The Wrong Frame of Mind

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In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information by sharing relevant background and reasoning with the reader (regular type). The authors' commentary follows.

A 62-year-old woman with hypertension and depression presented to a urology clinic with a 15-month history of episodic dysuria, hematuria, and polyuria. She reported suprapubic discomfort but no flank pain, nausea, or early satiety. She reported no fever, chills, night sweats, weight loss, anorexia, dyspepsia, or cough. She had visited five health care providers for these symptoms. All the urinalyses showed 3+ leukocyte esterase, no nitrites, more than 10 white cells per high-power field, and 1 to more than 50 red cells per high-power field. The patient received empirical treatment for urinary tract infection on each occasion. Trimethoprim–sulfamethoxazole was prescribed twice and ciprofloxacin on three occasions, but she had no reduction in symptoms. All the urine cultures were negative. She had no history of sexually transmitted infections, abdominal surgery, nephrolithiasis, or urinary tract infections. She was a homemaker and lived with her son. She had no history of alcohol, tobacco, or illicit-drug use. She was not sexually active.

Urinary tract infection may be recurrent because of structural issues (e.g., impaired bladder empting in postmenopausal women), patterns of sexual activity, or reservoirs of infection (e.g., kidney stone), but often the precise cause of a recurrent infection is not determined. Urogenital atrophy, which is common among postmenopausal women, confers a predisposition to recurrent urinary tract infections but may also cause symptoms that mimic urinary tract infection. A false negative urine culture may occur because of low bacterial burden or because of the use of an antibiotic agent. However, five consecutive negative urine cultures and ongoing symptoms despite the use of antibiotics make bacterial cystitis a highly unlikely diagnosis. Alternative infections to consider with the appropriate epidemiologic evidence are sexually transmitted infections, intracellular pathogens (e.g., ureaplasma), and tuberculosis. Ciprofloxacin may partially treat a mycobacterial infection. A urothelial tumor can manifest as hematuria, sterile pyuria (i.e., the presence of white cells in the urine despite the absence of bacteria), and irritative symptoms. The patient's persistent pyuria, hematuria, and suprapubic discomfort suggest ongoing inflammation within or adjacent to the genitourinary tract. Acute appendicitis or diverticulitis can induce sterile pyuria, but on a more chronic basis, any cancer (e.g., colorectal, ovarian, or endometrial) may irritate the ureter or bladder; however, the absence of weight loss over the 15-month period makes cancer unlikely.

On physical examination, the patient's temperature was 36.4° C, heart rate 70 beats per minute, and blood pressure 134/72 mm Hg. She appeared comfortable. Heart
and lung examinations were normal. Her abdomen was soft and without hepatosplenomegaly. There was no flank tenderness.

The white-cell count was 6800 per cubic millimeter, with 65% neutrophils, 24% lymphocytes, 8% monocytes, and 3% eosinophils. The hemoglobin level was 12.7 g per deciliter, and the platelet count was 239,000 per cubic millimeter. The serum electrolyte levels were normal. The creatinine level was 0.82 mg per deciliter (72.5 μmol per liter). The levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin were normal. A radiograph of the chest revealed hypoinflated lungs without consolidation or edema. Urine studies showed pyuria (>50 white cells per high-power field), hematuria, and a negative bacterial culture. Urine nucleic-acid amplification tests for *Chlamydia trachomatis* and *Neisseria gonorrhoea* were negative.

Common sexually transmitted infections have been ruled out by highly sensitive tests in the context of a low pretest probability. There is no clinical evidence of multiorgan disease to suggest endocarditis or vasculitis (e.g., polyarteritis nodosa). Genitourinary tuberculosis often manifests as sterile hematuria and pyuria but most often develops in patients who have risk factors for tuberculosis. The radiograph does not show evidence of previous or active tuberculosis, but genitourinary tuberculosis often progresses independently of disease at other sites in the body.

Results of urine cytologic testing revealed urinary lymphocytes but no evidence of cancer. A computed tomographic (CT) urogram, performed on an outpatient basis, showed a 2.0-cm heterogeneous mass in the lower pole of the right kidney, multifocal ureteral thickening with masslike features along the right ureter, hydronephrosis of the right kidney, diffuse thickening of the gastric wall, haziness along the anterior omentum, and numerous subcentimeter retroperitoneal lymph nodes (Fig. 1).

