A 57-year-old man was referred to the hospital because of fever and jaundice.

The patient had been in good health until four years earlier, when a noninvasive, papillary transitional-cell carcinoma of the bladder, grade 1 on a scale of 1 to 3, was excised. Similar tumors were excised 12 and 18 months later. One year before admission, live bacille Calmette–Guérin (BCG) microorganisms were administered intravesically, with six weekly instillations followed by seven monthly instillations and periodic cystoscopic examinations. There were multiple difficult catheterizations because of total or partial erections and sphincter spasm. The patient recalled having had “fever and chills” after one treatment. Six and a half weeks before admission, the results of a cystoscopic examination were normal, and microscopical examination of a bladder-biopsy specimen showed only chronic cystitis. Five days before admission, the patient received an instillation after a difficult insertion of the catheter, accompanied by gross hematuria. That evening, severe dysuria developed, with fever, shaking chills, and malaise. A urinary analysis and urine culture, performed elsewhere, showed normal findings. Trimethoprim–sulfamethoxazole was prescribed empirically. During the next three days, the patient had jaundice, dark urine, light stools, vague abdominal discomfort, anorexia, and fatigue, and his temperature rose to 38.7°C. Laboratory tests were performed (Table 1). On the evening before admission, epistaxis occurred. He was admitted to the hospital the next day.

There was a history of hypertension for which the patient took enalapril. He reported no risk factors for human immunodeficiency virus infection.

The temperature was 37.8°C, the pulse was 100, and the respirations were 16. The blood pressure was 170/95 mm Hg.

On examination, the patient was deeply jaundiced and appeared ill. There was no rash or lymphadenopathy. A grade 1 systolic ejection murmur was heard along the right upper sternal border. The results of an abdominal examination were normal; the liver and spleen were not felt, and no tenderness or mass was palpated. There was no peripheral edema or digital clubbing. The results of a neurologic examination were normal.

The urine was orange; it was positive (+++) for bilirubin and positive (trace) for ketones and protein, with a pH of 5.5 and a specific gravity of 1.019. The sediment contained 3 to 5 red cells, 10 to 20 white cells, and a few bacteria per high-power field. The results of laboratory tests are shown in Tables 1 and 2. A radiograph of the chest was normal. An ul-

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**Table 1. Blood Chemical Values.**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>TWO DAYS BEFORE ADMISSION</th>
<th>ON ADMISSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (mg/dl)*</td>
<td>9.8</td>
<td>12.2</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>Conjugated</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase (U/liter)</td>
<td>319</td>
<td>635</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/liter)</td>
<td>115</td>
<td>203</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/liter)</td>
<td></td>
<td>311</td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/liter)</td>
<td></td>
<td>307</td>
</tr>
</tbody>
</table>

*To convert the values for total and conjugated bilirubin to micromoles per liter, multiply by 17.1.

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**Table 2. Hematologic Values on Admission.**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>43.8</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/hr)</td>
<td>16</td>
</tr>
<tr>
<td>White-cell count (per mm³)</td>
<td>7,900</td>
</tr>
<tr>
<td>Differential count (%)</td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>73</td>
</tr>
<tr>
<td>Band forms</td>
<td>3</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>15</td>
</tr>
<tr>
<td>Monocytes</td>
<td>8</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count (per mm³)</td>
<td>97,000</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>Normal</td>
</tr>
</tbody>
</table>
trasonographic examination of the abdomen revealed normal hepatic size and contour with a homogeneous echographic texture. There was no dilatation of the extrahepatic or intrahepatic biliary ducts. The gallbladder was contracted and contained no stones. The spleen and the head and body of the pancreas appeared normal; the tail was obscured by gas. Bacterial cultures of blood and urine were negative.

A diagnostic procedure was performed.

