Granulomatous Hepatitis as a Complication of Intravesical Bacillus Calmette-Guerin Therapy for Bladder Carcinoma

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ABSTRACT

Bacillus Calmette-Guerin (BCG) therapy has been proven to be effective treatment for superficial bladder carcinoma with complications that are usually minor and self limited. Although rare, granulomatous hepatitis can develop, and it is important to recognize it and treat it promptly. The hepatitis which occurs appears to be the result of a hypersensitivity reaction to antigens present in the BCG vaccine. Pathological findings include hepatocellular necrosis and pleomorphism, microgranulomas and non-caseous epitheliod granulomas with giant cells. A case of BCG-hepatitis, which developed in a 74-year-old white male following immunotherapy for superficial bladder carcinoma, is described.

Introduction

Bacillus Calmette-Guerin (BCG) vaccine is an attenuated strain of bovine tuberculin bacterium developed in 1910 which consists of living bacilli, dead microorganisms, and subcellular debris. The bacilli maintain the immunological properties and antibiotic sensitivities of the parent strain. The use of intravesical BCG immunotherapy has been proven effective treatment for superficial bladder cancer.1,2 Haff et al.2 reported a 10 to 20 percent recurrence rate of bladder cancer in patients treated with resection and BCG immunotherapy, a 40 percent recurrence rate for resection and intravesical thiotepa, and a 60 percent recurrence rate for resection alone. Although the exact mechanism remains unknown, BCG appears to work either by causing a severe inflammatory reaction which results in the complete destruction of the mucosa and thereby causing tumor sloughing, or by inciting a specific immunological response against tumor cells as a result of enhanced immune responsiveness.2 Side effects of BCG therapy are not uncommon, but are usually minor (irritative bladder symptoms, fever, malaise, and myalgia) and self limited.1 In a review of 2,602 patients, Lamm et al3 found serious complications occurred
only in 5 percent of patients. Complications included fever greater than 102°F, granulomatous prostatitis, major hematuria, granulomatous pneumonitis and/or hepatitis, arthritis, arthralgia, ureteral obstruction, epididymo-orchitis, and bladder contracture. A literature search revealed only eight biopsy proven cases of granulomatous hepatitis after intravesical BCG immunotherapy for bladder cancer. An additional case is reported.

Case Report

A 74-year-old white male with a history of insulin dependent juvenile diabetes and hypertension presented to the urologist in May of 1992 with complaints of 2 months duration of hematuria, nocturia, and decreased urine stream. Physical examination showed stable vitals a slightly obese abdomen without tenderness or masses, a left testicular hydrocele and an enlarged prostate. Physical examination was otherwise unremarkable. Intravenous pyelogram was normal and medications included insulin, Induron, K-Tabs, and Tenormin. Cystoscopy revealed multiple tumors of the bladder wall. The patient was admitted and underwent transurethral resection of the bladder tumor and cold cut biopsy. The tumor was a papillary transitional cell carcinoma, grade II, T1, NX, B2, with invasion of the lamina propria. The post-operative course was uneventful. Liver function tests at this time were aspartate amino transferase (AST) 24, and alanine amino transferase (ALT) 76.

On June 12, the patient began the first of five weekly intravesical treatments with TICE strain BCG. He did well with the first three treatments, but the evening after the fourth treatment he developed headache, dry heaves, rigors, malaise, and a fever (range 101 to 104°F). He denied gastrointestinal or pulmonary complaints and noted no rash. The next day he suffered from malaise, and the episode did not return. One week later after the fifth treatment, he developed the same syndrome which persisted for three days. Subsequently, he suffered from poor appetite, malaise, night sweats and chills with persistant low grade fevers of approximately 100°F. Glycemic control was erratic. Following adjustment of the insulin dose, he had improvement in energy, appetite, and overall condition; however, the low grade fever persisted. He denied dysuria, polyuria, change in bowel habits, back pain, cough, sore throat, skin rash, pruritis, stiff neck and change in vision. He had a five pound weight loss in 7/92. He denied alcohol use, history transfusions, and family history of liver disease. Urine and blood cultures were negative for acid-fast bacilli. Liver function tests have remained normal and there have been no other liver abnormalities.

