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Case Report

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Reduction of Bladder Volume after BCG Immunotherapy

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Keywords
Bladder cancer · Bacillus Calmette-Guérin immunotherapy · Adverse effects · Bladder volume

Abstract
Bacillus Calmette-Guérin (BCG) immunotherapy is the most effective treatment for carcinoma in situ and high-risk non-muscle invasive bladder cancer (NMIBC). However, it can also provoke diverse side effects. We found 1 patient with a significantly and rapidly reduced bladder volume after the instillation of BCG. Few such cases and corresponding treatments have been reported. We speculated that the tuberculosis infection existed, so antitubercular therapy was given. After a 3-month oral intake of rifampicin, isoniazid, and ofloxacin, the volume of bladder returned to normal and the voiding symptoms disappeared. This case indicated that the reduction of bladder volume caused by BCG instillation could be treated with antitubercular therapy. Prompt and accurate diagnosis was important for the management.

Introduction

Bladder cancer is a common malignant tumor of urinary system, which can be divided into muscle invasive bladder cancer and non-muscle invasive bladder cancer (NMIBC). NMIBC refers to the tumor that confines to the mucosal layer. Approximately three-fourths of patients with bladder cancer present with NMIBC [1]. The standard therapy for NMIBC is transurethral resection of bladder tumor (TURBT) and the following intravesical therapy. Bacillus Calmette-Guérin (BCG) immunotherapy now has been considered as the most effective treatment for carcinoma in situ and high-risk NMIBC. This therapy can prevent tumor recurrence and reduce the risk of progression with the greatest possible degree. However, it can provoke diverse adverse reactions. Most of them are transient and self-limited, while serious side effects are encountered in <5% of patients [1]. Medical interventions are needed for some of the serious complications. Rischmann et al. [2] first put forward that BCG-related adverse effects could be divided into 4 grades depending on the severity. Among those complications, cystitis is the most common one, occurring in approximately 80% of patients [3, 4].

We encountered and treated a patient with a significantly and rapidly reduced bladder volume (<20 mL) after the instillation of BCG. Few such cases and specific treatment for this condition have been reported throughout the world. Therefore, we present this case and share our experience for better understanding of the side effects of BCG immunotherapy.

Case Presentation

A 54-year-old female was admitted for drastic urinary urgency and frequency, which was refractory to anticholinergic agents. This patient underwent TURBT for NMIBC 3 years ago. She followed routine cystoscopic examinations and was found no relapse

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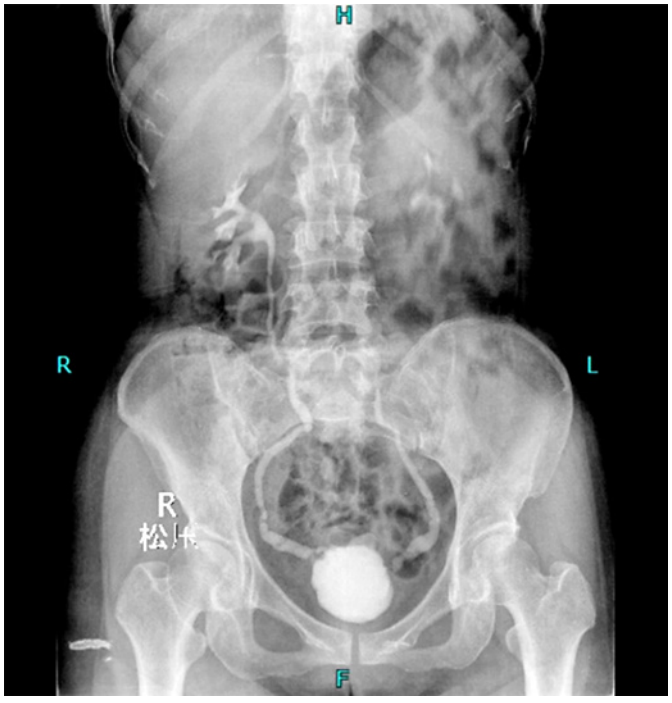

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Fig. 1. A small bladder with dilation of distal ureters showed by intravenous pyelography.

