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Fatal Systemic Complications after Bacillus Calmette-Guérin Immunotherapy: A Case Report

Bacillus Calmette-Guerin İmmünoterapisi Sonrası Gelişen Ölümcül Sistemik Komplikasyonlar: Olgu Sunumu

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ABSTRACT

Approximately 70% of bladder transitional epithelium cell carcinomas are non-invasive muscular bladder cancers, and for the treatment and prevention of recurrence of this type of cancer, Bacillus Calmette-Guerin (BCG) is applied prophylactically. This practice is generally considered reliable and rarely causes systemic complications. We present here a case in which the patient underwent transurethral resection due to bladder carcinoma and subsequently received intravesical BCG immunotherapy. After the fifth application of BCG, hypersensitivity, tuberculosis sepsis, acute kidney injury, DIC, metabolic acidosis and simultaneous pulmonary embolism were observed.

ÖZET

Mesanenin değişici epitel karsinomlarının yaklaşık %70'ini kasa invaze olmayan mesane kanserleri oluşturur ve bu kanserlerde Bacillus Calmette-Guerin (BCG) tedavi ve nüksü önlemek için profilaktik olarak uygulanmaktadır. Bu uygulama genel olarak güvenilir kabul edilmekte ve nadiren sistemik komplikasyonlara neden olmaktadır. Biz bu yazıda mesane karsinomu nedeniyle transüretral rezeksiyon uygulanan ve daha sonra intravezikal BCG immünoterapisi başlanan hastada 5. kür BCG uygulanmasından sonra hipersensitivite reaksiyonu, tuberküloz sepsisi, akut böbrek yetmezliği, DIC, metebolik asidoz gelişen ve eş zamanlı pulmoner emboli saptanan olguyu sunmak istedik.

Keywords: Bacillus Calmette-Guerin, systemic complications, vesical carcinomas
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Anahtar Kelimeler: Bacillus Calmette-Guerin, sistemik komplikasyonlar, mesane kanserleri
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Introduction

BCG is prophylactically applied in non-invasive muscle bladder cancer for the treatment and prevention of recurrence. Initially, BCG, which was developed by Calmette and Guérin, was used as an attenuated live vaccine mycobacterium (bovine strain) against tuberculosis and as an intradermal treatment against melanoma between 1908 and 1921. In 1976, Morales and colleagues applied BCG intravesically for the first time against high-risk superficial bladder cancer. This application is generally considered reliable, but it can frequently cause minor side effects such as cystitis, dysuria, hematuria and fever. It has also been observed that intravesical BCG applications can sometimes cause localized reactions such as prostatitis, retroperitoneal abscesses as well as systemic reactions such as the development of hepatitis, pneumonia, mycotic vascular infections, acute renal failure, rhabdomyolysis and/or multi-organ dysfuntion (1).

We present a case of transurethral resection due to bladder carcinoma followed by intravesical BCG immunotherapy. Disseminated intravascular coagulopathy (DIC) and multiple organ dysfunction syndrome (MODS) were observed after the fifth application of BCG.

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Case Report

A 63-year-old male patient presented to the emergency department (ED) with complaints of dyspnea, chills, redness and bruising on his body after receiving BCG 3 hours prior. On his presentation to the ED, the patient appeared ill and demonstrated altered mental status. The Glasgow coma scale (GCS) score was 13 ($E_3 M_6 V_4$). The patient's vital signs were as follows: blood pressure 90/60mmHg, pulse 128 beats/min, respiratory rate 26/min and body temperature 38.1ºC. His physical examination was normal except for altered mental status, cyanosis, ecchymotic and petechial lesions on the face and body and abdominal distension (Figure 1).

