CASE REPORT

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# A Rare Case Seen in a Patient with Intravesical Bacillus Calmette-Guerin (BCG) Intolerance: Autoimmune Myopathy

## İntravezikal Bacillus Calmette-Guerin (BCG) İntoleransı Gelişmiş Hastada Nadir Bir Olgu: Otoimmün Miyopati

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## ABSTRACT

**Aim:** We present a case of autoimmune myopathy observed in a patient who developed intolerance to intravesical Bacillus Calmette-Guerin (BCG), which is used in the treatment of non-muscle invasive bladder cancer.

**Case:** Intravesical BCG, which is used for the treatment of non-muscle invasive bladder cancer, probably effects by increasing autoimmunity in the bladder. This increased autoimmunity sometimes causes local or systemic reactions. In this case report, we would like to present a 61-year-old male patient who developed intolerance while taking the first dose of maintenance BCG, and then on-going treatment was stopped. The patient had convulsive painful cramps and muscle twitches in the left quadriceps femoris region one month later BCG intolerance. When the patient's anamnesis, electromyography (EMG) results, elevated Creatine Kinase value and other laboratory data were evaluated together, BCG triggered autoimmune myopathy was considered. Therefore, steroid treatment was started and the patient recovered seven weeks later. This is a rare case of autoimmune myopathy in a patient who received intravesical BCG therapy for a bladder tumor.

**Conclusion:** The case of BCG-associated autoimmune myopathy is extremely rare. When this situation is suspected, it is beneficial to start steroid treatment without delay.

**Keywords:** Bacillus Calmette-Guerin, bladder cancer, non-muscle invasive bladder cancer, myopathy

## ÖZ

**Amaç:** Kasa invaze olmayan mesane kanserinin tedavisinde kullanılan intravezikal Bacillus Calmette-Guerin (BCG)'ye karşı intolerans gelişen hastada gözlenen otoimmün miyopati olgusunu sunuyoruz.

**Olgu:** Kasa invaze olmayan mesane kanserinin tedavisinde kullanılan intravezikal BCG mesanede otoimmüniteyi artırarak etki etmektedir. Bu artan otoimmünite bazen lokal veya sistemik reaksiyonlara neden olabilmektedir. Bu olgu sunumunda, 61 yaşında bir erkek hastada idame BCG tedavisinin ilk dozu alındıktan sonra intolerans gelişti ve daha sonra tedavisine devam edilemedi. BCG intoleransı gelişiminden 1 ay sonra hasta sol kuadriseps femoris bölgesinde konvülsif ağrılı kramplar ve kas seğirmeleri şikâyeti ile kliniğimize başvurdu. Hastanın anamnezi, elektromiyografi (EMG) sonuçları, kreatin kinaz yüksekliği ve diğer laboratuvar verileri birlikte değerlendirildiğinde BCG ile tetiklenen otoimmün miyopati geliştiği düşünüldü. Bu nedenle steroid tedavisi başlandı ve hasta yedi hafta sonra sağlığına kavuştu. Bu olgu mesane tümörü için intravezikal BCG tedavisi alan hastada görülen nadir bir otoimmün miyopati olgusudur.

**Sonuç:** BCG ile ilişkili otoimmün miyopati olgusu son derece nadirdir. Bu klinikten şüphelenildiğinde steroid tedavisinin zaman geçirilmeden başlanılmasında fayda vardır.

