An Unintended Consequence

Nasia Safdar, M.D., Cybele L. Abad, M.D., Daniel R. Kaul, M.D., David Jarrard, M.D., and Sanjay Saint, M.D., M.P.H.

In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors’ commentary follows.

A 79-year-old man with a 5-month history of fatigue and 20-lb (9-kg) weight loss presented to his local physician. The patient also reported intermittent episodes of high temperature, night sweats, and chills during this period. A review of systems and physical examination were unrevealing with the exception of mild nasal congestion. The results of blood and urine cultures and chest radiography were normal. He was treated with a short course of ciprofloxacin, followed by a course of levofloxacin, for a presumed sinus infection, without improvement in his symptoms.

The patient described has a classic fever of unknown origin — fever persisting for more than 3 weeks and no obvious cause after initial evaluation. The most common causes of fever of unknown origin include infections, malignant conditions, and rheumatic or connective-tissue diseases such as temporal arteritis and polymyalgia rheumatica. Among malignant conditions, renal cancer, leukemia, and lymphomas are most likely to cause fever. A number of less common conditions that do not fit neatly into the above categories (e.g., pheochromocytoma, drug fever, and thyroiditis) should also be considered. The negative blood cultures for bacteria in this case, assuming they were obtained before the patient received antibiotics, make bacterial endocarditis unlikely. Empirical antimicrobial therapy is generally discouraged during the diagnostic evaluation of patients with fever of unknown origin, since antibiotics may reduce the yield of diagnostic testing and rarely result in a lasting resolution of symptoms. Sinusitis would be an unlikely cause of this patient’s constellation of symptoms.

The patient’s medical history was significant for coronary artery disease (he had undergone coronary-artery bypass grafting 5 years earlier), gastroesophageal reflux disease, hypothyroidism, and transitional-cell cancer of the bladder, which had been diagnosed 4 years earlier and was currently in remission. His medications included atorvastatin, levothyroxine, aspirin, and omeprazole. The patient lived in the upper midwestern United States with his wife and children. He did not smoke, and he drank alcohol occasionally. He enjoyed the outdoors and lived in a wooded area, but he did not recall any recent tick bites. He did not have any contact with animals. His last travel was to Florida 1 year previously, when he spent several weeks helping to prepare supplies to send to the communities affected by Hurricane Katrina.

Transitional-cell cancer of the bladder may recur locally or at a metastatic site, and tumor fever may result, although bladder cancer does not typically cause fever. Infection with nocardia species or endemic fungi (e.g., Histoplasma capsulatum or Blas-
T. dermatitidis) may be acquired in wooded areas in the upper Midwest.

Two weeks after completion of antimicrobial therapy, he returned to his physician. The intermittent fever, fatigue, and night sweats persisted. Another detailed review of systems and a thorough physical examination were unrevealing, and an evaluation for fever of unknown origin was undertaken. The results of a complete blood count were normal. The results of renal-function and liver-function tests were within normal limits. Serologic tests for ehrlichia, Lyme disease, and West Nile virus were negative. Computed tomography (CT) of his chest, abdomen, and pelvis revealed an infrarenal aneurysm surrounded by inflammatory changes that were highly suggestive of a mycotic aneurysm (Fig. 1). (CT performed 1 year before as follow-up for the bladder cancer had revealed no evidence of the aneurysm.) He was admitted to an academic medical center for further evaluation.

CT of the abdomen and pelvis is recommended in patients with fever of unknown origin, and the most common finding is an abscess or lymphadenopathy. In this patient, the CT study revealed an infrequent cause of fever of unknown origin — namely, a likely mycotic aneurysm of the infrarenal aorta. Infected aneurysms of the aorta are rare but potentially catastrophic. They may arise from hematogenous seeding of the intima of the aorta (particularly in patients with preexisting atherosclerotic disease), local extension from a contiguous source (e.g., vertebral osteomyelitis), or embolic seeding of the wall of the artery (the typical mechanism in patients with endocarditis). Staphylococci, streptococci, and salmonella are the most common organisms isolated, but other gram-negative organisms, brucella species, anaerobes, Listeria monocytogenes, fungal organisms, and mycobacterial organisms have been reported. A mycotic aneurysm may occur with cardiovascular syphilis, but the infrarenal aorta is rarely involved.