Laboratory examination revealed the following values: hemoglobin 16.6 g/dL, leukopenia (1500/mm^3), thrombocytopenia (28000/µL), blood urea nitrogen (BUN) 64 mg/dL, creatinine 2.9 mg/dL, aspartate aminotransferase (AST) 264 U/L, alanine aminotransferase (ALT) 202 U/L, activated partial thromboplastin time (aPTT) 160 sec, prothrombin time (PT) 57.1 sec and INR 6.1, D-dimer >10000 ng/mL. In the arterial blood gas analysis, the following values were obtained: pH 7.12, PCO_2 19.9 mmHg, PO_2 81.7 mmHg, sO_2 93.9, $NaHCO_3$ 9.3 mmol/L and lactate 10.2. No growth was determined in the blood or urine cultures.

Head computerized tomography (CT) and abdominal ultrasonography of the patient showed normal findings. CT angiography of the thorax showed enlargements and filling defects in the pulmonary artery subsegmental branches of the bottom lobes of both lungs. These findings were suggestive of pulmonary thromboembolism.

The medical history of the patient revealed that he had been diagnosed with non-invasive muscular bladder cancer (high grade papillary urethral carcinoma) two months prior and transurethral resection (TUR) was performed. Two weeks after the resection, intravesical BCG immunotherapy (immucyst R) application was initiated. BCG immunotherapy was applied once a week, and 3 hours after the fifth application, the current complaints developed.

Figure 1. Cyanosis, ecchymotic and petechial lesions on the face and body

Early goal-directed therapy was initiated in the ED. A 500 mL bolus of crystalloid was given every 30 minutes to achieve a central venous pressure of 8 to 12 mm Hg. Mean arterial pressure fell below 65 mmHg so vasopressors were administered, and empiric intravenous (i.v) ceftriaxone (2 g) was started. The other treatment protocol comprised of the following: 100 mg prednisolone i.v to prevent hypersensitivity, fresh frozen plasma and a platelet suspension against DIC, piperacillin-tazobactam 2.25 g i.v as well as isoniazid 300 mg and rifampicin 600 mg per oral (p.o) against systemic BCG infection. In monitoring the blood pressure associated with central venous pressure, 0.9% NaCl dopamine followed by adrenaline were infused. The patient was admitted to the intensive care unit with a diagnosis of septic shock and MODS as complications associated with BCG immunotherapy application. Since blood gas acidosis deepened and respiratory arrest developed, $NaHCO_3$ was provided. The patient was connected to a mechanical ventilator. One hour later, and after five hours of treatment, the patient died of cardiac arrest.

Discussion

Approximately 70% of bladder transitional epithelium cell carcinomas are non-invasive muscular bladder cancers. Of these cancers, 70% are Ta, 20% are T1 and 10% are carcinoma in situ. Primary treatment of these tumors is indisputably performed by TUR. Nevertheless, treatment with TUR alone causes tumor recurrence in 70% of patients, and 20-30% show progression (2). Thus, to prevent the recurrence or further progression of the tumor, intravesical treatment (chemotherapy or immunotherapy) should be applied following TUR. The efficacy of BCG immunotherapy in the treatment of non-invasive muscular bladder cancer is indisputable today. Although the anti-tumor activity of BCG is not known, it is assumed that the hypersensitivity reaction due to BCG causes the migration of lymphocytes and macrophages to the tumor region, leading to the removal of tumor cells (3). The success of BCG application in the bladder has been reported to vary between 63% and 100% (3). On the other hand, intravesical BCG application may cause complications such as bacterial virulence, allergic reactions or nosocomial urinary system infections.

Systemic side effects are rarer than local side effects (4). As a result of the excessive resection of the tumor and traumatic catheterization, the transitional epithelium can be damaged. Because of this damage, the hematogenous spread of bacteria or/and immunoallergic reactions may occur, leading to systemic complications (4). According to a study by Orihuela and colleagues, the most frequently encountered systemic symptom was a flu-like syndrome (fever, myalgia and fatigue) in 43% of patients (5). In addition, patients may experience a bacterial type 4 hypersensitivity reaction, granulomatous hepatitis, pneumonia, vascular mycotic infections, osteomyelitis, acute renal failure or severe systemic complications such as sepsis and multiple organ failure (6).

