OLGU SUNUMU CASE REPORT

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Disseminated Bacillus Calmette-Guérin (BCG) Infection Caused By Inadvertent Intravenous Infusion of BCG for the Treatment of Bladder Cancer: Case Report

Yanlışlıkla Yapılan İntravenöz Bacillus Calmette-Guérin (BCG) İnfüzyonu Sonucu Görülen Yaygın BCG Enfeksiyonun Sonuçları

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ABSTRACT Nonmuscle invasive bladder cancer is a common malignancy. After transurethral resection, intravesical administration of Bacillus Calmette-Guérin (BCG) is a treatment that is generally used for non-muscle-invasive bladder cancer. Intravesical BCG treatment decrease the number of tumor recurrence and progression. The complications of BCG therapy are important that clinicians are aware of these. Serious complications are uncommon with BCG treatment, but life-threatening side effects such as sepsis, hepatitis and pneumonia may occur. The person who applies the intravesical BCG must be very careful throughout the entire administration procedure. We present a patient whom an intravenous BCG infusion was inadvertently administered and the patient was successfully treated with anti-tuberculin therapy. A review of available literature on the possible complications of this treatment have been performed.

Keywords: BCG vaccine; sepsis; urinary bladder neoplasms

ÖZET Kasa invaze olmayan mesane kanseri oldukça sık karşılaşılan bir hastalıktır. Transüretral rezeksiyon sonrası mesane içi Bacillus Calmette-Guérin (BCG) uygulaması kasa invaze olmayan mesane kanseri tedavisinde kullanılmaktadır. Mesane içi BCG tedavisi mesane tümörü rekürrens sıklığını ve progresyonunu azaltmaktadır. BCG tedavisinin komplikasyonları önemlidir ve bu tedaviyi öneren hekimlerin bu konuda dikkatli olmaları gerekmektedir. BCG tedavisi sonrası ciddi komplikasyonlar nadir gözlenmektir fakat sepsis, hepatit ve pnömoni gibi hayatı tehdit edici komplikasyonlar da görülebilmektedir. BCG instillasyonu yapan tıbbi personel işlem esnasında çok dikkatli olmalıdır. Bu çalışmada yanlışlıkla intravenöz BCG verilen ve antitüberküloz tedavi ile başarılı olarak tedavi edilen bir vaka güncel literatür değerlendirilerek sunulacaktır.

Anahtar Kelimeler: BCG aşısı; sepsis; mesane neoplazileri

In the years following the first use of Bacille Calmette-Guerin (BCG) at other types of cancer in the 1930s, urologists began to use BCG for the treatment of bladder cancer.[1] Intravesical BCG therapy was first reported by Morales, Eidinger and Bruce as a successful available treatment for managing non-muscle invasive bladder cancer. Intravesical instillation of live-attenuated BCG has been used for the treatment of in-situ carcinoma (CIS) and high-risk non-muscle invasive bladder cancer for 30 years. However, BCG immunotherapy has local and systemic side effects. The local side effects are frequent and mild, whereas the systemic side effects are associated with significant toxicity and numerous serious issues. Here, we present a patient with a non-muscle invasive bladder tumor who presented with

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persistent fever after unintentional intravenous BCG infusion.

