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Authors

Manios, Elizabeth

Cheng, Mindy

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CLINICAL VIGNETTE

Urogenital Tuberculosis: Not Such an Uncommon Problem

Elizabeth Manios, M.D., Mindy Cheng, M.D.

Introduction

Urogenital tuberculosis (TB) is the second most common type of extrapulmonary tuberculosis in the United States, and the incidence is on the rise, especially in certain immigrant populations and in immunocompromised patients^{1,2}. Urogenital TB can be a challenge to diagnose, often overlooked until late in the disease when the patient has already developed significant morbidity from the infection^{3,4}. As clinicians, it is important to keep this diagnosis in mind in high-risk individuals, even though initially they may have minimal symptoms and relatively normal laboratory and radiological studies.

Case Report

A 43-year-old, previously healthy, Mexican female presented to a county-run primary care clinic with a 3-month history of intermittent left flank pain, radiating to the groin with dysuria and increased urgency and frequency of urination. At approximately the same time, she also began to experience diffuse joint pains in her hands, wrists, and knees, as well as fatigue and morning stiffness typically lasting an hour. She had been treated for urinary tract infection/pyelonephritis on two separate occasions over the 3 months, the last being approximately 1 month prior, with a 10-day course of ciprofloxacin; but her symptoms persisted. She has a family history of kidney stones, but she herself has never been diagnosed with such. Review of systems was negative for hematuria, vaginal discharge, fevers, chills, cough or night sweats; but she did report an approximate 10-pound unintentional weight loss over the past few months. The patient's past medical history reveals a positive mantoux test in 1994 with a negative chest radiograph at the time. She takes no medications on a regular basis. Social history reveals she was in a long-standing monogamous relationship with her husband without contraception. Patient is a non-smoker who emigrated from Mexico as a teenager.

In clinic, the patient was depressed and tearful but otherwise well appearing. She was afebrile, 36.2 degrees Fahrenheit, with a regular pulse of 79 beats per minute, and a blood pressure of 114/79 mm Hg.

Her exam was largely unremarkable with no erythema, swelling, nor warmth on joint exam bilaterally; no suprapubic or CVA tenderness; and a negative pelvic exam without cervical wall motion tenderness, discharge, or adnexal mass.

Initial laboratory work-up included a urine analysis, a preliminary rheumatologic work-up, including antinuclear antibody test (ANA) and rheumatoid factor (RF) for her joint complaints, and urine for gonorrhea and chlamydia, which were all negative or within normal limits. Her complete blood count and basic metabolic panel were all within normal limits as well. Her urine analysis on two previous visits to the urgent care clinic were positive for leukocyte esterase, white blood cells, and red blood cells, but both urine cultures were negative for any growth. A renal ultrasound was ordered to evaluate for kidney stones, which revealed a left-sided mild hydronephrosis and hydroureter. A follow-up computed tomography urogram showed a filling defect within the left inferior calyx, mild dilatation of the ureter with a 4 cm segment of significant ureteral wall thickening in the mid aspect, and a 5 cm segment of wall thickening in the distal left ureter.

The patient was referred to urology and was scheduled for biopsy of a presumed ureteral tumor. She underwent ureteroscopy, cystoscopy, and retrograde pyelogram with ureteral and bladder biopsies. They found a fixed bladder, infiltrative lesions surrounding the left ureter, and bloody, friable tissue at the renal pelvis. The official pathology report showed acute and chronic inflammation with eosinophils and histocytes suggestive of granulomatous inflammation. The urine was tested for acid-fast bacilli at that time and found to be positive. Patient was started on Rifampin, Isoniazid, Pyrazinamide and Ethambutol (RIPE) therapy for urogenital tuberculosis.

Discussion

The urogenital system is the second most common extrapulmonary site of tuberculosis (TB) infection, usually resulting from hematologic spread from a

primary pulmonary infection^{1,5}. We will be focusing on the urological system, as this was the presentation of our patient, but TB can affect the entire genital system including the prostate, seminal vesicles, epididymides, penis and testicles in men and the pelvic organs in women¹. Diagnosing urogenital TB is fraught with difficulty, from the minimal amount of symptoms and laboratory signs to the dearth of diagnostic tools available^{1,4}. In patients with persistently vague urinary symptoms, a high index of suspicion is key to making the diagnosis of urological TB. Early diagnosis is crucial as prolonged infection can result in renal or ureteral stenosis and, ultimately, renal failure^{1,5}. Urogenital TB should be considered in individuals from high risk areas and anyone with a history of primary pulmonary TB, latent TB, and positive PPD and/or quantiferon gold.