Histological Findings

The overall histological finding was primarily a granulomatous lobular hepatitis (figure 1) which was characterized by the following: hepatocellular necrosis, hepatocellular pleomorphism, Kupffer cell hyperplasia, lymphocytic infiltrates, microgranulomas, moderate fatty change, Councilman bodies, cholangitis, and epithelioid non-caseous granulomas with giant cells (figure 2). Special stains for acid fast bacilli and fungi were negative.

Discussion

Intravesical BCG immunotherapy has proven to be safe and effective treatment for superficial bladder cancer. Most of the side effects are of moderate severity and short duration. Less than 2% of patients experience any type of systemic complication, and only 0.7% of a study of 2,602 patients was reported to have granulomatous hepatitis and/or pneumonitis. Although the complication rate is limited, more complications have been shown in BCG treated cancer patients than in the general population given BCG vaccinations for the prevention of tuberculosis. The mortality rate for BCG vaccinations is only 1/50 million, while the mortality rate for BCG treated cancer
patients is 1/12,500. The mortality rate for bladder cancer alone is estimated to be slightly lower. The theoretical explanation for this disagreement is that many cancer patients have impaired immunological status.3

Factors that influence toxicity of BCG immunotherapy are the route of administration (either intrallesional or intravesical), the number of living bacilli, and the number of treatments.3 Other contribut-

FIGURE 1. Light microscopic view of granulomatous lobular hepatitis with focal hepatocellular necrosis, microgranulomas, epithelioid granulomas with giant cells, chronic inflammatory infiltrates in sinusoids and portal areas, and pleomorphic hepatocytes. Also evident are nuclear vacuolization and fatty change of hepatocytes characteristic of the patient’s diabetes and not directly related to the BCG hepatitis. (x100, Hematoxylin and Eosin)

FIGURE 2. Light microscopic view of epithelioid granuloma with giant cells and surrounding chronic inflammation within an area of lobular hepatitis. (x250, Hematoxylin and Eosin)
The typical clinical presentation of BCG hepatitis, as adapted from Rosenberg, is as follows: one to three days following the BCG treatment, the patient develops a fever of 102 to 104°F. Approximately one week post treatment, liver function tests begin to rise, specifically serum glutamic pyruvic transaminase (SGPT), serum glutamic oxalacetic transaminase (SGOT), and lactate dehydrogenase (LDH). A persistent low grade fever occurs accompanied by chills. There is a progressive rise in the liver function tests which peaks around 25 to 30 days after the BCG treatment. Liver biopsy specimens taken show non-caseous granulatous hepatitis (see histological findings). Most often, all cultures and special stains remain negative for acid fast bacilli. Only three reported cases in the literature could be found in which organisms were cultured from patients treated with BCG immunotherapy for bladder cancer and/or melanoma.8,11,12

The pathogenesis of BCG hepatitis remains unknown, but two theories currently exist. The hepatitis could represent a disseminated BCG infection owing to systemic spread of the organism or it could be a hypersensitivity reaction to antigenic particles within the BCG vaccine. More evidence is available to support the latter hypothesis. Most often, all cultures remain negative.

Molina et al.7 reported a case of BCG hepatitis and pneumonitis in which cultures of blood, urine, liver, sputum, and bronchoaveolar lavage all remained negative throughout the course of the disease. Additionally, blood lymphocytes were highly sensitive to purified protein derivate as shown by analysis of their proliferation index in vitro. Recovery in this patient was not influenced by treatment with the standard therapy for microbacterium; however, complete recovery was achieved with steroids alone.7

Rosenberg et al12 also reported several cases of BCG hepatitis following intrale-

sional BCG treatment for melanoma in which the disease course was not affected by Isoniazid treatment, although prednisone treatment effectively abated the fever and helped in the patients' recoveries.12 The three cases in which organisms were successfully cultured might represent true dissemination of the organism with an additional hypersensitivity reaction. It is worthy to note that true microbacterium infection gives rise to caseous granulomatous reaction which was demonstrated in only one of the three afore mentioned cases.8,11,12 All other reported cases of BCG hepatitis have shown non-caseous granulomatous reactions which are more typical of a hypersensitivity reaction.

Current therapy for BCG hepatitis is observation and anti-tuberculosis medications, if necessary. It has been observed that some cases may be resolved on their own. Although it is noted as a rare complication of BCG immunotherapy in treatment of bladder cancer, BCG hepatitis can be severe and, therefore, it is important to recognize it and treat it promptly.

References


