Hepatic Injury without Granulomatous Formation Associated with Intravesical Bacillus Calmette-Guérin Therapy

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Abstract:
A 74-year-old man developed hepatic injury after intravesical Bacillus Calmette-Guérin (BCG) therapy for bladder carcinoma. Although hepatitis-associated disseminated BCG was suspected, granulomatous formations were undetectable. The hepatic injury was considered to have resulted from an allergic reaction to BCG therapy because a histopathological assessment revealed enlarged portal areas with eosinophils and neutrophils. The hepatic injury was resolved by prednisolone. This case suggested that hepatic injury associated with BCG therapy might be due to an allergic mechanism unrelated to disseminated BCG disease. A liver biopsy is needed to confirm the histopathological findings of hepatic injury after BCG therapy in order to differentiate allergic hepatic injury from infectious hepatic injury.

Key words: bladder carcinoma, complication, steroid, allergic mechanism, liver biopsy

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Introduction
Intravesical Bacillus Calmette-Guérin (BCG) therapy is effective against superficial bladder carcinoma (1, 2). This therapy is safe, and serious complications rarely arise. However, intratumoral BCG injection has been associated with some complications, including marked malaise and influenza-like syndrome (3) as well as hepatitis (4-8). The characteristics of hepatitis caused by BCG are granulomatous liver tissue formation and the efficacy of anti-tubercular treatment against hepatitis (6, 7). Acute hepatitis derived from intravesical BCG might be attributed to disseminated BCG infection.

We herein report an elderly man who developed acute hepatic injury after receiving intravesical BCG therapy. However, he had no granulomatous hepatic tissues, and steroid therapy resolved the hepatic injury.

Case Report
A 74-year-old man was referred to our hospital with a chief complaint of acute liver damage. He had been aware of hematuria for about four months before being diagnosed with hepatic injury. A urologist diagnosed him with superficial bladder carcinoma, which was treated by transurethral resection (TUR-Bt) followed by a course of intravesical BCG therapy. After completing eight courses of intravesical BCG therapy, he developed a fever and elevated hepatic enzymes (Table 1). His fever continued for about 2 weeks after BCG treatment completion, with a peak body temperature of 38.2°C. He was positive for anti-M2 mitochondrial antibody (AMAM2) but showed normal findings for immunoglobulin M (IgM) (Table 2). He was admitted to our hospital for an abdominal echo-guided liver biopsy.

The histopathological findings of the liver specimen re-
vealed enlarged portal areas with inflammatory cells, including eosinophils and neutrophils, bile duct damage and proliferating bile ductules (Fig. 1), but no granulomatous changes and few plasma cells and lymphocytes. In addition, no abnormal findings, including necro-inflammatory changes, were observed in the hepatic parenchyma. Ziehl-Neelsen staining of the specimen was negative, and polymerase chain reaction for serum *Mycobacterium tuberculosis* and non-tuberculous mycobacteria was negative (data not shown). He had no history of *M. tuberculosis* infection or any allergic diseases. Chest X-ray and computed tomography did not reveal any findings of *M. tuberculosis* infection (data not shown).

We diagnosed the patient with hepatic injury derived from a source other than *M. tuberculosis* infection that involved allergic mechanisms induced by intravesical BCG. Because valsartan, amlodipine, atorvastatin and allopurinol had been prescribed to the patient for over three years, we considered these drugs unlikely to have caused the hepatic injury, and he continued to take them. We initially suspected that the hepatic injury might spontaneously recover, as the patient had already finished the BCG treatment.

His temperature returned to a normal level.

He also had an average alcohol intake of about 33 g/day before admission but stopped consuming alcohol after admission. However, the aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) values increased after the liver biopsy (Fig. 2). One week later, we had decided to treat the hepatic injury with prednisolone (0.5 mg/kg per day). The dosage of prednisolone was set in the present case based on a previous hypersensitive case associated with BCG treatment (9). The patient was started on prednisolone (25 mg/day orally), which gradually resolved the hepatic injury. The prednisolone was tapered and finally discontinued after five months.

The patient has remained free of relapse (Fig. 2). The eosinophil count is slightly increased, while the IgM value has remained normal (Table 2). However, the AMAM2 remained positive during the follow-up period (Table 2). We ultimately diagnosed this as a case of drug-induced liver injury due to BCG treatment. The DDW-J 2004 drug-induced liver injury score was 5.

