture	5
Hydronephrosis + ureter stenosis/stricture + poor function of unilateral kidney	4
Hydronephrosis only	1
Poor function of unilateral kidney alone	4
Ureter stone alone	2
Hydronephrosis (total)	10 (58.8)
Ureter stenosis/stricture (total)	9 (52.9)
Poor function of unilateral kidney (total)	8 (47.1)
Hydronephrosis on renal ultrasonography	19/24 (79.2)

Abbreviation: IVP = intravenous pyelography

ureter stone in 2 (11.8%). Renal ultrasonography was performed in 24 patients, and hydronephrosis was detected in 19 patients (79.2%). Hydronephrosis was the most common finding in the imaging studies (Table 3). The duration between onset of symptoms and diagnosis ranged from 5 days to 18 months (mean, 2 months).

Of the 23 patients with histological evidence of infection, 20 had negative microbiological findings on repeated urine culture for *M. tuberculosis* and smear for acid-fast bacilli, and 3 had both histological and microbiological evidence. PCR for the detection of *M. tuberculosis* in urine was positive in 12 of 25 patients tested; 6 of them also had histological proof and the remaining 6 had microbiological findings.

Tuberculosis involved the testis/epididymis in 6 patients (19.4%) and prostate in 3 (9.7%). Diagnosis was made by pathology in all of these patients, 3 of whom had a positive finding for acid-fast bacilli in urine and 2 of whom also had positive PCR detection in urine.

All patients except the 7 classified as having defaulted from treatment were given antituberculosis chemotherapy with rifampin, isoniazid, ethambutol, and pyrazinamide for 6 to 18 months (median, 10 months; 18 patients with successful treatment, 6 months; 6 patients with treatment failure, 12 to 18 months). Thirteen patients (41.9%) underwent additional surgical intervention (nephrectomy in 7 cases; orchiectomy/epididymectomy in 5 cases; both in 1 case). Default from treatment in the 7 patients was due to loss of follow-up in 5 and poor compliance with treatment in 2. Of the remaining 24 patients with data up to the study endpoint, 18 (75%) were classified as treated successfully. Of the 7 patients with positive microbiology findings, excluding the 4 who defaulted treatment, 2 (28.6%) were treated successfully and 5 (71.4%) had treatment failure; however, excluding the 3 patients who defaulted from treatment, only 1 (5.9%) of the 17 patients with negative microbiological findings had treatment failure ($p=0.003$). Among the 15 patients without surgical intervention, excluding the 3 who defaulted from treatment, 10 (66.7%) were treated successfully and 5 (33.3%) had treatment failure. In contrast, 1 treatment failure (11.1%) was found in 9 patients with surgical interventions, excluding the 4 patients who defaulted from treatment ($p=0.351$, Table 4).

Discussion

Genitourinary tuberculosis is the second most common form of extrapulmonary tuberculosis after peripheral tuberculosis lymphadenopathy. Previous studies estimated that genitourinary tuberculosis comprised 13.4% to 30% of extrapulmonary tuberculosis [5,10,13-15]. In Taiwan, about 20% of all newly diagnosed tuberculosis cases are extrapulmonary and 4% of these cases have genitourinary tract involvement [10].

Although genitourinary tuberculosis has generally been considered a disease of young adults (60% of patients are between the ages of 20 and 40 years) [2,14,16], in this study, only 9.7% of patients were younger than 40 years. The older age of these patients may be related to the relatively longer period required from the time of initial infection to the development of renal disease. The male to female ratio was 1.5:1 in most reported studies [2,14,16,17], but was the reverse (0.8:1) in this study.

Eight patients (25.8%) had a past history of pulmonary tuberculosis, which is similar to previous reports (22-34.6%) [14,15,18]. A study from Turkey reported that 82.2% of cases were combined with active or healed pulmonary tuberculosis, which contributed to the high prevalence of pulmonary tuberculosis and poor health conditions [17]. Although pulmonary tuberculosis was not found in all patients, it may provide a clue to diagnosis.