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Fig. 2. Diffuse irregular thickening of bladder wall and a small bladder showed by CT.

until gross hematuria. CT scanning and cystoscopic biopsy showed multiple NMIBC recurrences. She underwent second TURBT according to the guidelines' recommendation [1]. Pathology showed a high-grade urothelial carcinoma. BCG instillation was conducted 2 weeks later. The proposed instillation regime was "6 + 3 protocol," which consisted of 6-week induction course, followed by 3 weekly instillations at months 3, 6, 12, 18, 24, 30, and 36. Symptoms mentioned above appeared when the seventh instillation was carried out and became intolerable after the ninth was completed. The patient was admitted to the ward for further evaluation.

The cystoscopy indicated severe mucosal edema and inflammation but no cancerous recurrence or neoplasm. Numerous leukocytes appeared in urine. Intravenous pyelography showed a small bladder and dilation of distal ureter (Fig. 1). Diffuse irregular thickened bladder wall was demonstrated by CT examination (Fig. 2). Patient's manifestation did not change after a 3-day antibiotic therapy. Both T-spot test and tuberculosis antibody turned positive and the urine culture for tuberculosis also turned positive. We believed that a BCG-related cystitis existed. The patient was prescribed oral intake of rifampicin (RFP), isoniazid (INH), and ofloxacin in standard dosages. The symptoms were improved and the patient was discharged from hospital 4 days later.

After a 3-month therapy of RFP, INH, and ofloxacin, the thickness of bladder wall distinctly improved (Fig. 3). Patient's voiding symptoms disappeared and no evidence of recurrence was found.

Discussion

Adverse events of BCG immunotherapy can be categorized into 4 grades [2]. Grade 1 is moderate and usually subside within 48 h, which can be treated by taking anticholinergics and analgesics with or without anti-inflammatory drugs. Grade 2 is severe symptoms and last more than 48 h. Treatments include drugs for Grade 1 complications. Antibiotic therapy can be empirical or adapted to urine culture results, and INH should be administrated. Instillation should be suspended until complete resolution of symptoms. Grade 3 is regional or systemic complications and immunoallergic reaction. Oral intake of INH and RFP should be given for patients with local infection. Antihistamines and anti-inflammatory drugs should be given for patients with allergic reaction. We have observed a tendency toward grade 3 complications in our presented case. Grade 4 is the most severe complication, which can lead to multiple organs' failure. Four-agent antibiotic therapy is urgently required and early, high-dose corticosteroids should be given because of the BCG sepsis. Cessation of BCG therapy is mandatory.

Most complications were caused by the absorption of BCG-contaminated urine because the attenuated strain

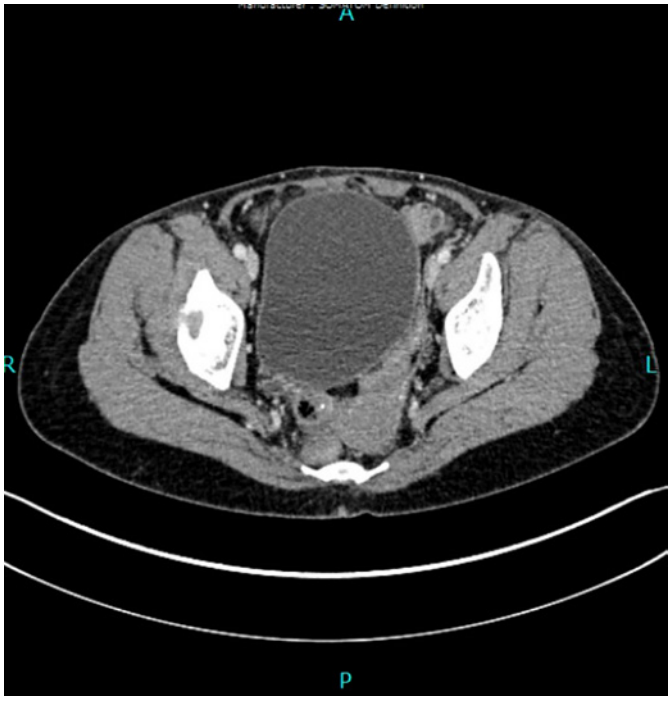

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Fig. 3. Bladder recovered to normal after 3 months of antitubercular therapy.

