Super Acute-onset Disseminated BCG Infection: A Case Report

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Abstract

Intravesical Bacillus Calmette-Guérin (BCG) instillation is an established immunotherapy for superficial bladder cancer. Herein, we describe a case of disseminated BCG infection that developed immediately after the first BCG injection. A 76-year-old man diagnosed with non-invasive bladder cancer underwent intravesical BCG instillation; he developed high fever and systemic arthralgia later that night. General examination did not reveal any infectious sources, and a combination therapy of isoniazid, rifabutin, and ethambutol was initiated after collecting his blood, urine, bone marrow, and liver biopsy samples for mycobacterial cultures. Three weeks later, *Mycobacterium bovis* was detected in the urine and bone marrow samples, and pathological investigation of liver biopsy revealed multiple small epithelial granulomas with focal multinucleated giant cells, leading to a diagnosis of disseminated BCG infection. The patient recovered after long-term antimycobacterial therapy without remarkable sequelae. Most cases of disseminated BCG infection occur after several doses of BCG injections, and its onset reportedly varies among cases, ranging from a few days to several months. The present case was notable as disease onset was observed only a few hours after the first BCG injection. Although rare, development of disseminated BCG infection should be considered as a differential diagnosis in patients at any time after intravesical BCG instillation therapy.

Keywords: Bacillus Calmette-Guérin (BCG); *Mycobacterium bovis*; intravesical BCG instillation therapy; disseminated infection.

Introduction

Bacillus Calmette-Guerin (BCG) vaccine derived from *Mycobacterium bovis* is a live vaccine for tuberculosis prevention [1,2]. The vaccine is a part of the routine childhood immunization and is widely administered to infants in Japan. Interestingly, the clinical application of intravesical BCG instillation therapy has been established for patients with non-muscle-invasive bladder cancer, and it is the gold standard adjuvant treatment recommended by clinical guidelines [3,4]. Although the precise mechanism of action of intravesical BCG therapy is unknown, its anticancer efficacy is assumed to due to a local immunological boost that recruits immunocompetent cells [5]. After injection, bladder-stimulating symptoms, such as urgency and frequent urination, mild fever, and fatigue, are frequently observed, which naturally resolve within 24–48 h. However, studies reported that systemic dissemination of *M. bovis* occurs in approximately 0.4 to 4.3% of patients receiving BCG instillation therapy [6,7]. Usually, disseminated BCG infections develop in patients after repeated BCG injections; the median number of instillation therapies before developing a disseminated infection has been reported as six (interquartile range: 4–9) [7]. Therefore, the onset of systemic disease shortly after the first injection is rare. Herein, we report a case of disseminated BCG infection in a patient immediately after the first BCG instillation therapy.

Case Report

A 76-year-old man with a history of benign prostatic hyperplasia, dyslipidemia, and arteriosclerosis obliterans was presented with hematuria. Contrast-enhanced computed tomography detected a 2-3 mm-sized mass located at the apex of the urinary bladder, without any findings suggesting metastatic mass or ureteral obstruction. Under the suspicion of a bladder tumor, the patient underwent transurethral resection of the bladder tumor (TUR-BT). The cystoscopy detected a papillary tumor, accompanying mucosal erythema. Seven weeks later, he was followed up by the 2nd TUR-BT. As a result, the patient was diagnosed with pT1 (non-invasive bladder cancer in the muscle layer) and cN0M0 (stage I). Six weeks after the 2nd TUR-BT, the patient received intravesical BCG instillation therapy, the first-line therapy for early-stage bladder cancer, at our hospital. Urinalysis examined at that time showed a normal urine color without no evidence of red blood cells in the urine. Later that night, the patient suddenly developed high fever up to more than 38 °C. No abdominal, respiratory, or urinary symptoms were observed. The fever did not subside with oral acetaminophen, and the patient visited us five days after BCG instillation therapy.

