
CASE REPORTS

Genitourinary Tuberculosis in the USA: An Academic Center Experience and Literature Review

Jessica Lange, MD, J. Burnell, MD, M. Mirzazadeh, MD

ABSTRACT

Objective: To discuss the diagnosis and treatment of genitourinary tuberculosis (GUTB) in the United States.

Methods: We prospectively looked for any possible cases of GUTB in our patients from 2008 to 2013. We collected demographic information, clinical presentations, diagnostic findings, treatments, and outcomes of all diagnosed cases and report that information here.

Results: Eight patients had a confirmed diagnosis of GUTB in our center since 2008, including three cases related to intravesical Bacillus Calmette-Guerin (BCG) instillations. In the GUTB group, there were two males and three females, aging from 54 to 72 years (mean 62 ± 7.8 years). Symptoms started 3-14 years prior to diagnosis. Diagnosis was confirmed with positive urine culture in three, urine polymerase chain reaction testing in one, and surgical pathology in one patient. In disseminated BCG infection cases, difficult catheter insertion prior to development of disseminated TB was the highlight of history in two patients. Urine cultures were negative in all three patients.

Conclusions: GUTB still exists in the United States. Patients usually present with long-standing urinary symptoms. A high index of suspicion is required for timely diagnosis and management. Urine culture is the mainstay of diagnosis of GUTB. BCGosis can present with severe systemic symptoms. Urine culture is usually negative. Difficult catheterization is a significant risk factor.

Introduction

Tuberculosis (TB) is the second leading infectious cause of mortality in the world after human immunodeficiency virus (HIV), and the World Health Organization (WHO) estimates that one third of the world's population is currently infected with *Mycobacterium tuberculosis*.¹ 13% of those with TB are HIV positive.¹ Though pulmonary TB infections are the most common, 10% of cases are extrapulmonary.^{2,3} Genitourinary TB (GUTB), tuberculous infection of any portion of the genitourinary tract, represents 30-40% of extrapulmonary cases. It is thought to be caused by hematogenous spread of TB from primary pulmonary infection or by reactivation of latent disease.³ Nearly 10,000 new cases of GUTB were reported in the United States in 2012. The case rate was 1.4/100,000 U.S.-born persons and 15.9/100,000 for foreign-

Address correspondence to:
Jessica Lange, MD
Wake Forest Baptist Health
Medical Center Blvd.
Winston-Salem, NC
Phone: 336-716-9601
Fax: 336-716-5711

born persons.⁴ In North Carolina, four cases of GUTB were reported in 2012.⁵

GUTB can also be caused by dissemination of intravesical instillation of Bacillus Calmette-Guerin (BCG), a live attenuated strain of Mycobacterium bovis used to treat superficial bladder cancer. Side effects of BCG occur most commonly from injury to the urothelium (such as with traumatic catheterization) leading to systemic absorption. Typical presentation of BCGosis includes acute, severe, yet non-specific symptoms such as fever, chills, and malaise. Urine culture is typically negative.

There is a paucity of literature about GUTB in the United States. Herein, we present five cases of GUTB and three cases of BCGosis discovered in a large urology practice in Winston-Salem, North Carolina. This is the largest series reported in the United States to date.

Methods and Materials

We prospectively collected data about all cases of GUTB and BCGosis diagnosed or managed at Wake Forest Baptist Hospital in Winston-Salem, North Carolina, from 2008 to 2013. Demographics, symptoms, laboratory studies, radiographic data, treatments, and outcomes are reported below.

Results

GUTB Cases

1) A 54 year old Mexican male was admitted to our institution for upper gastrointestinal bleeding in 2008. Urology was consulted regarding bilateral scrotal swelling, urinary frequency, hematuria, and dysuria. Urinalysis showed sterile

pyuria and microscopic hematuria. Urine cultures and AFB stain were negative. Urine polymerase chain reaction (PCR) testing and purified protein derivative skin testing were positive for TB. Scrotal ultrasound revealed bilateral hypoechoic scrotal masses. He was treated with RIPE therapy but continued to have severe urinary symptoms. Next, he was hospitalized for renal failure. CT revealed a contracted bladder and atrophic left kidney as well as calcified pulmonary nodules, calcified hilar lymph nodes, and splenic calcifications. CT cystogram revealed small bladder capacity, right ureteral reflux, and right hydronephrosis. He subsequently underwent right nephrostomy tube placement and appropriate antibiotic treatment; however, he developed end stage renal disease and dialysis was initiated. He has elected renal transplant and is undergoing transplant evaluation.