**DIFFERENTIAL DIAGNOSIS**

**DR. MICHAEL J. BARZA**: This patient with bladder cancer was treated with multiple intravesical instillations of BCG. A few hours after the most recent treatment, he experienced severe dysuria, fever, chills, and malaise. A few days later, he was found to have hepatitis. Urethral catheterization for this instillation had been difficult, and hematuria had occurred. There had been problems with past catheterizations, and one had been followed by fever and chills. The results of biochemical tests performed during this admission suggest the diagnosis of cholestatic hepatitis. Because abdominal ultrasonography showed no evidence of biliary obstruction or gallstones, the problem appears to be in the liver rather than in the biliary tract. The patient also had mild thrombocytopenia and an episode of epistaxis.

An acute bacterial or viral infection must be included in the differential diagnosis. Among bacterial infections, a urinary tract infection, probably pyelonephritis, would be a primary consideration, especially because the illness developed shortly after manipulation of the urinary tract. However, urinalysis and culture performed before the administration of antibiotic therapy showed normal findings. Trimethoprim—sulfamethoxazole, which is active against many bacterial pathogens, was ineffective. Blood and urine cultures performed on admission were negative, but they followed the antibiotic therapy, which might have been responsible for the negative results. More subtle findings that are not consistent with the presence of bacterial infection are the minimal neutrophilia after several days of acute illness and an erythrocyte sedimentation rate of only 16 mm per hour. The history, physical examination, and laboratory tests provide no evidence of a portal of entry for bacteria other than the urinary tract.

The finding of hepatitis raises the possibility of a viral infection — for example, hepatitis A, B, or C or infection with Epstein—Barr virus or cytomegalovirus. I cannot rule out an acute viral infection, but there is no history of exposure to any hepatic agents. There are no signs of Epstein—Barr virus or cytomegalovirus infection, such as sore throat, lymphadenopathy, or atypical lymphocytosis. A viral infection would not explain the acute dysuria that heralded the illness, but the dysuria could have been unrelated to the subsequent events.

Thrombocytopenia accompanying an acute septic illness suggests a rickettsial infection, such as Rocky Mountain spotted fever or ehrlichiosis, but there is no mention of travel to an area where such infections are endemic, and the patient did not have a rash or headache. A rickettsial infection would not be manifested predominantly as hepatitis.

A number of noninfectious illnesses can cause an acute febrile disorder, including collagen—vascular diseases, drug reactions, cancer, intoxications, and endocrine diseases. Vasculitis, acute lupus erythematosus, and juvenile rheumatoid arthritis developing in an adult may cause an acute febrile illness. This patient had none of the skin or joint manifestations of such disorders, however, and the low erythrocyte sedimentation rate would be unusual in a patient with a collagen—vascular disease.

Drug reactions can cause high fever, but before the onset of the illness, the patient had received only enalapril, which he had taken for some time, and BCG. Trimethoprim–sulfamethoxazole can cause fever and hepatitis, but it was given only after the onset of the illness. The patient had no history of intolerance to trimethoprim–sulfamethoxazole.

In rare cases, an acute febrile syndrome is caused by some types of cancer, primarily hematopoietic tumors, but there is no evidence of a neoplasm. Nor is there evidence of either of the two forms of intoxication that can result in high fevers: the toxic shock syndrome and pseudomembranous colitis. Endocrine diseases that can present with high fevers, especially if the tumor is undergoing rapid necrosis, include acute hypoadrenalism, thyroid storm, and pheochromocytoma, but this patient had none of the characteristic features of these illnesses.

The disorders that remain to be considered are rare syndromes directly related to BCG treatment. The short interval between the last BCG instillation in this patient and the development of acute symptoms makes it tempting to postulate a connection between these two events. In many cases of BCG-related syndromes, the interval between the events is so long that the physician does not recognize the relation between them.

BCG is a live attenuated strain of *Mycobacterium bovis*, a member of the *M. tuberculosis* complex. *M. bovis* causes disease similar to that caused by *M. tuberculosis*. BCG, given by intradermal inoculation, has long been used to stimulate cell-mediated immunity as prophylaxis against tuberculosis. In the 1970s, BCG began to be used to stimulate antitumor immunity in patients with cancer — for example, leukemia or melanoma. It was injected intrave-
nously or into lesions or other intradermal sites. The intravenous dose usually contained about 1 million organisms, or about 100th the amount injected by other routes.