Imaging characteristics that are helpful in distinguishing infected from noninfected aneurysms include para-aortic soft-tissue stranding or fluid, associated psoas fluid collections, vertebral-body destruction, and the presence of gas surrounding the inflamed site. In equivocal cases, an indium scan may be helpful in determining whether infection is present. Negative blood cultures may occur with infected aortic aneurysms, but blood cultures are generally positive if endocarditis is present.

On physical examination, the patient was alert and oriented. He appeared chronically but not acutely ill. His temperature was 38.3°C. His blood pressure was 111/65 mm Hg, pulse 72 beats per minute, respiratory rate 16 breaths per minute, and oxygen saturation 99% while he was breathing ambient air. His lungs were clear on auscultation. Cardiovascular examination showed distinct heart sounds that were normal, with no audible murmur. His abdomen was soft and nontender, with no organomegaly. His arms and legs were warm, with no edema. The rectal examination revealed no masses; a test for fecal occult blood was negative. The neurologic examination was normal. The skin examination revealed no rash or other lesions. There was no joint swelling or erythema.

The absence of findings on physical examination that are suggestive of infective endocarditis (e.g., murmur, Roth spots, splinter hemorrhages, or swollen joints) combined with negative blood cultures make endocarditis an unlikely source of the probable mycotic aneurysm. However, these are not universal findings in endocarditis, and negative blood cultures may result from previous antibiotic use. I would proceed with echocardiogra-

Figure 1. CT Scan of the Abdomen Showing the Aneurysm (Arrowhead) and Perianeurysmal Inflammatory Changes (Arrow).
There is no report of back pain, which, if present, might suggest extension into the vertebral spine. Urgent surgical intervention is warranted for the aneurysm.

The white-cell count was 9900 per cubic millimeter, with 55% neutrophils, 27% lymphocytes, 16% monocytes, and 2% eosinophils. Immature band forms were not noted. The hematocrit was 32%, and the platelet count was 199,000 per cubic millimeter. Levels of serum electrolytes were normal. The blood urea nitrogen level was 20 mg per deciliter (7.1 mmol per liter), the creatinine level 1.0 mg per deciliter (89 μmol per liter), the aspartate aminotransferase level 75 U per liter (normal value, <50 U), and the alanine aminotransferase level 50 U per liter (normal value, <65 U). Levels of total bilirubin and alkaline phosphatase were normal. Serum antibody tests for hepatitis A, B, and C virus were negative. A urinalysis showed moderate heme, with no leukocyte esterase or white cells, and between 11 and 20 red cells. A chest radiograph on admission showed prominent interstitial markings without infiltrates (Fig. 2).

The laboratory findings and chest radiography are not particularly helpful in determining the cause of the patient’s mycotic aneurysm. The hematuria may be related to his history of bladder cancer. To reduce the risk of postoperative sepsis and infection of graft material, it would be reasonable to begin antibiotic therapy preoperatively, but I would hope to proceed rapidly to surgery. Vancomycin and a broad-spectrum beta-lactam antibiotic would be reasonable empirical therapy.

At the time of the patient’s admission to the hospital, treatment with vancomycin and ceftriaxone was initiated empirically. Two sets of blood cultures were obtained before treatment with antibiotics was initiated; both were negative. The Westergren erythrocyte sedimentation rate was 16 mm per hour, and the C-reactive protein level was 1 mg per deciliter. Magnetic resonance imaging (MRI) of the abdomen and pelvis revealed a wide saccular aneurysm that had an irregular periphery with a cranial-to-caudad length of 3 by 2 cm (Fig. 3). There were inflammatory changes with heterogeneous enhancement surrounding the aneurysm anteriorly.