**Anahtar Sözcükler:** Bacillus Calmette-Guerin, mesane kanseri, kasa invaze olmayan mesane kanseri, miyopati


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## INTRODUCTION

Bladder cancer is the seventh most commonly diagnosed cancer in the male population worldwide and ranks tenth when both sexes are considered (1). Approximately 75% of patients with bladder cancer present with disease limited to the mucosa (stage Ta, CIS) or submucosa (stage T1). Due to the high prevalence of non-muscle invasive bladder cancer, it has been a disease that has been studied for years. Although intravesical chemotherapeutic agents that prevent disease recurrence have also been discovered, only one medication has been found to prevent progression. Intravesical instillation of Bacillus Calmette-Guerin (BCG, Mycobacterium bovis) is used for treatment of intermediate and high-risk non-muscle invasive urothelial bladder cancer that prevents progression and recurrence (2). Patients in the high-risk group have a higher risk of disease progression (14.1% and 14.2% after 10 years according to the 2021 EAU NMIBC scoring model). A full dose of intravesical BCG for one to 3 years is indicated in these patients (induction plus 3-week instillations at 3, 6, 12, 18, 24, 30 and 36 months) (2). Although this therapy has been used for a long time, its mechanism of action is not clear. The immune response due to local T cell activation in the bladder mucosa could be the potential mechanism (3). This increase in autoimmunity can sometimes lead to systemic or local side effects and even complications. The pathogenesis of BCG-associated disease may be active infection or hypersensitivity reaction, and complications may involve many organ systems. Local complications arise from urine contaminated with BCG and affect the genitourinary system. Systemic complications are the result of the spread of BCG into the bloodstream and may be vascular, musculoskeletal, hepatic, pulmonary or involve other organ systems. These rare complications can be immune-mediated reactions such as arthritis, polyarthritis, uveitis, and Reiter syndrome. Because the imaging findings of BCG-related complications may mimic cancer or infection by another organism, knowledge of prior BCG therapy and possible complications is essential to make an accurate diagnosis prospectively and guide appropriate treatment without delay (4).

Autoimmune myopathy associated with BCG is extremely rare. Here we present a case of autoimmune myopathy that developed after BCG intolerance.

## CASE REPORT

A 61-year-old man was diagnosed with T1G3 bladder cancer who presented with hematuria. Thereafter intravesical BCG induction therapy (120 mg of SII ONCO BCG-once a week for 6 weeks) was given into the bladder via a urethral catheter. BCG intolerance developed, acute renal failure occurred when taking the first dose of BCG maintenance. Clinical and laboratory findings were improved with hemodialysis. Thus BCG therapy was not continued. Convulsive painful cramps and muscle twitching were observed in the left quadriceps femoris region seven months later diagnosis of bladder tumor and one month later development of BCG intolerance. There was no cutaneous lesion, fever, arthralgia, or other symptoms. No bacteria were isolated in the urine culture and the patient did not have any signs of sepsis. Hemogram data were as follows: Hgb:12.7 g/dL, WBC:10.5 $10^3/\mu$L, PLT: 368 $10^3/\mu$L. Elevated creatine kinase (CK), renal and liver function test results was seen under balanced fluid intake and urine output (CK:25800 U/L, N:0-190 U/L, Urea:280 mg/dL, N:14-50 mg/dL, Creatinine:8,4 mg/dL, N: 0-1,4 mg/dL, AST:741 U/L, N:0-40 U/L, ALT:342 U/L, N:0-41 U/L, LDH: 1170 U/L, N:135-225 U/L). But the Gamma Glutamile Transferase (GGT: 44 U/L) value was normal. Radiological assessment didn't reveal hepatic or renal impairment. Hereupon electromyography (EMG) was performed and myopathic processes with low amplitude and short duration motor unit potentials were observed very often (Figure 1). There was no evidence to explain etiology like drug use, trauma or comorbidity. Antinuclear antibody (ANA), anti-microsomal antibody, anti-mitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), viral markers (anti-HIV, anti-HCV), extractabel nuclear antigens (Jo-1, Sm, Sm-RNP, scl-70, SSA, SSB) were analyzed and all were within normal limits. Higher hydration and regular hemodialysis for the first three days was planned and 80 mg per day steroid therapy was started. In the first three weeks myalgia improved, laboratory results started to decrease, but still greater than normal limits. After that, the steroid treatment was extended for four more weeks with a tapering regimen and the patient's laboratory findings were resolved.

## DISCUSSION

BCG was first discovered as a vaccine against tuberculosis by Albert Calmette and Camille Guerin in 1921 (5). In a study conducted in 1975, BCG was found to cause strong inflammatory reactions in the healthy bladder of dogs by local action (6). Thus, in 1976, intravesical BCG was applied for the first time in the treatment of non-muscle invasive bladder tumor (7). Although this treatment has been used for a long time, its mode of action is not clear. Intravesical instillation of BCG immunotherapy used in bladder cancer does not have a direct effect on tumor cells. BCG attaches to the bladder wall through fibronectin and integrins then triggers the immune mechanism. IL-6, IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF), CD4 and CD8 T cells, natural killer (NK) cells, macrophages and TH-1 cytokines are involved in the formation of immune response (8). This autoimmune reaction has been found to have many side effects, such as septic manifestations, orchitis, epididymitis, granulomatous cystitis, arthritis, and Reiter's syndrome during the acute or chronic period.