On the day of visit, the patient was conscious and alert, and his vital signs were as follows; blood pressure, 146/74 mmHg; pulse rate 100 beats/min; and body temperature, 37.2 ℃. A physical examination revealed no abnormalities. Laboratory testing showed mild

thrombocytopenia (platelet counts, $14.4 \times 10^4/\mu L$), elevated levels of liver enzymes (aspartate aminotransferase, 142 U/L; alanine aminotransferase, 322 U/L), and an increase in C-reactive protein level (1.08 mg/dL). Urinalysis results were unremarkable. Systemic computed tomography detected no pulmonary findings, lymphadenopathy, or splenomegaly; however, reduced attenuation was observed in the area surrounding the portal vein of the liver. The patient was followed up without hospitalization and was found to have persistent fever, suggesting the possibility of a sequela of disseminated BCG infection. The patient was admitted for further investigation and treatment.

Blood, urine, liver tissue biopsy, and bone marrow samples of the patient were collected for mycobacterial culture, and a combination therapy of isoniazid (INH), rifabutin (RBT), and ethambutol (EB) was initiated. Microscopic examination of liver biopsy revealed multiple small epithelial granulomas and focal multinucleated giant cells, suggesting a response to mycobacterial infection (**Fig. 1**). The patient was discharged after two weeks of hospitalization along with administration of the triplet therapy. After 21 and 25 days of incubation, respectively, the urine and bone marrow samples were confirmed to be positive for mycobacterial infection through a positive reaction to conventional PCR testing clinically used for *Mycobacterium tuberculosis* complex. *M. bovis* belongs to the *M. tuberculosis* complex, leading to a positive PCR test result. To identify the pathogen, we used PCR primers to

differentiate between mycobacteria, IS1561', Rv1510, and Rv3877/8, as recommended in previous studies [8,9]. A clinical strain of *M. tuberculosis* was used as control. Consequently, the isolate was demonstrated to be *M. bovis*, with a positive result for IS1561' and negative reactions to Rv1510 and Rv3877/8 (**Table 1**).

Collectively, the patient was diagnosed with disseminated BCG infection. Antimicrobial susceptibility testing suggested that the pathogen was susceptible to INH, rifampicin (RIF), EB, streptomycin, and levofloxacin (LVFX). The patient subsequently developed an allergic eruption. RBT was switched to LVFX, whereas INH was continued after desensitization. After approximately three months, the combination therapy was switched to a combination of INH and LVFX. At the time of manuscript drafting, six months have passed since the initiation of the treatment. The patient reveals no clinical signs of deterioration or side effects of the combination therapy and is scheduled for an additional three-month treatment.

Discussion

Herein, we describe a case of disseminated BCG infection in an elderly Japanese man. Usually, disseminated BCG infection develop after multiple BCG therapy sessions [7]; however, the present case developed the disease immediately after the first intravesical BCG instillation therapy. Thus, it was first perplexing to consider the disease as a differential diagnosis of

persistent fever.

The underlying mechanism of super-acute onset of the systemic infection needs to be discussed. First, the incidence of BCG dissemination is largely dependent on the injury to the bladder mucosa. Damage to the urinary bladder mucosa may lead to dissemination; thus, a history of TUR-BT within two weeks, urethral catheter-related trauma, and presence of gross hematuria are considered the major contraindications for intravesical BCG therapy [1]. In fact, most patients with disseminated BCG infection had a history of repeated TUR-BT procedures [7]. However, no such causative factors were identified in this case. Second, higher dosage of BCG administered might have triggered disseminated infection. However, BCG was administered at the recommended dose (80 mg). Therefore, we conclude that it was unfortunate for the patient to develop disseminated BCG infection just after the first-single injection.

We performed a literature review to uncover the clinical characteristics of super-acute-onset disseminated BCG infection. We searched PUBMED for the keywords "disseminated Bacillus Calmette-Guérin infection" within 10 years (Mar 2013 to Mar 2023). A total of 382 references were identified, of which 45 were case reports or literature reviews of disseminated BCG infections occurred after BCG therapy for bladder cancer. Among these, only two cases have been reported to develop the disease after the first BCG injection [10,11]. **Table 2** summarizes the key components of the presented and reported cases. All cases were elderly

male patients who manifested fever. One patient died, and two survived. Due to the small number of cases, it is difficult to comprehend the features of super-acute-onset cases. Although there could be underreporting of such cases, publication bias, or incomplete searching, our literature review suggests that such cases are extremely rare.

