

Inadvertent Administration of the Bacillus Calmette-Guérin (BCG) Vaccine: A Case Report and Review of the Literature

İrem AKIN ŞEN^a,
Hakan DOĞAN^a,
Hülya SUNGURTEKİN^a

^aAnesthesia Intensive Care Unit,
Pamukkale University
Faculty of Medicine,
Denizli, TURKEY

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Correspondence:

İrem AKIN ŞEN
Pamukkale University
Faculty of Medicine,
Anesthesia Intensive Care Unit,
Denizli, TURKEY
rosewellufo@hotmail.com

ABSTRACT Intravesical Bacillus Calmette–Guérin (BCG) has proven effective in the treatment of carcinoma in situ and is known to prevent recurrences in superficial bladder cancer, the local and systemic side effects of which are associated with attenuated live *Mycobacterium bovis* in the bladder. The rare administration of BCG such as through intramuscular (IM) or intravenous (IV) administration is more likely to cause systemic infections. Although serious and life-threatening systemic complications are rare, most such complications are tolerable. This case report examines the course of reaction and treatment after the accidental IV administration of high dose BCG vaccine.

Keywords: BCG vaccine; bladder cancer; *Mycobacterium bovis*; drug use disorders

The attenuated live *Mycobacterium bovis* (*M. bovis*) strain Bacillus Calmette–Guérin (BCG) was developed by Calmette and Guérin. The first use of BCG was in tuberculosis and malignant melanoma; it was administered intravesically in high-risk superficial bladder cancer for the first time in 1976.^{1,2} The BCG vaccine used in superficial bladder cancer and carcinoma *in situ* (CIS) treatment is thought to have an anti-tumor effect by forming T cell-related immunoreactivity in the bladder; more than 95% of patients respond well to this treatment. Intravesical BCG causes frequent local side effects such as pollakiuria, dysuria, and cystitis, which often heals without treatment.²⁻⁴ Severe side effects include acute respiratory failure, septic shock, hemolytic uremic syndrome, disseminated intravascular coagulation, granulomatous hepatitis, pneumonia, and epididymoorchitis.⁴⁻⁷ These side effects are observed in <5% of patients.⁴ The incidence of granulomatous hepatitis was 0.7-0.9%.^{7,8}

In the case of granulomatous hepatitis, antituberculous treatment and steroid treatment are recommended.⁸

This article presents a case of transurethral resection-bladder (TUR-M) and intravesical BCG that was made about a month ago in which the intravenous BCG was made mistakenly and discusses the clinical factors and treatment management for such cases.

CASE REPORT

A 69-year-old male patient who had no known disease other than hypertension was admitted to the hospital due to hematuria about three weeks ago. The patient was diagnosed with bladder cancer and went to surgery of TURB. During follow-up, the patient was deemed appropriate for intravesical BCG, but when the patient applied to the hospital for treatment the vaccine was administered intravenously instead of intravesically. Approximately 24 hours after the BCG administration, he applied to our emergency department for the onset of chills. The patient was admitted to our intensive care clinic with a preliminary diagnosis of BCG sepsis, information about all scientific and interventional procedures was given and the patient's and his relatives' approvals were obtained.

First clinical examination: Respiratory voices are equally involved in respiration in both hemithoraces, no rales-rhonchi. Blood pressure: 88/54, pulse: 112, fever: 38.2, saturation: 92, the general situation was moderate-good conscious open, oriented, cooperative.

Laboratory: In urine microscopy; pH: 5.0, density: 1026, leucocyte: ++, protein: trace amounts.

Complete blood counts and biochemical values were as given in below (Table 1).

Blood and urine cultures were taken upon admission, chest X-ray was taken and echocardiography (ECG) was performed, and antituberculous treatment (INH, RIFAMPINE, and ETAMBUTOL) was started immediately. For hepatic function test, elevation N-acetylcysteine infusion was initiated with preservation. Patient who was hypotensive and febrile on admission was given 5 mg/kg pentaglobin infusion.