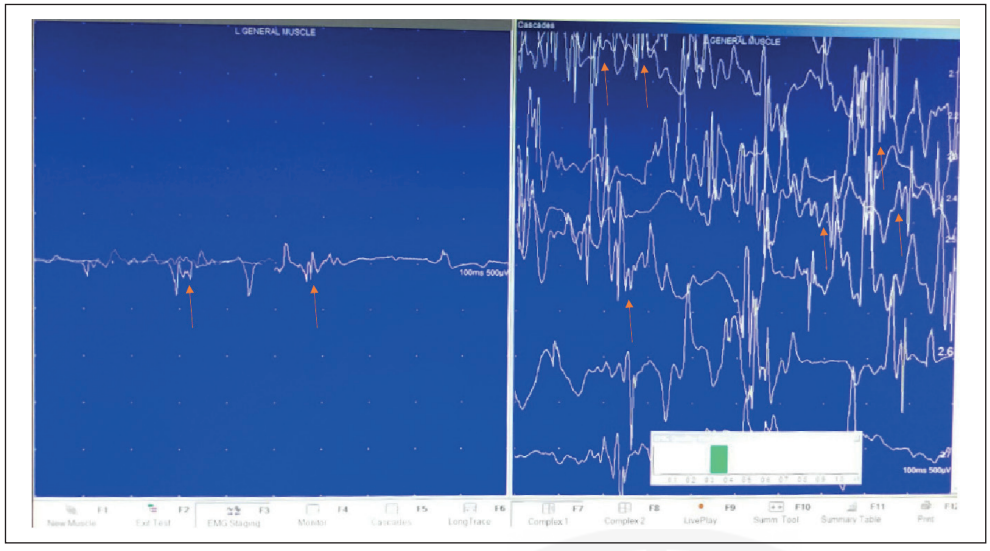

**Figure 1:** Myopathic process with low amplitude and short duration motor unit potentials were frequently detected in electromyography (EMG). Some of the myopathic motor unit potentials are shown with red arrows.

It has always been thought that vaccination can trigger the myopathic process (9). Dermatomyositis cases have been reported after BCG vaccination (10). In addition, a few cases of dermatomyositis have been reported in patients with bladder tumors (11).

There are two different conditions in which the CK level is very high in acquired myopathies. Inflammatory myopathies and rhabdomyolysis. Performing muscle biopsy in acquired myopathies is the second step examination and should be applied only if necessary. Rapid response to steroid treatment reassures an underlying autoimmune disorder in our patient who had no history of traumatic injury, medication nor chronic illness may lead to rhabdomyolysis. In our case, the diagnosis of dermatomyositis and polymyositis were excluded because there was no skin lesion and the findings were regressed with the treatment unlike them (12). The inclusion-body myositis diagnosis was excluded with a response to steroid therapy (13). The reason why we think BCG-associated autoimmune myopathy is that it is a late immune response since myopathy occurs following BCG intolerance. Our patient's condition deteriorated very rapidly and autoimmune myopathy was considered with the present findings, steroid treatment was started quickly, so muscle biopsy was not taken.

It was thought that the current situation developed as a result of a systemic autoimmune response caused by BCG, because the last dose of BCG resulted in intolerance and myopathy in the following period.

It should not be forgotten, there is a possibility of different autoimmune disorders developing in cases with BCG intolerance.


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## Author Contributions

Both authors have equal contributions.

## Conflicts of Interest

We have no conflict of interest.


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None.


## Ethical Approval and Consent

The study is approved by the Zonguldak Bülent Ecevit University Non-Interventional Clinic Research Ethics Committee (ID 2020/20, Meeting date: 14 October,2020).

## Review Process

Extremely peer-reviewed and accepted.

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