CASE REPORT

A 67-year-old male patient with a medical history of heavy smoking (45 pack/year) presented to our outpatient clinic with macroscopic hematuria that had been occurring for one month. The patient had no previous urological history. After cystoscopy, multiple papillary bladder tumors were resected transurethrally and a low-grade transitional cell carcinoma with invasion of the lamina propria (pT1a) was confirmed on histological examination. The patient underwent a second transurethral resection after three weeks, and the histological results were consistent with the previous diagnosis, which was pT1 and low-grade transitional cell carcinoma. Intravesical BCG instillations were recommended due to the high risk non-muscle invasive bladder cancer. At the first instillation, a retired healthcare worker who was a neighbor of the patient administered the 81 mg of live-attenuated BCG (ImmuCyst®) by intravenous infusion at the patient's home. The patient presented to our university hospital emergency department four hours after the instillation with flulike symptoms such as weakness, high fever and nausea. Physical examination revealed no signs of hepatosplenomegaly, lymphadenopathy or meningeal irritation. The patient was immediately admitted to our clinic with a diagnosis of BCG sepsis. His temperature was recorded as 38.2°C. Blood studies including complete blood count and biochemistry values showed elevation of the liver and kidney function markers and pancytopenia (Table 1). Triple anti-tuberculin therapy, which includes ethambutol 1200 mg, isoniazid (INH) 300 mg and rifampin 600 mg was started after urine and blood specimens had been obtained for culture. Three days later, the treatment regimen was changed because test results showing elevation of the liver and kidney function markers as well as pancytopenia had led the gastroenterologist and nephrologist to suspect prerenal azotemia and drug toxicity. Antituberculosis therapy was continued using INH 300 mg 1x2, PO only, and imipenem 2x250 mg, IV was added. The haematologist considered that progressive pancytopenia was the cause of what was possibly a systemic disease related to multi-organ failure, suppression of bone marrow or hypersplenism. The patient's clinical status improved at the end of the second week, and he was discharged with INH therapy recommended for use for six months. The complete blood count and serum biochemistry values of the patient returned to normal levels after three months. Regular follow-up for control of the bladder tumor was performed for four years, until the present time, and 24 months later the highest diameter multiple papillary tumor, measuring 5 mm was resected transurethrally. Pathological examination showed a low malignancy potential urothelial neoplasm. We continue regular follow-up, using cystoscopy, of patients who have no detected recurrence at the postoperative period. When we decided to write this case as a case report, we obtained an informed consent form from the patient.

DISCUSSION

BCG is a live attenuated strain of *Mycobacterium bovis*, which is generally used as a relatively safe and effective treatment for non-muscle invasive transitional cell carcinoma and carcinoma in situ of the bladder.[2] BCG action is not yet fully elucidated. It is believed that BCG contacts tumor cells, and antitumor activity is started by local modulation of the immune responses. Increased expression of IL-2, IFN-γ and IL-12 result in the positive effect of the CD-4 helper and the CD-8 cytotoxic T cells. Adverse reactions that occur may be grouped into two categories: infectious and noninfectious (inflammatory).[3] The side effects of intravesical BCG include local infection, multi-organ granulomatosis, reactive arthritis, hypersensitivity reactions and severe BCG sepsis, and up to 50% of patients can develop certain local side effects. Most patients may not report any significant side effects. BCG instillation should be postponed if a patient exhibits gross haematuria, has had a recent bladder biopsy or has active systemic or urinary tract infections, a history of recent transurethral resection of prostate (TURP) or traumatic catheterization.[4]

TABLE 1: Changes in the laboratory parameters during the follow up of the patients.

		Hospitalisation				
Variables	**Normal Values**	**On Admission**	**First week**	**Second week**	**Fourth week**	**Sixth month**
Haemoglobin (g/L)	13-17	10.5	11.8	9.3	10.7	10.9
Haematocrit (%)	40-54	33.3	37.2	26.9	30.1	33.6
Platelet (×109/L)	150-500	79	124	86	78	174
CRP (mg/dl)	0.0-0.8	7.9	3.6	2.3	1.6	0.5
BUN (ug/dL)	17-43	28	48	116	59	34
Creatinine (U/L)	0.7-1.4	1.1	2.2	4.2	1.9	1.6
Sodium (mEq/L)	134-146	137	130	131	134	137
Potassium (mEq/L)	3.5-5.2	2.7	4.9	4.4	3.7	4.1
Chloride (mEq/L)	97-108	97	99	104	99	102
Calcium (mmol/L)	8.6-10.6	8.1	8.4	7.6	8.2	8.1
AST (U/L)	0-35	27	782	181	56	15
ALT (U/L)	0-45	23	469	245	36	10
Albumin (g/dL)	3.5-5.2	3.5	2.6	2.2	2.2	2.9
Bilirubin (direct) (mg/dL)	0.0-0.2	0.1	0.9	1.52	1.4	0.3
Bilirubin (total) (mg/dL)		0.7	1.42	2.72	3.3	0.7