Most of these therapeutic uses of BCG have been abandoned because of concern about disseminated BCG infection and because of the superiority of other forms of treatment. For transitional-cell carcinoma of the bladder, however, intravesical instillation of BCG remains the most effective therapy. Typically, a vial of BCG, containing about 100 million organisms, is suspended in 50 ml of saline.1 The urethra is catheterized, and the suspension is instilled into the bladder, where it is retained for about two hours. A typical treatment schedule might include one instillation weekly for six weeks, followed by a series of monthly treatments. A prospective, randomized study comparing BCG with chemotherapeutic agents showed no substantial difference in local toxic effects, such as cystitis.2 However, because systemic reactions are more severe with BCG than with chemotherapeutic agents, BCG tends to be reserved for patients with cancers that are multifocal, recurrent, or particularly invasive. BCG instillations are contraindicated in patients with active tuberculosis and in those who are immunosuppressed or pregnant.

In infections with M. bovis, as well as M. tuberculosis and M. leprae, most of the symptoms are manifestations of the host’s immunologic reaction to the bacilli, which is mediated by cytokines produced by activated macrophages. In the absence of cell-mediated immunity, the mycobacteria grow apace, but there are few symptoms. With well-developed specific immunity, there may be marked inflammatory reactions, but live organisms are few or undetectable. Immune reactions appear to have a role in the antitumor effects of BCG, which seem to be greatest in patients who have local and systemic reactions to the treatments. In one study, the rate of recurrent tumor was lower for patients with purified-protein-derivative (PPD) tests that became positive during treatment than for those with tests that remained negative.3

When M. bovis is used therapeutically, access of the organisms to the bloodstream is an important consideration. Administration of BCG by vein or into vascular skin tumors leads to striking systemic inflammatory reactions. Such reactions are uncommon when BCG is injected intradermally for prophylaxis against tuberculosis or when it is instilled into the urinary bladder for treatment of bladder cancer, because access to the circulation is minimal. Even with intravesical instillation, however, the enormous inoculum may cause severe reactions if the uroepithelium is disrupted. Thus, BCG treatment should be withheld if there has been recent urologic trauma or hematia. In the patient under discussion, catheterization was difficult and caused hematuria.

There has been extensive experience with the use of BCG for prophylaxis against tuberculosis. By 1974, more than 1.5 billion such immunizations had been performed. Although a small percentage of immunized children had persistent local infectious ulcers or abscesses, only 35 died of disseminated BCG infection, and most of those children were immunocompromised.4 BCG should not be given to persons with known or suspected immunosuppression. The rate of death from BCG immunization as prophylaxis against tuberculosis has been estimated to be 1 in 50 million persons.2

BCG is no longer given by intravenous or intradermal injection because of the relatively high frequency of severe adverse effects, which are probably caused by the bacteremia and the deficient immune status of patients with cancer. Granulomas have reportedly been widespread in the liver, lungs, spleen, lymph nodes, and bone marrow.5,6 The rate of BCG-related death among patients treated by these routes was estimated to be 1 in 12,500.2

BCG has been administered intravesically in tens of thousands of patients. In 80 percent of patients with in situ or superficially invasive transitional-cell carcinoma, treatment with BCG results in complete, long-term elimination of the tumor.4 Although minor side effects are common, serious ones occur in fewer than 5 percent of patients.2 Lamm and colleagues2,7 have determined the frequency of BCG reactions after intravesical instillation in two studies, the second of which involved 2602 patients. The reactions may be local, involving the urinary tract or adjacent structures, or systemic and may be mild or severe. Their frequency does not vary among the several commercial preparations of BCG.2 Mild cystitis develops in most patients after the intravesical instillation of BCG, and hematuria develops in about a third of the patients.7,8 The symptoms of cystitis usually start within 2 to 4 hours after instillation and abate within 48 hours. Mild transient fever and malaise develop in most patients, usually after the third instillation. These mild side effects should be managed symptomatically, but further BCG treatments should be withheld until the symptoms have resolved.2 Isoniazid should not be given to prevent the symptoms, because it may cause hepatitis, and the administration of isoniazid with BCG in animals appears to reduce the antitumor effect of BCG.3,8 Furthermore, complications can occur despite prophylaxis with isoniazid.4

