Hypersensitivity Reaction After Intravesical Bacille Calmette Guerin Administration for the Treatment of Bladder Carcinoma: Case Report

Mesane Kanseri Tedavisinde İntravezikal Bacille Calmette Guerin Uygulamasını Takiben Gelişen Aşırı Duyarlılık Reaksiyonu

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Geliş Tarihi/*Received:* 10.06.2015
Kabul Tarihi/*Accepted:* 19.03.2016

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ABSTRACT Intravesical administration of Bacille Calmette-Guérin (BCG) vaccine is widely used for the treatment of bladder carcinoma, even though it can cause some local and systemic complications. Therefore, meticulous follow-up of patients that receive this treatment is essential. Herein, we present a patient treated with intravesical BCG who had a hypersensitivity reaction that progressed to multi-organ failure. The initial clinical presentation suggested pulmonary tuberculosis; however, based on hepatic and renal toxicity findings and bone marrow depression, multi-organ failure was suspected to have developed in association with a hypersensitivity reaction to intravesical BCG. Although most of the patient's symptoms regressed following initiation of corticosteroid treatment, renal insufficiency resulted in continuous ambulatory hemodialysis. The aim of presenting this case was to highlight the importance of awareness of the potential for a hypersensitivity reaction to BCG, as well as close follow-up and early initiation of specific treatment following administration of intravesical BCG.

Key Words: Urinary bladder neoplasms; BCG vaccine; adverse effects; hypersensitivity; case reports

ÖZET İntravezikal Bacille Calmette Guerin (BCG) uygulaması karsinomların tedavisinde yaygın olarak kullanılmasına rağmen bazı lokal ve sistemik komplikasyonlara neden olmaktadır. Bu yüzden, tedaviyi alan hastaların titizlikle takibi şarttır. Burada intravezikal BCG ile tedavi sırasında aşırı duyarlılık reaksiyonu gelişen ve takiben çoklu organ yetmezliği oluşan bir hasta sunulmuştur. İlk klinik bulgular pulmoner tüberkülozu düşündürmüştür; fakat hepatik ve renal toksisite bulgularına ve kemik iliği depresyonuna dayanarak intravezikal BCG'ye karşı oluşan aşırı duyarlılık reaksiyonunun bağlı gelişen çoklu organ yetmezliğinden şüphelenilmiştir. Her nekadar kortikosteroid tedavisinin başlanması ile bulguların çoğu gerilemiş olsa da, renal yetmezlik nedeni ile hasta ayaktan sürekli hemodiyalize ihtiyaç duyar hale gelmiştir. Bu olgu sunumunun amacı, intravezikal BCG uygulaması sonrası aşırı duyarlılık reaksiyonuna karşı uyanık olunması, hastaların yakın takip edilmesi ve spesifik tedaviye erken başlanmasının önemini vurgulamaktır.

Anahtar Kelimeler: Mesane neoplazileri; BCG aşısı; istenmeyen etkiler; aşırı duyarlılık; olgu sunumları

Turkiye Klinikleri J Case Rep 2016;24(2):164-8

Intravesical administration of Bacille Calmette-Guérin (BCG) vaccine for the treatment of superficial transitional cell carcinoma of the bladder has been used since 1976.[1] Despite its success in the prevention of cancer progression, BCG treatment can cause a number of complications. In addition to local reactions, BCG vaccine can also cause systemic adverse ef-

doi: 10.5336/caserep.2015-46651

fects than may be life-threatening or fatal in <5% of patients.[2] Complications associated with BCG treatment include pneumonitis, hepatitis, sepsis, and multi-organ failure.[2-6] Herein we present a patient with a hypersensitivity reaction to BCG that progressed to multi-organ failure and chronic renal failure.

CASE REPORT

A 72-year-old male underwent surgery following the diagnosis of bladder carcinoma, and was then scheduled to receive intravesical BCG 81 mg once a week for 6 weeks. Two weeks after transurethral resection of the bladder tumor, intravesical BCG administration was initiated. The patient had fever (38.5°C), fatigue, nausea, and vomiting 8 hour after the second dose of BCG was administered. Moreover, liver enzymes were elevated the following day (d 1, Table 1) and remained elevated during subsequent follow-up laboratory evaluations (d 7, Table 1). As no other pathology was identified as the cause of this abnormality, the diagnosis was made as toxic hepatitis on the 7th day of hospitalization, and the patient was discharged after discontinuation of hepatotoxic medications, including atorvastatin, metformin, and repaglinide.

The patient was admitted to hospital 5 d post discharge with high fever, cough, and dyspnea. Physical examination showed inspiratory crackles at the base of the right lung. The diaphragm contours could not be seen clearly on the right side and reticular infiltration was observed on lower zone via chest X-ray. The right costophrenic angle was closed and the left costophrenic angle was blunted (Figure 1), and the CRP level was elevated on d 12 (Table 1). Based on these findings, the patient was pre-diagnosed as pulmonary tuberculosis and combination antituberculosis treatment (isoniazid, rifampicin, ethambutol, and pyrazinamide) was initiated; however, the treatment was discontinued after 1 week because liver enzyme levels continued to increase and the drugs were thought to be the cause of hepatotoxicity. Thoracic computed tomography (CT) showed ground glass opacity on the right lower lobe posterior segment. Moreover, bilateral pleural effusion, which was more evident on the right side, was also noted (Figures 2 and 3). A sample of the pleural fluid was obtained via thoracentesis and was evaluated as transudate. Nonspecific culture and *Mycobacterium bovis* PCR were negative. The adenosine deaminase level in the pleural fluid was normal.