2) A 59 year old African-American female with a history of recurrent UTIs and urolithiasis presented to our institution in 2008 with multiple outside urinalyses showing sterile pyuria, and renogram revealing 20% right renal function. She was found to have bilateral nephrolithiasis on CT and underwent left ureteroscopic stone manipulation with laser lithotripsy and right percutaneous nephrostolithotomy. Four months after surgery, she developed a urocutaneous fistula

Table 1 – Demographic Information for GUTB Patients

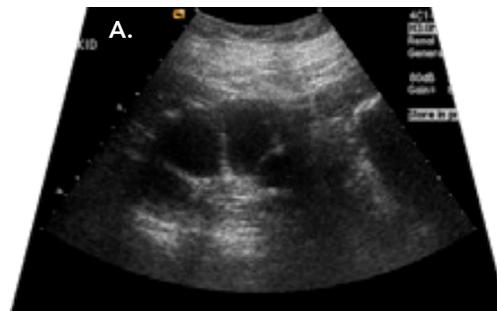
Type of infection	5
Gender	Male – 2 Female – 3
Ethnicity	Caucasian – 1 African-American – 2 Hispanic – 2
Immigration Status	Non-immigrant – 3 Immigrant – 2

Table 2 – Demographic Information for Patients with Disseminated BCG Infection

Type of infection	3
Gender	Male – 3 Female – 0
Ethnicity	Caucasian – 2 African-American – 1 Hispanic – 0
Immigration Status	Non-immigrant – 3 Immigrant – 0



Figure 1: Right hydronephrosis and urocutaneous fistula in patient with *Mycobacterium avium* infection



Figures 2A and 2B: Infundibular stenosis and parenchymal loss in the left kidney on renal US and CT scan

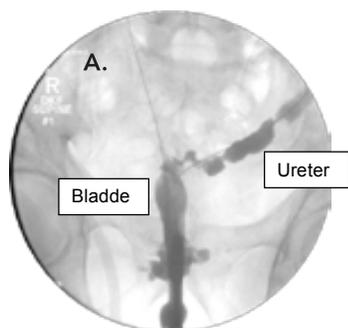
in the region of her nephrostomy tract (Figure 1) and was referred to our institution. Repeat renogram revealed 12% right renal function, and a nephrectomy was performed. Pathologic examination showed multifocal necrotizing granulomatous giant cell inflammation with extensive dystrophic calcification, granulomatous ureteritis, and Ziehl-Neelsen staining positive for AFB. Urine culture grew *Mycobacterium avium*-intracellulare at 14 days. She underwent RIPE therapy for six months and is doing well.

3) A 73 year old African-American female with a history of recurrent urinary tract infections (UTIs) and poorly functioning left kidney was referred to our practice in 2011 for management of recurrent left ureteral strictures. Multiple urine specimens demonstrated sterile pyuria. Renal ultrasound and CT scan revealed infundibular stenosis and parenchymal loss in the left kidney (Figure 2). Cystoscopy and retrograde pyelography demonstrated a narrowed

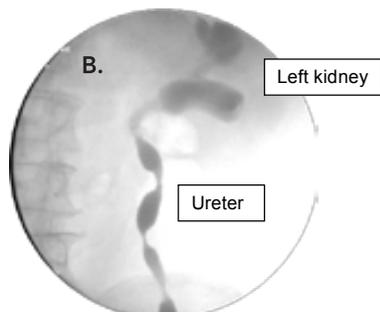
left ureter and mild left hydronephrosis without bladder abnormalities, and a left ureteral stent was placed. One urine culture was positive for *Mycobacterium tuberculosis*, and she was treated with RIPE therapy. Subsequent urine cultures were negative. Her left ureteral stent was removed, and she is now doing well.