Severe local effects of intravesical BCG administration include, in order of decreasing frequency, granulomatous prostatitis (in 0.9 percent of patients), epididymoorchitis, ureteral obstruction, bladder contracture, and renal abscess (in 0.1 percent). The most common symptom of severe systemic disease is a high temperature (>39°C), which occurs in 3 percent of patients. In most cases, such patients are not...
hospitalized, and the fever generally abates in one to two days, but very high or persistently high fever may signal active BCG infection or a severe immune reaction. In such cases, it is difficult to tell which patients will subsequently have more serious complications. It is therefore recommended that all patients with a temperature higher than 38.5°C for 12 to 24 hours be treated with isoniazid for three months and that BCG treatments be discontinued until the symptoms have disappeared.

Serious complications of disseminated BCG infection occur in fewer than 1 percent of patients. Lamm et al. reported granulomatous hepatitis and pneumonitis in 0.7 percent of patients and full-blown sepsis in 0.4 percent; seven deaths from sepsis followed the intravesical use of BCG. Because the denominator is not known, a death rate due to BCG infection cannot be calculated for patients with cancer who receive BCG intravesically, but the rate is thought to be less than the rate of 1 in 12,500 associated with direct intralesional injections. In the survey by Lamm et al., arthralgia occurred in 0.5 percent of patients and cytopenia in 0.1 percent.

When systemic reactions develop, the role of BCG can be difficult to establish because the mycobacteria usually cannot be demonstrated on acid-fast smears, cultures of the lesions, or cultures of blood or bone marrow. Even attempts to detect organisms by DNA hybridization have sometimes failed in cases of granulomatous hepatitis, sepsis, and local granulomatous reactions in the urinary tract. The paucity of organisms may reflect a high level of immunity. In contrast, cultures of soft-tissue abscesses or mycotic aneurysms of the aorta have yielded M. bovis organisms in a few patients.

The illness in the patient under discussion is consistent with the syndrome of granulomatous hepatitis due to BCG treatment. At least 12 patients with this disorder have been described. Among three of them who had received intralesional injections of BCG for malignant melanoma or squamous-cell carcinoma, the interval from the last treatment to the onset of symptoms ranged from 12 hours to 2 weeks. In two of these patients, hepatitis developed after only one dose of BCG. The hepatitis resolved with antimycobacterial treatment in two patients and without specific treatment in the third patient. Liver-function tests became abnormal in 12 of 21 patients with intradermal metastatic melanoma or breast cancer who were given intralesional BCG treatment. In 6 of these 12 patients, noncaseating granulomas were found on liver biopsy. Patients with and those without granulomas underwent similar regimens of BCG treatment and had a similar immunologic status. Among patients with negative PPD tests before BCG treatment, however, the tests became positive in three quarters of the patients who had hepatic granulomas but in only one quarter of those who did not. The average interval from the last BCG treatment to biopsy was 18 weeks. All the patients had received at least five doses of BCG. Of two patients with granulomatous hepatitis and pneumonitis after intravesical instillation of BCG, one had had urethral bleeding caused by a difficult catheterization. Both patients were treated with isoniazid, rifampin, and prednisolone.

Finally, in another case of granulomatous hepatitis after intravesical administration of BCG, the symptoms occurred a year and a half after the last instillation of BCG, and the role of BCG was unclear. The results of acid-fast smears and cultures of liver tissue were reported for 10 patients from the various series I have discussed; the results were negative in all of them. From these few case reports, I conclude that the interval between the administration of BCG and the onset of hepatitis can range from hours to months or longer, that the reaction can occur after a single dose of BCG, and that the lesions usually do not yield microorganisms on culture.