The imaging findings reveal an extensive burden of disease distributed among four intraabdominal organs: the kidney, ureter, stomach, and lymph nodes. The invasiveness and distribution arouse concern for cancer, although chronic infection is also possible. Any one of the aforementioned organs could harbor a primary neo-

![Figure 1. Computed Tomographic Urogram with Intravenous Contrast Enhancement.](image)

Panel A shows diffuse thickening of the gastric wall, with haziness along the anterior omentum and mesentery; Panel B, a heterogeneous enhancing mass at the lower pole of the right kidney; and Panel C, urothelial thickening involving a long segment of the right ureter.
nodes is plausible, metastases to the kidney and ureter would be unusual for a gastric neoplasm. Lymphadenopathy that is restricted to the retroperitoneum usually reflects metastatic cancer or a lymphoma arising within the retroperitoneum. The renal mass could be renal-cell carcinoma, which can spread to adjacent retroperitoneal lymph nodes, but it typically does not extend to the stomach, omentum, or distal ureters. If the mass in the lower pole of the right kidney arises from the renal pelvis, it may be transitional-cell carcinoma that has invaded the ipsilateral ureter. The patient does not smoke, which puts her at a lower risk for urothelial cancer.

Haziness of the omentum on imaging can reflect either a metastatic cancer or an infection such as tuberculosis but may also be seen in autoimmune serositis (e.g., systemic lupus erythematosus) or peritoneal mesothelioma. Gastric or ovarian cancers typically cause peritoneal carcinomatosis and are often accompanied by malignant ascites. The multifocal unilateral ureteral thickening with associated hydronephrosis is also characteristic of genitourinary tuberculosis, which can cause a granulomatous renal mass.

One month later, cystoureterscopy, performed on an outpatient basis, showed erythematous patches throughout the bladder. The right ureter had substantial inflammation with white fibrinous debris but no discrete lesion. Biopsy specimens of the bladder and ureter were obtained. A ureteral stent was implanted. The patient was discharged home.

Approximately 12 hours later, she presented to the emergency department with fever, rigors, and abdominal pain. Her temperature was 39.5°C, the heart rate 76 beats per minute, and the blood pressure 114/56 mm Hg. The hypogastrum was tender. The white-cell count was 10,200 per cubic millimeter, hemoglobin level 10.2 g per deciliter, and platelet count 114,000 per cubic millimeter. A urinalysis showed more than 50 white cells per high-power field. The creatinine level was 1.0 mg per deciliter (88 μmol per liter). No liver biochemical tests were performed. After the results of blood and urine cultures were obtained, ceftriaxone and vancomycin were prescribed for suspected periprocedural urosepsis, and she was admitted to the hospital.

Approximately 48 hours after admission, urine and blood cultures were negative, but the patient's fevers persisted. CT of the abdomen and pelvis showed that the position of the ureteral stent was stable and that the renal mass, ureteral thickening, hydronephrosis, and retroperitoneal lymphadenopathy all remained unchanged. Approximately 72 hours after admission, the total bilirubin level was 4.9 mg per deciliter (83.8 μmol per liter) (normal range, 0.0 to 1.4 mg per deciliter [0 to 23.9 μmol per liter]), alanine aminotransferase 233 U per liter (normal range, 0 to 55), aspartate aminotransferase 157 U per liter (normal range, 5 to 34), and alkaline phosphatase 355 U per liter (normal range, 40 to 150). The international normalized ratio was 1.2, and the albumin level was 2.6 g per deciliter (normal range, 3.5 to 5.0). The white-cell count was 3300 per cubic millimeter, hemoglobin level 11.0 g per deciliter, and platelet count 95,000 per cubic millimeter.

Pathological analysis of biopsy specimens from the bladder and ureter obtained during the cystoureteroscopy showed a benign urothelium with chronic inflammation (Fig. 2). A repeat radiograph of the chest showed bibasilar atelectasis. The patient had no respiratory symptoms or hypoxemia.

Bladder or ureteral perforation with peritoneal spillage and translocation of pathogens (e.g., bacteria, fungi, or mycobacteria) from the urinary system to the bloodstream are immediate considerations for her fevers, rigors, and abdominal pain. Periprocedural antibiotics are common.
ly administered at the time of urologic procedures and could result in negative cultures even when a bacterial infection is present.

The results of the liver biochemical tests indicate a mixed cholestatic and hepatocellular injury without hepatic synthetic dysfunction. Concomitant acute pancytopenia and hepatitis may arise from a viral infection that affects the liver and bone marrow simultaneously (e.g., Epstein–Barr virus) or from an adverse reaction to a medication. Sepsis can cause acute pancytopenia, hepatitis, and hyperbilirubinemia.

