Acute Hepatitis and Pneumonitis Caused by Disseminated Bacillus Calmette-Guérin Infection

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Abstract
Intravesical instillation of Bacillus Calmette-Guérin (BCG) is the treatment of choice for superficial bladder carcinoma. We report a case of disseminated BCG infection in an early stage bladder cancer patient that initially presented with hepatitis followed by pneumonitis and sepsis. A complete clinical response was achieved in 14 days with anti-mycobacterial therapy and prednisolone. Disseminated BCG is a rare treatment complication and is likely a combination of direct infection and hypersensitivity.

Introduction
Bacillus Calmette-Guérin (BCG) is a live, attenuated strain of the bovine tuberculosis bacillus, Mycobacterium bovis (M. bovis). Intravesical BCG instillation for the treatment of superficial bladder cancer was first described in 1976.1 Since then, BCG therapy has become the treatment of choice for early stage transitional cell carcinoma of the bladder, with response rates of 60%–94%.2 Although the virulence of attenuated BCG is low, serious and potentially life-threatening infections can rarely occur, even in immunocompetent patients.3 Disseminated BCG infections presenting as pneumonitis or granulomatous hepatitis are extremely rare. In the largest retrospective study reported to date, dissemination occurred in only 0.7% of more than 2,000 patients.4

Case Report
A 34-year-old man with an early stage bladder cancer (stage T1) presented with a 2-day history of fatigue, night sweats, and icterus. He was previously treated with cystoscopic fulguration of the tumor, followed by 8 weeks of intravesical BCG. The last course was administered 3 weeks prior to presentation. No immediate complications or traumatic instillations were reported.

Physical examination was significant for diffuse icterus and hepatomegaly. Laboratory work-up showed an alkaline phosphatase 432 U/L, AST 70 U/L, ALT 90 U/L, total bilirubin 11.1 mg/dL, direct bilirubin 9.2 mg/dL, and prolonged PT and PTT at 22 s and 45 s, respectively. Polymerase chain reaction serum assays for cytomegalovirus and Epstein-Barr virus, and serology tests for viral hepatitis, autoimmune hepatitis, and primary biliary cirrhosis were negative. Liver ultrasound showed homogenous hepatomegaly without any lesions or biliary dilatation. Abdominal/pelvic and chest computed tomography (CT) scans were normal apart from the hepatomegaly. Liver biopsy revealed multiple, non-caseating granulomas in the portal tract and parenchyma, in addition to mild, patchy inflammation in the portal tract with eosinophilic infiltration (Figure 1). Stains for cytomegalovirus, HSV, fungi, and acid-fast bacilli were negative.
Three days after his presentation, the patient’s status deteriorated. He was found to have severe hypoxic respiratory failure and hypotension requiring mechanical ventilation and vasopressors support. Chest CT revealed bilateral, diffuse parenchymal infiltrates, consistent with pneumonitis, without hilar lymphadenopathy (Figure 2).

Due to the high suspicion of BCG sepsis and dissemination, triple anti-mycobacterial therapy with rifampin (600 mg daily), isoniazid (300 mg daily), and ethambutol (1200 mg daily) was initiated. A 3-day course of prednisolone was added to treat a possible hypersensitivity reaction. Bronchial lavage was negative for bacteria, fungi, and acid-fast bacilli. Four days later, the patient’s clinical status improved significantly and he was successfully extubated. In 2 weeks, liver enzymes and function tests returned to normal ranges. Fungal cultures from the liver and lungs were negative after 6 weeks. Anti-mycobacterial therapy was continued for 12 months.

Discussion

BCG is an attenuated strain of the tuberculosis bacillus *M. bovis*. BCG induces an intense, localized inflammatory response upon instillation into the bladder. Its therapeutic mechanism of action is thought to involve the ingestion of viable mycobacteria by urothelial cells. This triggers a cytokine-mediated inflammatory response that results in the destruction of tumor cells. Since its introduction in the 1970s, intravesical BCG treatment has been an effective adjunctive treatment option of superficial bladder cancer, with a favorable safety profile and typically localized and self-limited side effects. However, complications like granulomatous involvement of lung, liver, and bone marrow can rarely occur.

Acid-fast bacilli staining and organism cultures may fail to identify *M. bovis*, despite a high clinical suspicion of BCG infection. The fastidious growth nature of BCG in cultures and the doubling time of 24 to 48 hours might contribute to the difficulty of its isolation. Hepatic and pulmonary involvement have been reported as a part of BCG dissemination; however, the occurrence of hypotension and BCG sepsis has been only reported twice in the literature.

The mechanism of infectious complications caused by BCG immunotherapy is debatable. It can represent either a direct active infection or a hypersensitivity reaction. Leebeek et al demonstrated the presence of *M. bovis* in liver tissues by PCR amplification, thus supporting the concept of hematogenous dissemination and direct tissue damage. On the other hand, the response to glucocorticoids when added to the anti-tuberculous agents, the striking eosinophilic infiltration of liver tissues, the absence of necrosis in the granulomas, and the absence of recoverable organisms support the hypersensitivity reaction. Our case highlights the limitations of acid-fast bacilli and mycobacterium culture.

The mainstay therapy for severe systemic BCG infections is a multi-drug combination of isoniazid, rifampin, and ethambutol for at least 6 months. Pyrazinamide is not usually recommended due to high resistance. Cautious addition of glucocorticoids in patients with BCG sepsis is recommended if hypersensitivity is believed to be part of the pathogenesis.

Disclosures

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