The sepsis syndrome, although rare, is the most severe complication of BCG treatment. All the features of gram-negative bacterial sepsis are present, including high fever, shaking chills, hypotension, confusion, disseminated intravascular coagulation, respiratory failure, jaundice, and leukopenia. The clue to the cause is the temporal relation of the syndrome to BCG treatment, although in one case the syndrome occurred three years after the last BCG treatment.

Studies in animals and anecdotal data in humans suggest that the adjunctive administration of corticosteroids with antituberculous drugs markedly improves the outcome. BCG is susceptible in vitro to all antituberculous drugs except pyrazinamide. Amoxicillin–clavulanic acid, most aminoglycosides, tetracyclines, sulfamethoxazole, and norfloxacin are active in vitro. In animals, the combination of isoniazid and rifampin appears to be a satisfactory antituberculous agent, although many physicians would administer three or four agents, including ethambutol.

A very rare complication of BCG treatment is a mycotic aneurysm or pseudoaneurysm. This complication has been reported after intravesical treatment in several cases, most of them involving the aorta or femoral arteries. In such cases, BCG infection appears to spread from the urinary tract to retroperitoneal lymphatic vessels and from these vessels to the artery.

In summary, the short interval between the instillation of BCG in this patient and the development of symptoms of hepatitis, especially after traumatic catheterization and hematuria, suggests that intravascular dissemination of BCG caused granulomatous hepatitis. With a high temperature and severe malaise, as well as thrombocytopenia, the patient may have been at risk for the sepsis syndrome, although there is little evidence of this complication.
The diagnostic procedure was probably a liver biopsy, which showed the presence of granulomatous hepatitis. It is likely that acid-fast bacteria could not be detected in the specimens on staining or culture.

**CLINICAL DIAGNOSIS**
Granulomatous hepatitis due to intravesical instillation of BCG.

**DR. MICHAEL J. BARZA’S DIAGNOSIS**
Granulomatous hepatitis due to intravesical instillation of BCG.

**PATHOLOGICAL DISCUSSION**

**DR. JONATHAN H. BLUM:** We believed that hepatitis due to BCG treatment was by far the most probable diagnosis, and on that basis we proceeded with empirical treatment. Our clinical impression was eventually confirmed by a lysis-centrifugation culture of a blood specimen that had been obtained on admission, which yielded organisms of the *M. tuberculosis* group, including *M. bovis*. The organisms were shown to be susceptible to all the antibiotics tested except for pyrazinamide. When we began the treatment, we were reluctant to use a potentially hepatotoxic regimen because of the markedly elevated aspartate aminotransferase level. We administered ofloxacin and ethambutol. Although the aspartate aminotransferase level decreased, we switched to isoniazid and ethambutol because of the persistence of symptoms. The aspartate aminotransferase level subsequently increased markedly, and the temperature became higher, raising the question of isoniazid-associated hepatitis. Serologic testing was negative for hepatitis A and hepatitis B surface antigen and surface antibody but was positive for hepatitis B core antibody. We then switched to a regimen of ofloxacin, ethambutol, and amikacin administered intravenously, and the aspartate aminotransferase level declined. The high temperature (40.5°C) persisted, however. We obtained an abdominal computed tomographic scan to look for evidence of focal infection, but no evidence of an abscess was found. When the patient’s condition had not improved after three weeks on the last regimen, we considered instituting corticosteroid therapy but decided to confirm the diagnosis of hepatitis due to BCG by liver biopsy before administering corticosteroids.

**DR. FIONA M. GRAEME-COOK:** The liver biopsy was performed six weeks after admission. Microscopical examination revealed a lobular hepatitis, with scattered acidophil bodies (Fig. 1) and numerous noncaseating epithelioid granulomas, which were mainly intralobular (Fig. 2). Apart from the granulomatous inflammation, eosinophils were present in small numbers within the portal tracts and the lobules. Some of the portal areas were edematous, with peripheral proliferation of bile ductules, which were

**Figure 1.** Lobular Hepatitis with Granulomas (Hematoxylin and Eosin, ×130).

**Figure 2.** Noncaseating Granuloma with a Langhans’ Giant Cell (Hematoxylin and Eosin, ×350).
surrounded and focally infiltrated by neutrophils and eosinophils (Fig. 3). A few bile ducts were slightly inflamed (Fig. 4). Acid-fast and auramine–rhodamine fluorescent staining failed to reveal organisms. These findings are characteristic of granulomatous hepatitis. Examination of one of the bladder-biopsy specimens obtained after the instillation of BCG showed cystitis characterized by multiple noncaseating granulomas.