Genitourinary tuberculosis is difficult to diagnose because its symptoms are nonspecific. This might have contributed to the long period between the onset of symptoms and diagnosis in this study. Genitourinary tuberculosis should be suspected in the presence of any of the following situations: chronic cystitis unresponsive to adequate antituberculosis therapy; the finding of pus without bacteria in urine; gross or microscopic hematuria; a non-tender enlarged epididymis with a beaded or thickened vas deferens; a chronic draining scrotal sinus; or induration or nodulation of the prostate and thickening of one or both seminal vesicles [2]. The prevalence of nonspecific local symptoms, such as frequency/urgency, dysuria and hematuria, has varied from 60% to 95% in previous reports [14,16,19]. In this series, frequency/urgency was noted in 61.3% and dysuria in 58.1% of patients. Flank pain (35.5%) and gross hematuria (32.2%) were also common in this study, with higher rates than in previous studies (10-26.5% and 17.6-27%, respectively) [14,16]. Advanced stage at the time of diagnosis may contribute to the high rate of flank pain and hematuria in this study.

Table 4. Tuberculosis treatment outcomes according to diagnostic results and surgical intervention

Culture or acid-fast stain of urine	Total	No. of loss of follow-up patients	No. of poor drug compliance	Treatment failure/complete follow-up	<i>P</i>
Positive	11	3	1	5/7	0.003
Negative	20	2	1	1/17	
Surgical intervention	13	3	1	1/9	0.351
No surgical intervention	18	2	1	5/15	

Due to the insidious nature of genitourinary tuberculosis, only proper collection and examination of urine will enable the collection of useful diagnostic information. In this study, 28 (90.3%) patients had abnormal urinalysis findings. Suspicion in the remaining 3 patients with normal urinalysis was due to constitutional symptoms (e.g., fever, flank pain, and scrotal mass) and diagnosis was made based on histology of surgical specimens. In previous studies, isolated pyuria was detected in 36% to 46% of patients, isolated hematuria in 10% to 12%, and both in 12% to 34% of patients [14,16,20,21]. Although the frequency of isolated pyuria (25.8%) and isolated hematuria (12.9%) were slightly lower in this study, the frequency of pyuria plus hematuria was much higher (51.6%), which is similar to a study from Spain (59.3%) [15]. Although sterile pyuria is a diagnostic clue for genitourinary tuberculosis, superinfection has been reported in 12% to 50% of patients [16,22], and was found in 16% of patients in this study.

Intravenous pyelography revealed abnormalities in 65% to 91.4% of patients in previous studies and was frequently suggestive of the diagnosis based on the appearance and multiplicity of the lesions [14,16,23]. In this study, intravenous pyelography revealed abnormalities in 94% of patients who underwent the procedure. The majority of patients had advanced stage disease, such as hydronephrosis, poor kidney function, or ureter stenosis/stricture. Besides, a high rate (79.1%) of hydronephrosis was found by renal ultrasonography. Ureteral stenosis and vesical contraction may develop during the healing process [2]. These complications were also found in this series. This may be partly attributable to the advanced nature of disease at diagnosis.

All components of the genitourinary tract (kidney, ureter, bladder, prostate, epididymis, and testis) can be affected. Previous studies reported frequencies of prostate and testicular involvement ranging from 1.2% to 26.4% and 0% to 35%, respectively [14-16], and results in this study were within these ranges (9.7% and 19.4%).

Although excellent response to 6-month regimens of rifampin, isoniazid, ethambutol, and pyrazinamide have been reported [2], other studies demonstrated that 4-month regimens resulted in a high cure rate with only 1% treatment failure rate [3,19]. In contrast, the treatment failure rate after at least 6 months of therapy in this study was 25%. This higher rate of treatment failure may be due to a number of factors including the high drug resistance rate of *M. tuberculosis* in

Taiwan, older age of patients, and advanced stage of disease. In recent studies, the prevalence of resistance to any drug was 22.4% to 42.6%, and 3.9% to 24.6% had multidrug-resistant tuberculosis [24-27]. In addition, this study found a higher treatment failure rate in patients with positive microbiological findings (71.4%) than in those with histological proof alone (5.9%). This situation may be related to the high colonial counts in these patients. These data suggest the need for at least 6-months of antituberculosis chemotherapy and close observation of symptoms with repeated urine smear and culture. Although a lower treatment failure rate (11.1%) was found in patients with surgical interventions, this difference was not significant.

In conclusion, the results of this study illustrate 3 important points: genitourinary tuberculosis is more common among the older population in Taiwan; most cases are diagnosed in the advanced stage; and positive microbiological evidence may predict a poor outcome of treatment. Clinicians should be alert to the insidious nature and nonspecific symptoms of this disease.

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