Mycobacterium tuberculosis is not completely harmless. The key to manage adverse events is prevention [2]. A proper time and the correct catheterization techniques for BCG instillation are necessary to avoid side effects. BCG intravesical therapy should initiate at least 2 weeks after TURBT. If gross hematuria, urinary tract infection, or traumatic catheterization existed, instillation should be postponed until they are resolved. Besides, the administration of ofloxacin can reduce the incidence of adverse events and improve patient's tolerance to BCG instillation [5]. Although it is considered that the toxicity is associated with the dose of BCG, a phase III trial claimed that the reduction in dose or the duration of maintenance had no significant effect on the incidence of complications [6, 7]. A contracted bladder due to extravasation of intravesical therapy appears to be associated with multiple TURBTs and maintenance instillations. Management includes withholding intravesical therapy, hydrodistention, and even cystectomy [8].

The key clinical features of the presented case were the thickened bladder wall and small volume revealed by intravenous pyelography and CT scanning. The cystoscopy ruled out bladder cancer recurrence. Interstitial cystitis (IC) is a rare disease characterized by the chronic pain, pressure, and discomfort in the bladder area, usually associated with urinary frequency and urgency. There is no definitive test to identify IC. The diagnosis of IC is made on the basis of exclusion of other conditions such as urinary tract infections, bladder cancer, or inflammation [9, 10]. Given the medical history of BCG immunotherapy, the diagnosis of IC can be excluded. Bladder fibrosis, a rare but severe side effect of BCG immunotherapy, can also cause a small bladder and overactive bladder. However, it is a chronic condition, which usually takes years to form [11]. The deteriorating process in this patient was rapid. Bacterial or BCG-related cystitis is the most common adverse event of BCG intravesical therapy. Both the acute course of disease and the evidence of inflammation in bladder indicated that the changes in the bladder were closely related to cystitis. There were some studies reporting cystitis with a severe reduction of bladder volume after BCG immunotherapy. Garcia et al. [12] has reported case of bladder contracture, which was caused by BCG reactivation following transurethral resection of the prostate. The case was managed with instillation of intravesical BCG for NMIBC 3 years ago. The case indicated the need for increased awareness of BCG reactivation in patients undergoing transurethral resection of the prostate post-BCG instillation. Numakura et al. [13] reported that bladder hydrodistention can be used for decreased bladder capacity induced by intravesical BCG therapy. Their study demonstrated that bladder hydrodistention was a potentially optimal solution to the severe symptoms associated with seriously decreased bladder capacity. Wittes et al. [14] suggested that severe BCG-induced cystitis might be dealt with a short course of oral prednisone for treatment when anti-tuberculosis drugs and local steroids fail.

Considering the history of the case, we speculated that thickened bladder wall was caused by the acute edema rather than IC or fibrosis. Therefore, those treatments for IC or bladder contracture were not suitable for this patient. The main object for this patient was to control the excessive inflammatory reactions in bladder wall. The patient's symptoms did not improve after antibiotic was given, and urine culture for tuberculosis turned positive. We therefore believed that there was a BCG-related cystitis, which demanded antitubercular agents. Symptoms mentioned above were in remission after a 3-month antitubercular therapy and patient's shrunken bladder went back to normal. The prompt and accurate diagnosis was important in keeping patient's functional bladder in this case.

Although our close follow-up and prompt therapy made us successfully to stop the progression, there were still some limitations. The manifestations in the early phase were common, which did not attract enough attention until the symptoms became serious. Therefore, a close surveillance should be performed for the patients treated with BCG instillation. In our experience, urinary ultrasound and urine examination should be done at least every 2 weeks, so as to detect the severe cases of BCG-related cystitis. Antitubercular therapy should be given without hesitations.

Conclusion

BCG immunotherapy can lead to various complications and medical interventions are needed for some of them. Our case indicated that BCG intravesical therapy can bring serious cystitis with a significant reduction of bladder volume. However, it can be reversed by oral intake RFP and INH. The early recognition and prompt diagnosis are important to prevent it from evolving into chronic fibrosis.

Statement of Ethics

The subject has given her written informed consent to publish her case (including publication of images).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Y. L., C.Y., and Z.L. drafted and edited the final manuscript, and Y.L. made substantial efforts to the diagnosis and to determine the therapy. All authors read and approved the final manuscript.

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