TABLE 1: Laboratory findings of the case.

	Day 1	Day 7	Day 12	Day 18	Day 60	Day 80
Leukocyte (mm3)	4500	5600	3200	3100	3700	2400
Hemoglobin (g dL–1)	12.9	10.7	9.5	9.6	7.7	8.9
Thrombocyte (mm3)	156000	149000	272000	98000	66000	83000
CRP (mg L–1) (Range: 0-5)	8.3	49	130	79	30	23
aPTT (s)	32	-	32.3	32	43	35
INR	1.28	-	1.1	1.2	1.3	1.1
Creatinine (mg dL–1)	1.55	0.9	0.82	7.6	9.1	4.9
BUN (mg dL–1)	22	11	12	72	66	55
Bilirubin (T/D)	1.1/0.4	1.6/0.9	1.7/1	10.7/8.3	3.6/2.3	2.3/1.4
Alkaline Phosphatase (IU L–1)	81	235	315	607	514	346
GGT (U L–1) (Range: 7-64)	206	348	402	822	608	634
AST (U/L) (5-40)	54	63	34	23	17	25
ALT (U/L) (0-55)	76	122	48	6	6	6
LDH (IU/L)	197	270	293	244	252	361
PTT (seconds)	15.9	-	13.8	15	16.7	35

CRP: C-reactive protein, INR: International Normalized Ratio, BUN: Blood urea nitrogen, GGT: Gamma-glutamyl transferase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, PTT: Prothrombin time.

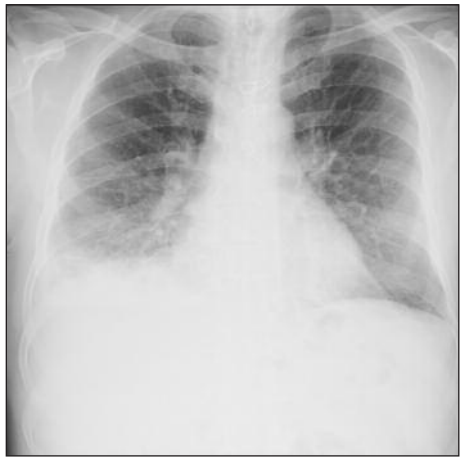
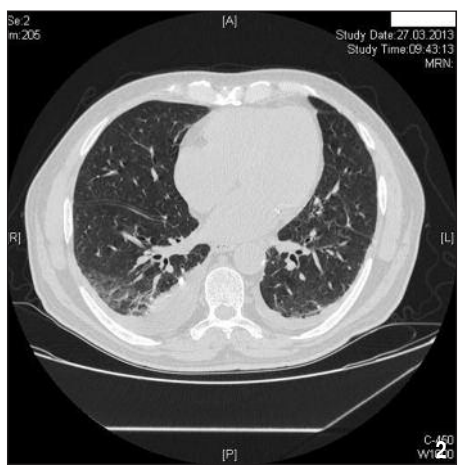


FIGURE 1: Chest X-ray shows ground glass opacity in the right lower lobe posterior segment.

Based on the abnormal findings, miliary tuberculosis was suspected and treatment with cycloserine, ethambutol, streptomycin, and ofloxacin was initiated; these drugs were chosen in order to minimize hepatotoxicity. In addition, the patient's total blood count exhibited a pancytopenic blood profile on d 18 (Table 1). As the blood counts continued to decrease (Table 1), thrombocyte and red blood cell replacement, and granulocyte colony-stimulating factor (G-CSF) treatment were initiated on an as-needed bases. On d 18 blood urea and creatinine levels were elevated (Table 1) and laboratory tests to eliminate the other possible immunological and malignant causes of renal insufficiency were performed. Antinuclear (ANA) and anti-DNA antibodies were negative, as were c-antineutrophil cytoplasmic (ANCA) and perinuclear (p)-ANCA antibodies, hepatitis B and C virus, and HIV infection. Plasma complement (C3 and C4) titers were normal and urine cytological findings were also normal. Renal ultrasonography (USG) and Doppler USG findings were normal, which excluded renal artery stenosis.