4) A 75 year old Peruvian male presented to the Emergency Department in 2011 with headache, fever, and chills. Urinalysis revealed sterile pyuria and microscopic hematuria. CT scan revealed left hydroureteronephrosis, a thickened bladder, and evidence of old granulomatous disease in the lung and spleen. He was treated for a UTI without improvement in symptoms. Shortly thereafter, he was diagnosed with meningitis, and sputum smear was positive for AFB. Urine culture was positive for *Mycobacterium tuberculosis* at 24 days, and ESR was elevated. RIPE therapy was initiated, and he was referred to our institution. He

complained of persistent urinary frequency, urgency, dysuria, and nocturia. Cystoscopic evaluation revealed a small contracted bladder, left hydroureteronephrosis, right ureteral inflammation, and distorted right renal calyces (Figure 3). Bilateral ureteral stents were placed. Renogram revealed 7% right renal function. He has been offered surgical management and is considering his options.

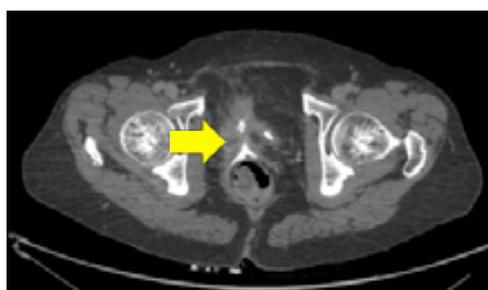
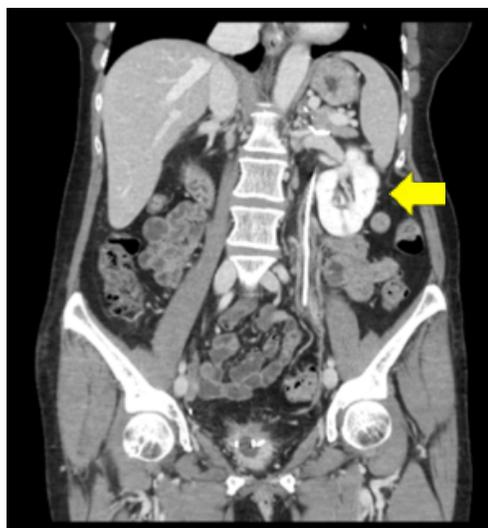


Figures 3A and 3B: Patient with history of tuberculous meningitis whose retrograde pyelogram shows small bladder capacity and chronic granulomatous ureteral changes



5) A 67 year old Caucasian female and North Carolina native with no history of international travel presented to a referring facility in 1999 due to hematuria and dysuria. Multiple urine specimens revealed sterile pyuria and microscopic hematuria. Open left renal biopsy of a complex cystic lesion revealed no malignancy. Computed tomography (CT) scan revealed bilateral hydronephrosis and bilateral ureteropelvic junction strictures. Renogram revealed 88% left renal function and 12% right renal function. Cystoscopy with retrograde pyelography demonstrated bilateral hydroureteronephrosis, and bladder biopsy showed chronic granulomatous disease. She had a left ureteral stent placed. Additional outside cystoscopy revealed a vesicovaginal fistula for which she was referred to our institution.

Upon presentation to our institution in 2012, she had a poorly-functioning right kidney, a contracted bladder, and a vesicovaginal fistula (Figure 4). She denied fever or night sweats. She underwent urine culture for acid fast bacilli (AFB), and two of three cultures were positive for *Mycobacterium tuberculosis* at 26 and 50 days. Erythrocyte sedimentation rate (ESR) was elevated. Cystoscopic evaluation revealed a small capacity bladder with patchy erythema, “golf hole” left ureteral orifice, left hydronephrosis, and left calyceal blunting (Figures 5 and 6). Vaginoscopy revealed a fistula at the vaginal apex. Multi-drug therapy with rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) was initiated. Her flank pain and incontinence worsened, so her left ureteral stent was replaced with a nephrostomy tube. She



Figures 4A and 4B: CT scan demonstrating left renal changes and vesicovaginal fistula from GUTB

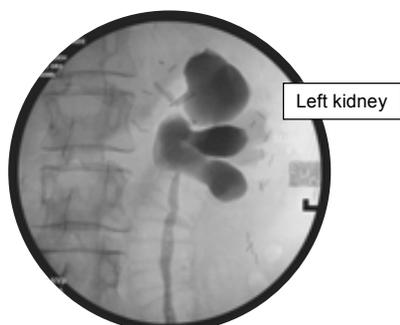


Figure 5: Retrograde pyelogram demonstrating severe hydronephrosis secondary to GUTB



Figure 6: Golf-hole ureter on cystoscopy

completed RIPE therapy in July 2013, and subsequent urine cultures were negative. Creatinine and ESR normalized. She began feeling better and gained weight, but failed a trial of nephrostomy tube capping. She was presented with options for management of her vesicovaginal fistula and functionally solitary kidney including chronic nephrostomy tube changes, ileal conduit urinary diversion, neobladder creation, and cutaneous ureterostomy. She elected to undergo cutaneous ureterostomy and is doing well. Of note, her only history of TB exposure was an uncle with TB when she was six years old.