The cystoureteroscopic findings (both visualized and histologic) confirm inflammation but do not distinguish between infection and cancer. The absence of malignant cells in a biopsy specimen makes transitional-cell carcinoma an unlikely diagnosis, but sampling error must be considered. No granulomas were seen on the biopsy specimen to suggest tuberculosis, but acid-fast bacilli staining, mycobacterial culture, and mycobacterial polymerase-chain-reaction (PCR) testing are needed to further evaluate the possibility of tuberculosis. Endemic mycoses, such as histoplasmosis, that could have been either newly acquired or reactivated can manifest as fever, hepatitis, cytopenias, and lymphadenopathy; genitourinary involvement, however, is unusual.

Additional history taking revealed that the patient had immigrated to the United States from Guadalajara, Mexico, 18 years earlier. During her childhood, she worked on her family’s dairy farm, where she would frequently consume unpasteurized milk. She had no known contact with persons who had tuberculosis, but before immigrating, she had a positive tuberculin skin test in Mexico. Isoniazid had been prescribed for latent tuberculosis, but she did not take the medication because she was concerned about its side effects.

The new epidemiologic information and the patient’s history of having had a positive tuberculin skin test for which she did not receive treatment substantially increase the probability of genitourinary tuberculosis. The genitourinary tract is a common site of extrapulmonary tuberculosis, and the infection can progress in that site without causing fever, night sweats, or weight loss. A history of consuming unpasteurized milk suggests additional possible pathogens, including listeria, campylobacter species, brucella species, and Mycobacterium bovis. The likelihood of each pathogen is modified by the timing of the patient’s last exposure. It would be important to ask whether she has had more recent exposure to unpasteurized dairy, either while travelling or by consumption of imported products.

Of the pathogens associated with the consumption of unpasteurized milk, only M. bovis can reactivate after decades and is clinically indistinguishable from tuberculosis. Brucellosis causes fever, hepatitis, and cytopenias and can involve the genitourinary system; however, the chronic form is often an extension of an acute illness, which the patient did not have. Q fever, which arises from exposure to livestock (and to their milk), manifests similarly to brucellosis, although genitourinary involvement is rare. Listeria and campylobacter species usually cause an acute gastrointestinal illness and have neither chronic forms nor prominent genitourinary symptoms; furthermore, listeria and campylobacter species would not account for the radiologic abnormalities. On the basis of the absence of respiratory symptoms and a nondiagnostic chest radiograph, the risk of transmission of tuberculosis could be assessed as low; however, 50% of patients with miliary tuberculosis have a normal chest radiograph. The high fever and multiorgan involvement suggest widely disseminated mycobacterial disease.

Tests for fungal antigens, serologic tests for brucella, and bacterial urine cultures were negative. Testing for human immunodeficiency virus (HIV) antigen and antibody was nonreactive. Six urine specimens revealed 1 to 9 acid-fast bacilli per 10 oil-immersion fields. Treatment with rifampin, isoniazid, and ethambutol was initiated for genitourinary mycobacterial infection. Pyrazinamide was not prescribed, given the presence of acute hepatitis and the possibility of M. bovis infection, which is resistant to pyrazinamide.

Mycobacterium tuberculosis and M. bovis infection are clinically indistinguishable in their pulmonary and extrapulmonary forms. The patient was probably exposed to both pathogens during her youth. Reactivation is a more likely possibility than newly acquired infection, and her age
rather than immunosuppression is her risk factor for reactivation.

The hepatitis and fever that occurred after the cystoureteroscopy resemble the reactions that are observed after intravesicular administration of bacille Calmette–Guérin (an attenuated strain of \textit{M. bovis}) for superficial bladder cancers. It is possible that the marked thickening of the gastric wall could reflect the primary gastrointestinal burden from ingestion of \textit{M. bovis}. These observations, along with the patient’s history of exposure to unpasteurized dairy, support consideration of \textit{M. bovis} infection. However, the high prevalence of \textit{M. tuberculosis} in Mexico makes tuberculosis the most likely diagnosis.

A urine PCR assay for \textit{M. tuberculosis} was positive. Treatment for tuberculosis was complicated by nausea, vomiting, and progressive hyperbilirubinemia (highest bilirubin level observed, 10.2 mg per deciliter [174 \(\mu\)mol per liter]). A liver biopsy showed necrotizing granulomas throughout the liver parenchyma (Fig. 3). The result of staining for acid-fast bacilli was negative; Grocott–Gomori methenamine silver staining and Warthin–Starry staining were also negative.