As the clinical and laboratory findings did not improve, bone marrow biopsy was performed 30 days after the initiation of symptoms and the sample was determined to be normocellular bone marrow, without any specific pathological findings. The bone marrow sample was also negative for acid-fast bacilli and *M. bovis* DNA (PCR). No mycobacterial growth was observed in urine, bone marrow or sputum samples. Next, liver biopsy was performed and no pathological findings (including granulomatous changes), other than mild inflammatory changes, were observed. Based on these findings, the patient's symptoms and findings were considered to be a hypersensitivity reaction to BCG and methylprednisolone 60 mg d^{-1} was initiated on d 60 following initiation of symptoms. After the patient's liver enzyme levels returned to normal, antituberculosis treatment was resumed using a 2-drug regimen (isoniazid + rifampicin), and then transfusion of blood products was no longer needed. Laboratory findings on d 1 and d 20 of steroid treatment are shown in the Table 1 (Day 60 and 80 after the initiation of symptoms). During 6-month follow-up visit, all of the patient's findings returned to nor-



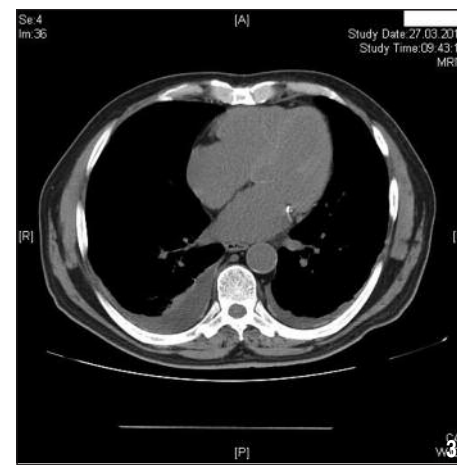


FIGURE 2, 3: Thoracic CT shows that the diaphragm contours could not be seen clearly on the right side, and reticular infiltration in the lower zone.

mal, except renal function, which required continuous hemodialysis. Corticosteroid treatment was gradually tapered and was discontinued after 5 weeks. Isoniazid + rifampicin antituberculosis treatment was discontinued after 3 months. The patient had no additional problems at the 1-year follow-up exam and has not been administered any more BCG. The patient provided written informed consent to have this case published.

DISCUSSION

The complications of local BCG administration for the treatment of superficial transitional cell carcinoma of the bladder are classified into 2 groups: major and minor. Although rare (0.5%), the most significant major complication with the highest risk of mortality is hypersensitivity reaction, which requires corticosteroid treatment.[5,7] Rapid and accurate differential diagnosis of this rare complication of mycobacterial infection is essential for a good prognosis.[8] Although rare, hypersensitivity reaction-associated mortality has been reported.[5]

The presented patient's initial clinical findings were high fever, nausea, and vomiting after the second intravesical dose of BCG was administered, and then the laboratory findings suggested toxic hepatitis. The presenting symptoms were followed by cough and sputum production, which were suggestive of pneumonia or pulmonary tuberculosis. It's been reported that the timing of the manifestation of complications of intravesical BCG treatment varies widely post administration.[5] Based on initiation time, patients are grouped as early or late onset complications. The early (within 3 months) onset group, of which the present patient belonged, is characterized by clinical presentation dominated by systemic signs. The late-onset group (>1 year) is characterized by local organ involvement, including the genitourinary tract, vascular tree, vertebral bones, retroperitoneal soft tissues, and the chest wall. *M. bovis* reproduction occurs in 30% of early onset patients, versus 67% of late-onset patients.[5]

In the presented patient the first symptoms of organ failure were hepatic findings, followed by bone-marrow depression and deterioration of renal function. The combination of these findings suggested multi-organ failure, similar to other reported cases.[3,7] The diagnosis of BCG hypersensitivity reaction in the presented case was based on histopathological liver and bone marrow findings, failure to identify *Bacillus* spp. microbiologically, and unresponsiveness to antituberculosis treatment.[5] Varying degrees of renal failure have been described in a small set of patients that developed complications associated with BCG. It was reported that clinical findings were resolved following treatment in patients diagnosed with interstitial nephritis, with or without granuloma formation;[9] however, renal insufficiency in the presented case did not resolve with treatment, which was most likely due to the late initiation of hypersensitivity-specific treatment. Initiation of corticosteroid treatment in the presented case was delayed because the clinical presentation initially suggested an infectious disease, and tuberculosis was suspected, which is not a rare complication of BCG administration.

A case similar to the presented case reported by Escribano et al.[9] had acute renal failure following intravesical BCG, with only partial recovery of renal function due to the late onset of corticosteroid treatment. The researchers reported that effective and timely steroid treatment is essential for the treatment of acute interstitial nephritis. In other reported cases of BCG hypersensitivity early initiation of steroid treatment prevented progression to chronic renal failure and the need for such advanced therapies as dialysis.[5,9,10]

The present case report aimed to increase awareness among physicians of this extremely serious and rare complication of BCG treatment and to highlight the importance of early diagnosis for preventing morbidity and mortality. Recognition of the risk factors, particularly traumatic catheterization or concurrent cystitis, that result in systemic BCG absorption, close monitorization for complications, and prompt and appropriate treatment of BCG side effects at an early stage should significantly decrease the probability of severe toxicity.

Acknowledgement

Some of the data presented herein were presented as a poster at the 5th Turkish EKMUD Congress, 21-25 May 2014, Antalya, Turkey.

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