Most but not all patients with mycotic aneurysm have increased levels of inflammatory markers. A saccular configuration is a common finding in a mycotic aneurysm, as are the inflammatory changes noted on the MRI. Although salmonella species and Staphylococcus aureus are the most common pathogens isolated, gram-negative organisms and streptococcus species may also be isolated.

The patient underwent surgery. Purulent material surrounding the aneurysm was seen. The aneurysm was excised after extensive irrigation and débridement, and a right axillary to right femoral and right femoral to left femoral crossover bypass graft made of synthetic material was placed. Gram’s stains of the purulent material and tissue samples were negative for organisms and polymorphonuclear cells, and bacterial cultures were negative.

The absence of growth in the surgical specimen may be due to previous antibiotic use or the presence of an organism that does not grow on routine bacterial mediums. Mycobacterial or anaerobic organisms (e.g., bacteroides species) would be the most common organisms in that category. I would be interested in any past exposure to Mycobacterium tuberculosis and the results of a purified-protein-derivative test. I would also specifically inquire whether the patient received intravesical bacille Calmette–Guérin (BCG) to treat his bladder cancer, since granulomatous disease may oc-
cur and involve the infrarenal aorta. In addition, any history of gastroenteritis or probable exposure to salmonella species — for example, through contact with reptiles — would be of interest.

A day after surgery, on further questioning, the patient reported that he had received intravesical BCG for his bladder cancer 11 months before admission and had tolerated this treatment well.

BCG is a live attenuated strain of *M. bovis* that is most commonly used as a childhood vaccine for tuberculosis. In rare cases, BCG results in granulomatous disease in a variety of locations when administered as intravesical treatment for bladder cancer. Although a bacterial pathogen (which could have been missed because of previous antibiotic use) is much more probable, the presence of granulomatous inflammation in the surgical specimen — particularly if necrotizing granulomas were observed — would suggest infection with a mycobacterial pathogen. The specimen could then be stained for acid-fast bacilli. It is hoped that cultures for acid-fast bacilli were obtained at the time of surgery, since this would be the most sensitive diagnostic approach and would allow definitive identification of the mycobacterial species. In most cases, however, the suspicion for this type of rare infection is very low, especially if the infection occurs months after exposure to BCG and such cultures are not performed. While these issues are sorted out, empirical antibacterial treatment should be continued.

After the additional history was obtained, a smear for acid-fast bacilli was performed on a tissue specimen obtained intraoperatively, and it was positive, with one to nine acid-fast bacilli per 10 oil-immersion fields. A DNA probe was positive for *M. tuberculosis* complex. Cultures subsequently grew *M. bovis*, BCG type, which was susceptible to commonly used antituberculosis agents, with the exception of pyrazinamide. A specimen was not sent for pathological analysis.

The patient was given isoniazid and rifampin for a planned duration of 1 year. At a follow-up visit 3 months after surgery, the patient was doing well, and all his systemic symptoms had completely resolved.

The patient’s fever of unknown origin was due to granulomatous disease from BCG infection that involved his infrarenal aorta. Given the prolonged duration of symptoms, he is fortunate that the aneurysm was diagnosed and surgically repaired before rupture.

**Commentary**

Diagnosis of fever of unknown origin requires a thorough, detailed history and physical examination and often laboratory testing and appropriate imaging. Consideration of unusual exposures, treatments, or procedures may provide clues to narrow down an otherwise extensive differential diagnosis. In our patient, the history of bladder cancer prompted questions regarding previous BCG immunotherapy, but only after surgery for the mycotic aneurysm had been performed. Although the incidence of systemic complications of BCG intravesical therapy is low and mycotic aneurysms are rare, this exposure should be considered in any patient with symptoms and signs of infection who has a history of superficial bladder cancer, for which BCG is often used. Earlier attention to this history could have expedited the diagnosis and reduced additional testing in our patient.