Stains of three sputum samples were negative for acid-fast bacilli. Nausea and vomiting abated after the patient’s treatment was changed from rifampin to rifabutin, and her liver biochemical levels gradually normalized. After a 1-month hospitalization, she was discharged home with continued prescriptions for isoniazid, rifabutin, ethambutol, and levofloxacin. Sensitivity of the pathogen to fluoroquinolones was not known at the time of discharge, but alternatives were considered to be too risky in the presence of existing hepatitis and pancytopenia. Urine cultures and one sputum culture were positive for pansensitive tuberculosis. Treatment with levofloxacin and ethambutol was discontinued. After 9 months of treatment with isoniazid and rifabutin, the patient had complete resolution of her urinary symptoms, pyuria, and imaging abnormalities.

**COMMENTARY**

Among the 3 billion people worldwide who are infected with tuberculosis, active disease will develop in approximately 10%.\(^2\) Within the United States, approximately 10,000 cases of active tuberculosis are diagnosed annually, and 20% of those cases are extrapulmonary.\(^2\) The incidence of tuberculosis is 13 times as high among foreign-born persons as it is among persons born in the United States, and Mexico is the most common country of origin for foreign-born U.S. patients with tuberculosis.\(^2\) The genitourinary system is the second most common site of dissemination (after lymphatic tissue) and is involved in approximately one third of extrapulmonary cases.\(^3\)

In a review of 39 studies involving a total of more than 9000 patients with genitourinary tuberculosis across 23 countries, 50% of the patients presented with lower urinary tract symptoms, 36% with hematuria, and 35% with lumbar pain.\(^4\) In a series involving 41 patients with renal tuberculosis who presented to a U.S. academic hospital, more than 70% presented with symptoms that involved the lower urinary tract; examination of the urine revealed sterile pyuria in 46% of the patients, pyuria and hematuria in 34%, and isolated hematuria in 12%.\(^3\) Among the patients who had genitourinary tuberculosis, 14 to 21% presented with classic symptoms that are associated with tuberculosis infection, such as fevers, weight loss, and night sweats, and only a third of the patients had evidence of previous tuberculosis on chest radiography.\(^5\) Late manifestations of genitourinary tuberculosis include...
fistulas, abscesses, infertility, ureteral strictures, and obstructive nephropathy. This patient’s symptoms of fever, pancytopenia, and hepatitis that occurred after the cystoureteroscopy probably reflected sepsis from tuberculous bacillemia. 7,8

The diagnosis of genitourinary tuberculosis is typically confirmed by microbiologic evidence of tuberculosis bacilluria on the basis of acid-fast bacilli cultures or urine PCR testing or on the basis of histopathological examination showing granulomatous changes with or without acid-fast bacilli. Staining for acid-fast bacilli is a rapid screening test, but its sensitivity is low in extrapulmonary sites, including in the urine, where the sensitivity is 25%. 9 Guidelines recommend 6 months of multidrug therapy for the treatment of extrapulmonary tuberculosis. 10 Although the choice of antimycobacterial agents is influenced by coexisting conditions, potential drug interactions, and the probability of drug-resistant tuberculosis, the 2-month induction phase usually consists of treatment with isoniazid, rifampin, pyrazinamide, and ethambutol and is followed by 4 months of consolidation treatment with isoniazid and rifampin.

Genitourinary tuberculosis readily comes to mind when a patient from Mexico who has had a positive tuberculin skin test but has never received treatment for tuberculosis presents with unresolved dysuria and sterile pyuria. However, for the first year of this patient’s illness, these features were apparently not appreciated in the context of isolated urgent care appointments with several different providers, each of whom prescribed conventional antibiotics for suspected bacterial cystitis. The eventual characterization of all the urine test results as sterile pyuria led to a urologic evaluation and CT scanning. It was only when sepsis developed after the patient underwent cystoureteroscopy that a comprehensive data set — including the patient’s country of origin, her potential exposure to pathogens during childhood, and her previous tuberculin skin test result — was amassed and was recognized as being characteristic of genitourinary tuberculosis.

In routine practice, most cases of dysuria do not warrant exhaustive history taking and a complete physical examination, and sterile pyuria rarely reflects tuberculosis. 11,12 However, given the repeated presentations, a detailed, problem-focused history that took into account the duration of the symptoms and the lack of response to previous antibiotic therapy was warranted and would have called into question the diagnosis of bacterial cystitis. Without this comprehensive reframing of the entire course of the illness and without an appreciation of the epidemiologic information, some of the patient’s providers remained in the wrong frame of mind.

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REFERENCES