Note: CRP: C- reactive protein; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Sepsis may occur with BCG instillation after traumatic catheterization, and the fatality rate can be up to 1 in 12,500 cases.[5] Rico et al. reported on a case in which intravesical connaught-strain of BCG was given after a traumatic bladder catheterization and the development of severe disseminated symptoms. Various cases involving inadvertent intramuscular or intravenous injection have been reported previously. Three such case reports have been found that were related to inadvertent intramuscular injection of BCG. Severe and prolonged local and systemic reactions occurred in both cases and were treated successfully with anti-tuberculosis drugs.[6-8] There is also a case report, published by Gul et al. involving inadvertent intravenous administration in a 39-year-old male with high-grade transitional cell carcinoma. Following intravenous administration, the patient developed systemic symptoms including high fever, shivers and nausea along with multi-organ failure. However, after three weeks the patient died in spite of having been treated in the intensive care unit.[9]Another case involving a 51-year-old male patient with pT1G3 urothelial carcinoma was published by Akbulut et al. intravesical 81 mg of BCG administration was recommended to prevent recurrence and progression of the superficial bladder cancer. He had taken 81 mg of BCG (ImmuCyst®) through an inadvertent intravenous route at another hospital. One day after the administration, the patient presented with fatigue, nausea, coughing, respiratory insufficiency and a high fever. He was immediately hospitalized, and anti-tuberculosis and supportive treatment were initiated for disseminated *Mycobacterium bovis* infection and multi-organ disorders. The patient was discharged four weeks later and had returned to his general state of health.[10] In our patient, the symptoms developed a few hours after the intravenous BCG instillation. During his initial visit, the patient received a complete physical examination along with blood work and radiological testing. The results of the patient's chest x-ray were normal, in spite of the probability that secondary hypersensitivity reaction or miliary pulmonary tuberculosis may have occurred after intravesical of BCG administration. In a review by Gonzalez et al. of 41 cases that involved suspicions of BCG sepsis after intravesical BCG instillation, the patients were categorized into two groups with respect to the timing of their hospital admissions. The organs that were involved in the BCG sepsis includes the lungs, the retroperitoneal soft tissues, the geni-

tourinary tracts, the vascular tree, the liver, the chest wall and the vertebral bones.[3] Definitive treatment of BCG sepsis is not yet fully established. Our patient's treatment lasted for six months; however, the literature reported lengths of anti-tuberculosis treatment ranging from six to 12 months.[11] Even if patients fully recover from BCG sepsis following inadvertant BCG administration or intravesical instillation of BCG, mortality due to BCG sepsis is very high. Gonzalez et al. reported a mortality rate of 25% for BCG sepsis.[3] Inadvertent intravenous administration of BCG may be fatal. Therefore, intravesical instillation of BCG should be conducted in a hospital setting by experienced healthcare personnel.

Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

***Design and Writing of the Case with literature Review**: Yavuz Onur Danacıoğlu; **Literature Review and Revision of Manuscript:** Turgay Turan; **Literature Review and Revision of Manuscript:** Asıf Yıldırım; **Revision of the Manuscript:** Turhan Çaşkurlu.*

REFERENCES

1. Luca S, Mihaescu T. History of BCG vaccine. Maedica (Buchar) 2013;8(1):53-8.
2. Elkabani M, Greene JN, Vincent AL, VanHook S, Sandin RL. Disseminated Mycobacterium bovis after intravesicular bacillus calmette-guerin treatments for bladder cancer. Cancer Control 2000;7(5):476-81.
3. 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.
4. Paterson DL, Anil P. Bacillus Calmette-Guerin (BCG) immunotherapy for bladder cancer: review of complications and their treatment. Aust N Z J Surg 1998;68(5):340-4.
5. Koya MP, Simon MA, Soloway MS. Complications of intravesical therapy for urothelial cancer of the bladder. J Urol 2006;175(6): 2004-10.
6. Yarmohammadi A, Ahmadinia H, Abolbashari M, Molaei M. Results of inadvertent administration of bacillus Calmette-Guerin for treatment of transitional cell carcinoma of bladder. Urol J 2007;4(2):121-2.
7. Gross S, Kahan E, Vesterman L, Havkin O, Leventhal A. Adverse reactions to accidental forearm injection of Bacille Calmette-Guerin vaccine in school children: 12-month cohort follow-up. Clin Infect Dis 2004;38(10):1495-7.
8. Banu A, Loganathan E. Inadvertent intramuscular administration of high dose Bacillus Calmette Guerin vaccine in a pre-term infant. J Family Med Prim Care 2013;2(1):95-7.
9. Gul U, Kuzgunbay U, Yaycioglu O. Fatal outcome caused by intravenous infusion of bacille Calmette-Guérin. Urology 2010;76(2): 518.
10. 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. NZ Med J 2010;123(1325):72-7.
11. Diner EK, Verghese M. Interstitial pneumonitis secondary to intravesical bacillus calmette-guerin for carcinoma in-situ of the bladder. Int Braz J Urol 2004;30(5):400-2.