The diagnosis of a disseminated BCG infection is challenging. After intravesical BCG instillation in a patient, fever or bladder irritation symptoms are common physiological responses to the injection, which subside within 72 h and are occasionally persistent. If the symptoms persist for over 72 h, especially when accompanied by high fever and severe systemic symptoms, disseminated infection should be considered. Sensitivity of sputum testing is low; 25.3% for acid-fast staining, 40.9% for mycobacterial culture, and 41.8% for PCR [7]. However, the diagnostic accuracy of tissue biopsies of the liver, lung, and bone marrow is reportedly high (86.3%); thus, tissue biopsy is recommended as a diagnostic approach [12].

Case fatality rate of disseminated BCG infection has been reported as 5.4%, in which higher age (≥ 65 years) and presence of vascular lesions are considered deteriorating factors [7]. The treatment of disseminated BCG infection requires a combination of multiple antituberculosis agents. The suggested regimen is a 3-drug therapy with INH, RIF, and EB for 2 months, followed by a 2-drug therapy with INH and RIF for 4 months [4]. *M. bovis* is resistant to pyrazinamide [6], which should be therefore avoided when treating patients with

disseminated BCG infections. In our case, we provided a successful empirical treatment to the patient with a combination of INH, RBT, and EB, followed by INH and LVFX. Although additional BCG instillation therapy is generally not recommended, a clinical indication needs to be determined, considering its risks and benefits [4].

In summary, we have described a case of disseminated BCG infection that developed immediately after the first intravesical instillation in an elderly Japanese man, although the majority of such cases develop after more than several series of BCG instillations in the bladder. Early and appropriate diagnosis followed by antimycobacterial treatment is essential for a better prognosis of iatrogenic disease.

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Conflict of Interest: The authors declare no conflicts of interest.

Ethics statement: Informed consent was obtained from the patient for publication of this case report.

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Figure Legends

Figure 1. Microscopic findings of liver biopsy.

The arrows show multiple small epithelial granulomas with focal multinucleated giant cells in the liver tissue (Hematoxylin and eosin staining, ×20).

Table 1. Identification of the causative organism by an algorithm to differentiate *Mycobacterium tuberculosis* complex subspecies

Organism	IS1561’	Rv1510	Rv3877/8
*Mycobacterium tuberculosis**	+	+	+
*Mycobacterium bovis**	+	−	+
Mycobacterium bovis BCG*	+	−	−
Present isolate	+	−	−

*Data was referred in references 8 and 9.

Table 2. **Super acute-onset cases of disseminated BCG infection.**

Age/sex	Number of BCG injection	Time to the disease onset after BCG injection	Symptoms	Examination findings Disseminated infectious foci	Treatment	Prognosis
76 year/Male (Present case)	1	A few hours	Fever	Urinary and bone marrow blood mycobacterial culture positive for *Mycobacterium bovis*	INH+RBT (LVFX)+EB (3 months) INH+LVFX (6 months)	Survived
77 year/Male[10)]	1	1 day	Fever	Multiple epithelioid cell granulomas with Langhans giant cells of the liver and bone marrow	INH+EB+RIF mPSL 500 mg (3 days) followed by PSL 50 mg/day	Died on day 35
81 year/Male[11)]	1	Details unknown	Fever, weakness, and confusion	Urinary mycobacterial culture positive for *M. bovis*	Antituberculosis therapy (6 months) (Details unknown)	Survived

INH, isoniazid; RBT, rifabutin; RIF, rifampicin; EB, ethambutol; PSL, prednisolone; mPSL, methylprednisolone; LVFX, levofloxacin.

The details of the present case and previous cases who developed disseminated BCG infection after the first dose of intravesical BCG injection are summarized.