BCGosis Cases

1) An 83 year old Caucasian male with carcinoma in situ (CIS) of the bladder underwent induction intravesical BCG therapy in 2008. After his fourth weekly treatment, he developed chills, fever, fatigue, hemoptysis, night sweats, and shortness of breath. He was admitted to the hospital for suspected miliary TB, and urethral catheterization was difficult.

Urine cultures were negative and three sputum smears were negative for AFB; however, chest radiograph showed pulmonary opacities consistent with BCGosis. He was started on RIPE therapy and completed it without incident; however, since presentation, he has had four abnormal urine cytologies concerning for malignancy. All other investigative measures including CT urogram, retrograde pyelograms, ureteroscopy, and biopsies have been negative.

2) A 73 year old African-American male with a history of T1G3 urothelial carcinoma of the bladder underwent transurethral resection of bladder tumor and induction intravesical BCG in 2011. He completed one treatment, and urethral catheterization became difficult during his second treatment. He completed his first three instillations but missed his fourth due to fever, diaphoresis, productive cough, and myalgia. Urine culture, urine and sputum AFB stains, and blood cultures were all negative. Chest imaging revealed diffuse reticulonodular pattern consistent with miliary TB (Figure 7). RIPE therapy was initiated, and he recovered uneventfully. He has since had seven positive urine cytologies and a negative work up for possible upper or lower tract urothelial carcinoma recurrence.

3) A 78 year old male presented to our institution with complaints of dysuria, urinary urgency, and urge incontinence in 2012. Urinalysis was normal, but urine cytology was positive for urothelial carcinoma. Bladder biopsies revealed CIS, and he completed



Figure 7: Miliary TB secondary to disseminated BCG

induction intravesical BCG therapy. Follow up cystoscopy revealed recurrent CIS, so he was prescribed maintenance BCG therapy. After one maintenance BCG treatment, he developed severe frequency and dysuria without fever or chills. His BCG treatments were stopped, and rifampin and

isoniazid were initiated. He completed six months of therapy, and his urinary symptoms resolved. His urine cytologies have remained negative since treatment.

Five patients have had a confirmed diagnosis of GUTB at our institution since 2008, and three have had infection following BCG administration. The GUTB group consists of two males and three females with average age of 62 ± 7.8 years at presentation. The three females are non-immigrant, while the two males are Hispanic immigrants. Common findings at presentation included dysuria, frequency, nocturia, urgency, and incontinence. None had generalized symptoms. Labs revealed sterile pyuria, hematuria, and elevated ESR. Imaging findings included reduced renal function on renogram, hydronephrosis, ureteral stricture, renal calcification, fistula, small bladder capacity, and renal atrophy. Diagnosis was confirmed with urine culture, PCR, and/or surgical pathology. Organisms isolated included *Mycobacterium tuberculosis* and *Mycobacterium avium-intracellulare*. No urine smears were positive for AFB. Surgical interventions included stent placement, nephrostomy tube placement, and nephrectomy. RIPE therapy resulted in resolution of infection in all patients as judged by improvement in clinical symptoms and negative urine culture; however, sequelae of disease persisted in multiple patients.

Two of three patients with BCGosis had episodes of difficult catheterization prior to developing generalized symptoms. This increases risk of BCG absorption due to disrupted urothelium. Two cases had false positive urine cytologies following treatment. All cases of BCGosis resolved with appropriate anti-tuberculous therapy.