Although granulomatous hepatitis has developed after intralesional BCG treatment for malignant melanoma,\textsuperscript{18} the majority of reported cases have followed immunotherapy for bladder carcinoma.\textsuperscript{2,3,11} In most of the cases, liver biopsy was performed, with findings of noncaseating granulomas and variable hepatocyte necrosis, variable numbers of granulomas, variable portal inflammation, and scattered eosinophils. An acid-fast stain was positive for tubercle bacilli in one case,\textsuperscript{19} and a fluorescent stain was positive in another.\textsuperscript{20} Mycobacterial DNA was identified in a bone marrow specimen by DNA hybridization in one case\textsuperscript{21} and in urine and liver specimens by the polymerase chain reaction in another case.\textsuperscript{20} Although BCG has been cultured from liver specimens in cases of granulomatous hepatitis that followed intralesional therapy for melanoma,\textsuperscript{18} cultures have been uniformly negative in cases that followed immunotherapy for bladder cancer.

The question is whether BCG-associated granulomatous hepatitis is due to sepsis, hypersensitivity, or both. The responses to antituberculous therapy and corticosteroid therapy suggest that both sepsis and hypersensitivity have roles in the reported cases. The eosinophilic infiltration of the liver in this case and others suggests the presence of hypersensitivity. It has been proposed that the absence of necrosis in the granulomas is additional evidence of a hypersensitivity reaction, but the granulomas in this case more closely resemble those of miliary tuberculosis, in which necrosis is usually absent, than the caseous lesions of primary tuberculosis involving the liver. The unusual finding of cholangitis in this case is consistent with the presence of either sepsis or hypersensitivity, since it is seen in both systemic sepsis and drug-related hypersensitivity reactions. Similarly, the number and distribution of the granulomas are of little value in distinguishing between sepsis and hypersensitivity.

The inability to identify the bacillus in tissue does not rule out infection. Acid-fast stains are positive in only 10 percent of cases of tuberculosis of the liver, and an estimated 10,000 organisms per gram of tis-
The patient was afebrile the next day, and within three weeks, his liver-function tests were normal. We then substituted rifampin for amikacin. The prednisone was tapered over a period of six weeks, and no relapse occurred after it had been discontinued for three months. There are no conclusive data on the optimal duration of combination therapy, but on the basis of the clinical presentation and the available data, we decided to continue the treatment for six months.

DR. NESLI BASGOZ: The patient has continued to undergo periodic cystoscopic examinations, which have shown no evidence of carcinoma.

ANATOMICAL DIAGNOSIS

Granulomatous hepatitis due to intravesical instillation of BCG for urinary bladder carcinoma.

ADDITIONAL

DR. BLUM: The patient completed the six-month course of antibiotics, but during the subsequent three months, he continued to have fatigue and his liver function worsened, with an increasing alkaline phosphatase level. At that point, we ordered another liver biopsy to determine whether the granulomatosus hepatitis had resolved. Examination of the specimen again showed numerous noncaseating granulomas, which were larger and better developed than those in the initial biopsy specimen. We then administered a second, longer course of treatment consisting of antibiotics (ofloxacin, rifampin, and ethambutol), followed by corticosteroids, which were tapered more slowly than they had been during the first course of therapy. Five months after the initiation of the second course, the results of liver-function tests were markedly improved, along with the patient’s general well-being. We are unaware of any previous reports of the recurrence of BCG-associated granulomatous hepatitis after the recommended six-month course of therapy.

REFERENCES


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