### Discussion

Although the effectiveness and safety of BCG immunotherapy for patients with cancer have been established, complications, such as disseminated BCG organic injury, should be considered during and after treatment. We initially suspected that the hepatic injury in the present patient had been induced by disseminated BCG because he had a fever and elevated hepatic enzymes, which are typical complications associated with BCG immunotherapy. However, the hepatic

### Table 1. Laboratory Data on Admission.

| CBC        | Chemistry                          |
|------------|------------------------------------|
| WBC (μL)   | FT3 (pg/mL)                        |
| seg(%)     | FT4 (pg/dL)                        |
| eosino(%)  | TSH (uIU/mL)                       |
| RBC (μL)   | Procalcitonin (ng/mL)              |
| Hb (g/dL)  | ALP isozyme1(%)                    |
| Ht (%)     | isozyme2(%)                        |
| Plt (μL)   | isozyme3(%)                        |

| Coagulation | Serology                            |
|-------------|------------------------------------|
| PT (s)      | IgG (mg/dL)                        |
| PT-INR      | IgA (mg/dL)                        |
| HPT(%)      | IgM (mg/dL)                        |

| Chemistry | Immunoochemistry and Viral marker |
|-----------|----------------------------------|
| Alb (g/dL)| ANA                               |
| AST (IU/L)| AMAM2 (index)                     |
| ALT (IU/L)| ASMA                              |
| LDH (IU/L)| HBsAg                             |
| ALP (IU/L)| HBsAb                             |
| γ-GT (IU/L)| IgM-Hbc Ab                        |
| T-Bil (mg/dL)| IgG-Hbc Ab                      |
| D-Bil (mg/dL)| HCV Ab                         |
| Ch-E (IU/L)| HCV RNA                           |
| CK(U/L)   | IgM-HAV Ab                        |
| T-Chol (mg/dL)| IgM-CMV Ab                    |
| BUN (mg/dL)| IgM-EBV Ab                        |
| Cr (mg/dL)| EBNA-Ab                           |
| Na(mEq/L)| IgA-HEV Ab                        |
| K(mEq/L) |                                   |
| Cl(mEq/L)|                                   |
| BS (mg/dL)|                                   |
| CRP (mg/dL)|                                   |
| TTT(U)   |                                   |
| ZTT(U)   |                                   |

WBC: white blood cell count, Hb: hemoglobin, Ht: hematocrit, Plt: platelet, PT: prothrombin time, HPT: heparinase test, TP: total protein, Alb: albumin, T-Bil: total bilirubin, D-Bil: direct bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, γ-GT: gamma-glutamyltransferase, ALP: alkaline phosphatase, Ch-E: Cholinesterase, BUN: blood urea nitrogen, Cr: creatinine, BS: blood sugar, CRP: C reactive protein, CK: creatine kinase, T-chol: total cholesterol, FT3: Free triiodothyronine, FT4: Free thyroxine, TSH: Thyroid stimulating hormone, ANA: anti nuclear antibody, AMAM2: anti-mitochondrial M2 antibody, ASMA: antismooth muscle antibody, HBsAg: hepatitis B virus surface antigen, IgM-Hbc Ab: anti hepatitis B virus core IgM antibody, HCV Ab: anti hepatitis C virus antibody, IgM-HAV Ab: anti hepatitis A virus IgM antibody, IgM-CMV Ab: anti cytomegalovirus IgM antibody, IgM-EBV Ab: anti EB virus IgM antibody, EBNA Ab: IgG – anti Epstein-Barr virus nuclear antigen antibody, IgA-HEV Ab: anti hepatitis E virus IgA antibody

### Table 2. The Values of Eosinophil Count, IgM and AMAM2 during the Follow-up Period.

|           | Day1 | Day132 | Day367 |
|-----------|------|--------|--------|
| Eosinophil count (μL) | 352  | 108    | 672    |
| IgM (mg/dL)      | 57   | *ND    | 110    |
| AMAM2 (index)   | 76.6 | *ND    | 196    |

*ND: no data
Histopathological findings were not compatible with disseminated BCG disease. It is reported that the histology of caseating granulomas had a median sensitivity of 68% (range: 14-100%), and polymerase chain reaction for *M. tuberculosis* had a median sensitivity of 86% (30-100%) (10). Although a liver biopsy was unable to evaluate the state of the whole liver, his temperature returned to a normal level and no evidence of any tuberculosis infection was detected. We therefore did not perform anti-tuberculous therapy for his hepatic injury. In addition, the patient refused the treatment with anti-tuberculocid medication, as there was no obvious evidence of infection, and his condition was not poor except for elevated hepatic enzymes.

We also suspected primary biliary cholangitis (PBC) because he had elevated serum biliary enzymes and was positive for anti-M2 mitochondrial antibody. However, his serum IgM value was normal, and a histopathological examination did not reveal any findings of chronic non-suppurative destructive cholangitis (CNSDC) or non-caseating epithelioid granuloma formation, which are compatible with PBC. A diagnosis of PBC was therefore ruled out.