Discussion

Current literature on GUTB is lacking, particularly in developed countries. Only two case reports of American-born patients with GUTB were found in a search of the available literature since 1945. One reports an African American woman with sterile pyuria and relapsing pyelonephritis whose urine stained positive for AFB and culture revealed *Mycobacterium tuberculosis*.⁶ The second, a Caucasian male with AIDS who presented with fevers, night sweats,

chills, and dysuria. Urine culture returned positive for *Mycobacterium tuberculosis*, and transurethral resection of prostate specimen also stained positive for AFB.⁷

Next, we review case reports of immigrants who have been diagnosed with GUTB in the United States. First is an Ethiopian infant who developed fever, sweats, and respiratory distress. Urine culture and bronchial washings were positive for *Mycobacterium tuberculosis*.⁸ Next is a Russian man with a left testicular mass whose urinalysis revealed sterile pyuria. The mass was excised. Ziehl-Neelsen staining of the surgical specimen was positive for AFB, and tissue culture was positive for *Mycobacterium tuberculosis*.⁹ The third is an Egyptian man who had a left scrotal mass and underwent orchiectomy. Pathology revealed AFB with a culture positive for *Mycobacterium tuberculosis*.¹⁰ The fourth case involves a young man from Sierra Leone who presented with right inguinal mass. Fine needle aspiration of the mass was AFB positive on Ziehl-Neelsen staining.¹¹ The fifth case is a male from El Salvador with uremia and bilateral ureteral obstruction from GUTB.¹² The final case is an elderly immigrant from Eritrea with sterile pyuria, ureteral stricture, hydronephrosis, and bladder wall thickening. Bladder biopsy revealed granulomatous disease.¹³

Our case series is the largest in the United States to date, possibly because TB is a rare illness with an incidence of 4.6 cases per 100,000 people.¹⁴ The average age of those suffering from GUTB in the Centers for Disease Control data is 52 years, whereas our patients presented at an average age of 62. Most reported cases of GUTB are male, but our series had a female predominance. It is important to note that GUTB can affect patients of any demographic or ethnic group, with or without immigration history.

High degree of suspicion and familiarity with GUTB symptoms are crucial to its prompt diagnosis and treatment. Particular attention should be paid to patients with chronic urologic complaints of unknown etiology. In our patient population, time from initial presenting symptoms to diagnosis varied from three to fourteen years. In cases where GUTB is suspected, a detailed medical history should be

taken. Diagnostic options include urine culture, AFB smear, urine PCR, and tissue biopsy. Urine culture for TB can take up to 8 weeks to finalize, possibly delaying initiation of anti-tuberculous treatment; however, it is highly sensitive (80-90%) and specific (100%).² Not all urine cultures return positive even when the patient has GUTB; therefore, three to five early morning urine cultures should be performed on successive days. In our series, two of four patients with positive cultures had at least one negative culture. AFB staining has 52% sensitivity and 97% specificity,² but this is rarely helpful due to paucity of Mycobacteria in urine specimens. This was never positive in our group. PCR can be useful if positive, but false negatives have been reported in 10% of cases.¹⁵ ESR is typically elevated in cases of GUTB, but it can be elevated in any inflammatory condition. Urine culture remains the gold standard for GUTB diagnosis. Diagnostic radiographic findings of long-standing GUTB may include kidney or prostate caverns, contracted bladder, or ureteral changes. In this era of increased international travel and immigration, emergence of drug-resistant TB, and increasing HIV incidence, clinicians must remain vigilant to diagnose GUTB in a timely manner. Undiagnosed GUTB can lead to renal failure, fistula formation, contracted bladder, urinary incontinence, and infertility. As shown in our series, patients' symptoms may persist or worsen despite appropriate treatment due to fibrosis. GUTB is typically treated with six months of RIPE therapy.

BCGosis differs in presentation from GUTB. Patients are often acutely ill and do not have positive urine cultures. In our series, traumatic catheterization was an important risk factor for BCG dissemination. BCG cystitis is treated conservatively with analgesics and anticholinergics. Termination of BCG instillations, broad-spectrum antibiotics, and isoniazid therapy for three months is recommended for febrile UTIs. For patients developing sepsis, hospitalization and RIPE therapy is indicated, and glucocorticoids can be added to aid in hypersensitivity-related symptoms. Duration of anti-tuberculous therapy is six months. It is important to note that urine cytology may remain persistently positive after treatment.

GUTB still exists in United States' patients of any ethnicity with or without immigration history. Patients present with long-standing genitourinary symptoms and no generalized symptoms. A high index of suspicion and experience is required for timely diagnosis and management. Urine culture is the mainstay of diagnosis. Disseminated BCG infection during intravesical therapy for bladder cancer may result in severe systemic symptoms. Urine culture is typically negative. Urine cytology may be persistently positive even after successful treatment. Difficult catheterization should preclude intravesical BCG installation as it is a known risk factor for disseminated BCG infection.

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