The infectious disease clinic was consulted because the patient showed subfebril fever and had a slight elevation in liver function tests. The infectious diseases clinic recommended follow up with close liver function tests and continuing medications.

Echocardiography showed EF 55% and no pathology such as abscess/vegetation/fistula structure was detected and the patient was followed up with daily liver function tests. When necessary, albumin replacement, fresh frozen plasma, and erythrocyte suspension were administered to the patient for supportive therapy.

The patient was followed up in our department for eight days in total, and no complications

TABLE 1: Laboratory data of the patient during treatment.

	Normal Values	Admission	One Week	Four Weeks	Three Months
BUN (mg/dL)	8-23	16	11	15	22
Creatinine (mg/dL)	0.67-1.17	0.71	0.61	1.00	1.00
Sodium (mmol/L)	136-145	139	139	140	141
Potassium (mmol/L)	3.5-4.5	3.99	4.26	3.97	4.14
Chlor (mmol/L)	98-107	103	98	100	99
Calcium (mg/dL)	8.8-10.2	8.11	8.63	9.00	9.12
AST (IU/mL)	< 40	96	92	39	19
ALT (IU/mL)	< 41	97	112	70	19
Albumin (g/dL)	3.5-5.2	3.37	3.18	3.22	3.62
Bilirubin (direct)(mg/dL)	≤ 0.3	0.96	0.68	0.75	0.34
Bilirubin (total) (mg/dL)	≤ 1.2	0.81	0.95	0.93	0.6
LDH (U/L)	135-214	310	261	192	212
Hemoglobin (g/dL)	12-18	13.6	13.1	13.6	14.4
Hematocrit (%)	37-52	44.2	38.6	41.5	42.8
Platelet (K/uL)	130-400	130.000	196.000	221.000	301.000

BUN: Blood Urea Nitrogen, **AST:** Aspartat Aminotransferase, **ALT:** Alanin Aminotransferase, **LDH:** Lactate Dehydrogenase.

developed during the follow-up period. Patient whose liver function tests was normalized was discharged by recommending polyclinic control of infectious diseases. Eight days after discharge, the patient was sent to the emergency department for high fever and elevated liver function tests. Consultation was sought regarding the patient's condition from the gastroenterology and infectious diseases departments and abdominal tomography (CT) were requested. In the CT, a 6 x 4 cm cystic lesion was found in the inferomedial neighborhood of the left kidney leaning against the psoas muscle; this was confirmed by dynamic MR and interpreted in favor of type-2 cyst hydatid. Hospitalization was recommended to the patient but he refused.

DISCUSSION

Bacillus Calmette-Guérin is a live-attenuated vaccine obtained from *M. bovis* strain. Intravesical BCG administration has been used for more than 30 years in non-invasive bladder cancer and carcinoma *in situ* (CIS) treatment.⁹ Although this treatment is mostly reliable, there are local and systemic side effects. The incidence of side effects is unclear due to the lack of the clear definition of side effects and the failure to maintain regular recordings.

Rates vary between countries, but the local side effect rate is 0.1-0.5 in 1,000 and the incidence of systemic side effects is 1 in a million.¹⁰ Side effects due to the BCG are rare and usually resolve without treatment.¹¹ Common side effects are: hematuria renal abscess, cystitis, bladder contracture, granulomatous prostatitis, epididymo-orchitis, and urethral obstruction.^{4,6} Local side effects of the BCG include inflammation in the urinary system as a result of being contaminated with BCG.⁶ After BCG administration, local side effects may occur after the second or third administration and continue for approximately two days; they usually improve without treatment.⁶ Systemic side effects are rare and include fever, BCG pneumonia, acute respiratory failure, hemolytic uremic syndrome, disseminated intravascular coagulation, granulomatous hepatitis, arthritis or arthralgia, rash, skin abscess, cytopenias, and sepsis.³⁻⁶ The use of BCG

during bladder biopsy, transurethral resection of the prostate or bladder tumor, traumatic catheterization and simultaneous cystitis are risk factors that increase the incidence of systemic side effects. Immunosuppressive drug use, diabetes mellitus, and genetic factors are also important risk factors.³ Our patient was diagnosed with bladder cancer and went to surgery of TURB. During his treatment, patient should have deemed appropriate for intravesical BCG, but the vaccine was administered intravenously instead of intravesically.