Among the causes of disorders associated with BCG, hypersensitivity phenomenon was implicated in a case of lung inflammatory disorder that developed during BCG therapy (9, 11), and steroid treatment was successful for its treatment (9). Steroid therapy also resolved the hepatic injury in the present patient. Overall, we believe that a hypersensitivity-like reaction with an allergic mechanism involving BCG rather than an infectious source induced the

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**Figure 1.** Histopathological findings of the liver specimen stained with Hematoxylin and Eosin staining. (a) A low-power view (×4) shows the enlarged portal areas with inflammatory cells but no granulomatous formation. (b) A high-power view (×40) shows that the enlarged portal area includes eosinophils and plasma cells.

**Figure 2.** The clinical course of the patient.
tivity might have also affected the timing of the liver damage onset.

The positivity for anti-M2 mitochondrial antibody might have been a non-specific reaction, as a high ratio of serum anti-M2 mitochondrial antibody has been detected in patients with drug-induced liver damage; hepatitis B, C and E; alcoholic liver disease; non-alcoholic fatty liver and primary hepatic carcinoma (14). Whether or not BCG therapy was involved in the anti-M2 mitochondrial antibody-positive reaction remains unknown because of a lack of relevant literature on the subject.

In conclusion, we speculate that hepatic injury associated with BCG therapy can not only be derived from disseminated BCG infection but also be mediated by an allergic reaction. Differentiating hepatic injury caused by an allergic reaction from that caused by disseminated infection after BCG therapy based solely on the clinical presentation is difficult, as the clinical course of our patient was similar to that of other reports of hepatic injury caused by disseminated BCG infection (5-8). Anti-mycobacterial therapy is likely to be effective against disseminated BCG infection, whereas steroids are effective against allergic reactions. A liver biopsy and histopathological findings are essential for the precise diagnosis and treatment of hepatic injury in patients who have received BCG therapy.

The authors state that they have no Conflict of Interest (COI).

References

1. Morales A, Eidinger D, Bruce AW. Intracavitary Bacillus Calmette-Guérin in the treatment of superficial bladder tumors. J Urol 116: 180-183, 1976.
2. Lam D, Thor DE, Harris SC, Reyna JA, Stogdill BD, Radwin HM. Bacillus Calmette-Guérin immunotherapy of superficial bladder cancer. J Urol 124: 38-40, 1980.
3. Sparks FC, Silverstein MJ, Hunt JS, Haskell CM, Pilch YH, Morton DL. Complications of BCG immunotherapy in patients with cancer. N Engl J Med 289: 827-830, 1973.
4. Bodurtha A, Kim YH, Lancius JF, Donato RA, Mastrangelo MJ. Hepatic granulomas and other hepatic lesions associated with BCG immunotherapy for cancer. Am J Clin Pathol 61: 747-752, 1974.
5. Enoki M, Mizuta T, Ozaki I, et al. Peliosis hepatitis in a patient with granulomatous hepatitis caused by BCG therapy. Kanro 38: 602-606, 1997 (in Japanese).
6. Nishita Y, Miwa K, Aoyagi H, Kyouri Y, Okada T, Mabuchi H. A case of mycobacteria-positive granulomatous hepatitis caused by Bacillus Calmette-Guérin therapy. Kanro 43: 364-369, 2002 (in Japanese).
7. Abe M, Matsuoka S, Koizumi S, et al. A case of granulomatous hepatitis caused by Bacillus Calmette-Guérin (BCG) infection after BCG bladder instillation. Kanro 49: 560-567, 2008 (in Japanese, Abstract in English).
8. Eso U, Mishima M, Arasawa S, et al. Two cases of granulomatous hepatitis due to disseminated bacillus Calmette-Guérin (BCG) disease. Kanro 58: 406-414, 2017 (in Japanese, Abstract in English).
9. Molina JM, Rabian C, D’Agay MF, Modai J. Hypersensitivity systemic reaction following intravesical bacillus Calmette-Guérin: successful treatment with steroids. J Urol 147: 695-697, 1992.
10. Hickey AJ, Gounder L, Moosa MY, Drain PK. A systematic review of hepatic tuberculosis with considerations in human immunodeficiency virus co-infection. BMC Infect Dis 15: 209, 2015.
11. Israel-Biet D, Venet A, Sandron D, Ziza JM, Chretien J. Pulmonary complications of intravesical Bacille Calmette-Guérin immunotherapy. Am Rev Respir Dis 135: 763-765, 1987.
12. Posadas SJ, Pichler WJ. Delayed drug hypersensitivity reactions - new concepts. Clin Exp Allergy 37: 989-999, 2007.
13. Onji M, Fujioka S, Takeuchi Y, et al. Clinical characteristics of drug-induced liver injury in the elderly. Hepatol Res 39: 546-552, 2009.
14. Sun L, Wang Y, Liu Y, et al. Differential characteristics of AMA-M2 autoantibody in primary biliary cirrhosis and non-PBC patients. Zhonghua Gan Zang Bing Za Zhi 23: 343-349, 2015 (in Chinese, Abstract in English).