Since the resurgence of tuberculosis in the early 1990's, due largely to the HIV epidemic and a lax public health infrastructure, there has been a subsequent heightened public health awareness campaign and the implementation of Directly Observed Therapy by the World Health Organization^{2,6}. With this new infrastructure in place, the incidence of TB in the United States has dropped to a record low of 3.8 per 100,000 in 2009². Now the majority of TB cases in the United States occur in foreign-born individuals emigrating from countries with high rates of endemic TB^{2,7}. The fraction of cases in the United States ascribed to foreign-born individuals increased from 22 to 58 percent between 1986 and 2007 with the majority of these cases being reactivation of latent infection^{2,8}. The countries accounting for the majority of U.S. cases of TB in foreign-born persons are Mexico, the Philippines, Vietnam, India, China, the Dominican Republic, and Haiti^{2,8}. California, New York, New Jersey, Texas, and Florida top the list of states accounting for the greatest number of cases^{2,8}. A second population of high risk individuals includes those with comorbidities that cause immunodeficiency. Because of HIV/AIDS and the increasing use of immunosuppressive medications such immunomodulators for inflammatory and autoimmune conditions, there has been a rise in the overall incidence of extrapulmonary TB^{1,6}.

Our patient emigrated from Mexico with a positive PPD. Though she had no symptoms of pulmonary infection and a previously clear chest radiograph, she warranted a high index of suspicion. Latency from a primary lung infection can last anywhere from one to forty-six years and a meta-analysis of extrapulmonary TB showed that in only 36% of cases was there any evidence of previous lung infection^{1,3}.

The most common presentation of urological TB is persistent dysuria, pyuria and/or hematuria^{1,3,4}. Similar to our patient they may present with recurring urinary tract infections with minimal or no response to normal antibiotic regimens. Interestingly, in autopsy studies of renal tuberculosis, only 50% of affected individuals were actually symptomatic¹. The differential diagnosis for urological TB includes renal colic, nephrolithiasis, pyelonephritis, chronic cystitis, epididymitis and urogenital malignancies^{3,4}.

Though hematuria and pyuria may be present in many cases, one cannot rely on such findings to diagnose urological TB. The current gold standard is a urine AFB culture, which has a very low sensitivity of about 50% (from 10-90%) and specificity of 90%¹. Bacilluria can be seen in urogenital TB but it is usually sporadic and faint so ideally three to six early-morning urine samples should be cultured for a reliable result. Intravenous urography (IVU) has a better sensitivity of 94%, but it carries the risk of contrast and radiation exposure and potentially subjecting the patient to unnecessary surgical intervention when pseudotumors from TB are mistaken for malignancies^{1,3,5}. The classic findings for urological TB on computed tomography are unilateral hydronephrosis caused by intrarenal ureteral stricture⁵. The earliest finding is a caliceal dilatation caused by infundibular stenosis⁵. The use of urine TB polymerase chain reaction (PCR) had appeared to be a promising means of early and accurate detection of urological TB. One study, published in *Urology* in 2000, showed PCR was the most sensitive in detecting 94% of cases compared to 88% with IVU and only 37% with AFB cultures⁷. However, a repeat study in the same journal in 2008 showed rapid PCR had only a sensitivity of 48.5%⁶. The take home point is that if there is a high index of suspicion for urogenital TB but rapid PCR is negative, one should still consider urine culture and imaging to rule out the diagnosis.

The treatment for urological tuberculosis does not differ from the treatment for active pulmonary TB. Our patient was put on RIPE therapy. Previously regimens differed only in duration with extended treatments of as long as two years for urological TB. However, given the good renal penetration and high urine concentrations of the drugs, efficacy was found to be similar between short and long courses of treatment^{1,3,4}. There does appear to be a greater incidence of relapse associated with urological TB, up to 6% of cases; therefore, a longer follow-up period, of at least 10 years, has been recommended^{1,4}. In those cases with delayed diagnosis, where there is evidence of renal destruction and or failure,

nephrectomy of the affected kidney with 4 to 5 months of pharmaceutical treatment can decrease the rate of relapse to 1%^{1,4}.

Of note, in our case, the patient later developed ANA positive arthropathy (titer of 1:1280) while on treatment with RIPE. It was thought to be likely a reactive arthritis, however, TB infections have been shown to precipitate systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and other autoimmune diseases (AI)^{9,10}. Interestingly, individuals with SLE, RA or AI have a significantly increased risk of developing TB due not only to the use of steroids and other immunosuppressive agents, but also to the immune derangements inherent in the diseases themselves^{9,10}.

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