There are over 5,000 publications worldwide related to the BCG. Among these, 28 adults with disseminated disease due to BCG have been identified. Twenty-four patients had a congenital disease or AIDS that caused immunosuppression, and 20 of these patients died despite anti-tuberculosis treatment. No significant immunosuppression was observed in the remaining four patients; they continued their lives as a result of treatment with various antituberculosis drugs.¹⁰

BCG cases occurring after the accidental administration either IV or IM is very rare. After the accidental IV administration of BCG; sepsis and disseminated BCG infection was seen in one case, which was treated successfully with antituberculous therapy consisting of isoniazid, rifampicin, and ethambutol plus methylprednisolone.¹² Patient who presented in our paper have accidental IV administration of BCG.

Headache, sweating, and fever have occurred with the accidental intramuscular use of four doses of BCG prescribed for intravesical use. Severe pain in the hypogastric region, pain at the injection site and induration developed three days after application. Despite the presence of active infection in this patient and no evidence of active respiratory system infection on chest X-ray, antituberculous therapy containing isoniazid and rifampin was administered prophylactically.¹³ Our patient have low blood pressure, high fever such as in the literature. He had moderate-good conscious, oriented, cooperative. Respiratory voices are equally involved in respiration in both hemi thoraces, no rales-rhonchi.

In another case previously susceptible to tuberculosis, the accidental IM application of BCG resulted in a serious local reaction that lasted quite a while; antituberculosis therapy was also used in this case.¹⁴

Another case in the literature is a 13-year-old patient with bladder dystrophy who was prescribed human chorionic gonadotropin (HCG) therapy before an interventional procedure. In total, of six doses of HCG ampoules were recommended to the patient, the prescription was written as β -HCG rather than HCG, and the pharmacy officer accidentally gave the patient six ampoules of BCG; six ampoules of intravesical BCG were administered IM twice a week for three weeks. After the first injection, the patient experienced fever and chills, but thought that was ordinary and all drugs were used. Two months after treatment, disseminated mycobacterium infection was considered in the patient who applied to the hospital with pancytopenia fever and urea-creatinine elevation. The patient was treated with isoniazid, ethambutol, and rifampin and was cured.¹⁵ Antituberculous treatment (INH, RIFAMPINE, and ETAMBUTOL) was started immediately to our patient. N-acetylcysteine infusion was initiated and were given 5 mg/kg pentaglobin infusion for ongoing sepsis.

Intravesical BCG is a very useful treatment for bladder cancer. However, if it is administered by

the wrong method and route, it can become a mortal toxin. Health personnel and patients should be clearly informed about how they will apply BCG therapy and they should be told to consult a doctor if the experience any side effects.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: İrem Akın Şen, Hakan Doğan, Hülya Sungurtekin; **Design:** İrem Akın Şen, Hakan Doğan, Hülya Sungurtekin; **Supervision/Consultancy:** Hülya Sungurtekin; **Data Collection and/or Processing:** İrem Akın Şen, Hakan Doğan; **Analysis and/or Comment:** İrem Akın Şen, Hakan Doğan, Hülya Sungurtekin; **Source Scanning:** İrem Akın Şen, Hakan Doğan, Hülya Sungurtekin; **Complete Writing:** İrem Akın Şen, Hakan Doğan; **Critical Review:** İrem Akın Şen; **Resources and Funding:** İrem Akın Şen; **Materials:** İrem Akın Şen.