BCG is a live attenuated strain of *M. bovis* that has been used as a vaccine for tuberculosis for many decades. Randomized, controlled trials have demonstrated that intravesical instillation of BCG reduces the risks of recurrence and progression...
of high-grade superficial bladder cancer. Of the approximately 70,000 new cases of bladder cancer that occur each year in the United States, 70 to 80% involve superficial tumors, for which BCG therapy may be appropriate; this therapy results in sustained elimination of the cancer in 80% of patients. The mechanism, although incompletely understood, involves triggering of a local cellular immune response with the induction of cytokines that have antiangiogenic activity, thus inhibiting tumor growth and progression.

Both local and systemic reactions to BCG instillation have been described, although serious side effects are rare. The common side effects are symptoms of cystitis such as dysuria and urinary frequency, often with low-grade fever and malaise. These effects develop in approximately 70% of patients within 2 to 4 hours after instillation and typically resolve within 48 hours. If the symptoms are severe, a lower dose of BCG is recommended for subsequent instillations; this has been shown to result in similar efficacy. A sepsislike syndrome with fever, hypotension, and respiratory failure occurs in 0.04% of patients soon after BCG instillation and is thought to represent a hypersensitivity reaction to BCG. Infection due to dissemination of BCG — rather than hypersensitivity — may result in granulomatous hepatitis, pneumonitis, and prostatitis. In the largest series to date, involving 2602 patients, granulomatous hepatitis occurred in 0.7% of patients, pneumonitis occurred in 0.7% of patients, and prostatitis occurred in 0.9% of patients. In these infections, granulomatous changes may be observed in histologic specimens, and mycobacteria can be recovered from the infected site. BCG infection at other sites has also been described, but this is rare. Our patient's infection had an unusual location; few cases of mycotic aneurysms after BCG treatment have been described in the literature.

In many of those cases, as in this one, the diagnosis was delayed.

Treatment recommendations for BCG-related infections are based on data from case series and expert opinion. This strain is intrinsically resistant to pyrazinamide but is susceptible to other antituberculosis drugs. For patients with severe symptoms of cystitis persisting for more than 72 hours after instillation, in the absence of bacterial infection, daily isoniazid with or without rifampin is recommended for 2 weeks. For disseminated infection or local infection outside the bladder, which is typically associated with systemic symptoms, both isoniazid and rifampin are recommended. The optimal duration of therapy is uncertain, but as with other mycobacterial infections, a prolonged course of treatment — usually 6 to 12 months — is common. In patients in whom isoniazid, rifampin, or both cannot be used because of concern about toxic effects in the liver or drug allergies, ethambutol and fluoroquinolones are other possible treatment choices. Corticosteroids are often added if a hypersensitivity reaction is thought to be complicating the infection, as indicated, for example, by a sepsislike syndrome; these drugs are then generally tapered once improvement occurs. For vascular infections such as mycotic aneurysms, early surgical resection is essential to minimize the risk of rupture.

Pharmacologic measures such as a short course of prophylaxis with isoniazid at the time of BCG instillation have not been found to be effective in reducing the systemic side effects of BCG treatment. Breaks in the urogenital epithelium have been shown to predispose patients to disseminated BCG infection. Thus, it is recommended that if the patient has a condition that would make urethral catheterization difficult or if the patient has preexisting cystitis or persistent hematuria after transurethral bladder resection, the administration of BCG be deferred until these problems have resolved. BCG also should not be administered to patients who have compromised cell-mediated immunity, including those infected with the human immunodeficiency virus and transplant recipients. The lack of a functional T-cell–mediated response would impede recruitment of activated T cells, which are needed to elicit the cytokine response.

This case highlights potential unintended consequences of BCG therapy and the need for patients and their clinicians to consider past BCG exposure when investigating new symptoms or signs. Because BCG-related infection can occur months to years after treatment, continued vigilance and a high index of suspicion must be maintained indefinitely after such treatment.
References


Copyright © 2008 Massachusetts Medical Society.