Several complications developed in our patient after BCG immunization. The most important and perhaps most influential in the formation of the whole clinical picture was a non-bacterial type 4 hypersensitivity reaction (4). Occurring within a few hours after application of BCG, a sudden high fever and hypotension should be considered to be a non-bacterial type 4 hypersensitivity reaction. Following this, the occurrence of high fever, hypotension, cyanosis and erythema in our patient after BCG application suggested non-bacterial type 4 hypersensitivity reaction. In addition, the laboratory values of our patient (AST 264 U/L, ALT 202 U/L, body temperature 38.1°C) prompted us to suspect granulomatous hepatitis, which is very rarely encountered in the literature. It has also been reported that, in the development of granulomatous hepatitis, hypersensitivity plays a role rather than the invasion of BCG (3). For the treatment of systemic BCG infection, the use of systemic corticosteroids is risky. However, it is recommended for cases with widespread granulomas that develop due to a non-bacterial type 4 hypersensitivity reaction (4). In light of this information, 100 mg prednisolone was intravenously administered to our patient.

One of the other important complications observed in the patient was acute kidney failure. Although, according to the previous tests conducted in the emergency room, the patient had normal kidney function, in the laboratory examination, the BUN level was 64 mg/dL and the creatinine level was 2.9 mg/dL. Four hours later, the BUN value was 92 mg/dL and the creatinine value increased to 3.9 mg/dL. The literature contains descriptions of a few cases of acute kidney failure following BCG immunization. As a result of hematogenous spread of bacteria or bacterial proteins due to traumatic interventions to the urinary tract, mesenchymal glomerulonephritis, epithelioid granuloma formation, interstitial nephritis and finally kidney failure have been observed (7, 8). Acute kidney failure in our patient may have occurred directly due to the effects of BCG or secondary to sepsis.

Another systemic complication diagnosed in our patient was DIC table. DIC table may develop due to various drugs and toxins. In our case, elongation of the PT and aPTT values, an increase in the D-dimer value and a decrease in platelets demonstrated DIC table. Considering this finding, fresh frozen plasma and a platelet suspension were also administered to our patient.

The literature review shows that approximately 2% of patients who develop systemic complications following BCG immunization require hospitalization, and that approximately 0.1% of these patients develop severe sepsis (9). A determination of no focus of infection, no growth in the blood or urine cultures, the presence of symptoms of systemic inflammatory response syndrome with high fever, tachycardia and tachypnea, functional disorders of various organs (liver and kidney), metabolic acidosis, severe sepsis and hypotension strongly suggest severe tuberculosis sepsis. Therefore, our patient was empirically treated with ceftriaxone (2 g i.v.) and tazocin (2.25 g) and for systemic BCG infection with oral isoniazid (300 mg) and rifampicin (600 mg).

Cancer is an important risk factor for venous thrombosis, and it increases the risk of venous thromboembolism (VTE) by 4-6 fold. VTE incidence among cancer patients is unclear, but autopsy studies show that 50% of patients have evidence VTE (10). We believe that the pulmonary thromboembolism observed in our patient was associated with increased susceptibility due to bladder cancer. However, subclinical signs of embolism may contribute to further degradation and should not be disregarded.

Conclusion

Considering the effectiveness BCG in non-invasive muscle bladder cancers, today it is almost certain that this vaccine should be used for the treatment of this type of cancer. Thus, to decrease complications due to BCG, especially during application, traumatic catheterization should be avoided, and if cystitis or hematuria exists, treatment should be postponed. Due to systemic complications, BCG application should be avoided under immunosuppressive conditions. Although the literature proposes methods such as the application of low-dose BCG and prophylactic isoniazid application during BCG instillation to prevent side effects due to BCG, there is no complete consensus on these issues. However, for the treatment of systemic complications, the use of isoniazid and rifampicin initially is the most common preference.

Conflict of interest

No conflict of interest was declared by the authors.

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