REFERENCES

- Morales A, Eidinger D, Bruce AW. Intracavitary Bacillus Calmette-Guérin in the treatment of superficial bladder tumors. *J Urol.* 1976;116(2):180-3. [Crossref]
- Catalona WJ, Rattiff TL. Bacillus Calmette-Guérin and superficial bladder cancer. Clinical experience and mechanism of action. *Surg Annu.* 1990;22:363-78. [PubMed]
- Soylu A, Ince AT, Polat H, Yasar N, Ciltas A, Ozkara S, et al. Peritoneal tuberculosis and granulomatous hepatitis secondary to treatment of bladder cancer with Bacillus Calmette-Guérin. *Ann Clin Microbiol Antimicrob.* 2009;(15):8-12.
- Lamm DL, van der Meijden PM, Morales A, Brosman SA, Catalona WJ, Herr HW, et al. Incidence and treatment of complications of bacillus Calmette-Guérin intravesical therapy in superficial bladder cancer. *J Urol.* 1992;147(3):596-600. [Crossref]
- Ersoy O, Aran R, Aydinli M, Yonem O, Harmanci O, Akdogan B, et al. Granulomatous hepatitis after intravesical BCG treatment for bladder cancer. *Indian J Gastroenterol.* 2006;25(5):258-9. [PubMed]
- Gonzalez OY, Musher DM, Brar I, Furgeson S, Boktour MR, Septimus EJ, et al. Spectrum of bacille Calmette-Guérin (BCG) infection after intravesical BCG immunotherapy. *Clin Infect Dis.* 2003;36(2):140-8. [Crossref] [PubMed]
- Ozbakkaloglu B, Tünger O, Sürücüoğlu S, Lekili M, Kandiloglu AR. Granulomatous hepatitis following intravesical bacillus Calmette-Guérin therapy. *Int Urol Nephrol.* 1999;31(1):49-53. [Crossref] [PubMed]
- Lamm DL. Complications of bacillus Calmette-Guérin immunotherapy. *Urol Clin North Am.* 1992;19(3):565-72. [PubMed]
- Jose Manzenara Escribano M, Morales Ruiz E, Odriozola Grijalba M, Gutierrez Martínez E, Rodriguez Antolin A, Praga Trente M. Acute renal failure due to interstitial nephritis after intravesical instillation of BCG. *Clin Exp Nephrol.* 2007;11(3):238-40. [Crossref] [PubMed]
- Casanova JL, Blanche S, Emile JF, Jouanguy E, Lamhamedi S, Altare F, et al. Idiopathic disseminated bacillus Calmette-Guérin infection: a French national retrospective study. *Pediatrics.* 1996;98(4 Pt 1):774-8. [PubMed]
- Lotte A, Wasz-Höckert O, Poisson N, Dumitrescu N, Veron M, Couvet E. BCG complications. Estimates of the risks among vaccinated subjects and statistical analysis of their main characteristics. *Adv Tuberc Res.* 1984;21:107-93. [PubMed]
- Akbulut Z, Canda AE, Atmaca AF, Cimen HI, Hasanoglu C, Balbay MD. BCG sepsis following inadvertent intravenous BCG administration for the treatment of bladder cancer can be effectively cured with anti-tuberculosis medications. *N Z Med J.* 2010;123(1325):72-7. [PubMed]
- Yarmohammadi A, Ahmadiania H, Abolbashiari M, Molaei M. Results of inadvertent administration of bacillus Calmette-Guérin for treatment of transitional cell carcinoma of bladder. *Urol J.* 2007;4(2):121-2. [PubMed]
- Pasteur M, Hall DR. The effects of inadvertent intramuscular injection of BCG vaccine. *Scand J Infect Dis.* 2001;33(6):473-4. [Crossref] [PubMed]
- Rafati MR, Kouchaki B. Active mycobacterium infection due to intramuscular BCG administration following multi-steps medication errors. *J Pharm Care.* 2014;2(3):132-6.