A case of ureteral obstruction and sepsis induced by bladder perforation following intravesical bacillus Calmette–Guérin successfully treated with an antituberculous agent, antimicrobial chemotherapy and percutaneous urine drainage

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Abstract

We report a case of ureteral obstruction and sepsis induced by bladder perforation following intravesical bacillus Calmette–Guérin (BCG) that was successfully treated non-surgically. A 56-year-old man was diagnosed with non-muscle invasive bladder cancer. He was treated with intravesical BCG instillation after transurethral resection of the bladder tumor. Just before the 6th course of intravesical BCG, the patient was diagnosed with bladder perforation and developed ureteral obstruction and sepsis associated with BCG. He was treated successfully with an antituberculous agent, antimicrobial chemotherapy and percutaneous urine drainage. Bladder perforation associated with BCG is a very rare adverse event that causes severe sepsis.

Keywords Bladder perforation · Bacillus Calmette–Guérin · Sepsis

Abbreviations

BCG	Bacillus Calmette–Guérin
EAU	The European Association of Urology
NCCN	National Comprehensive Cancer Network
TURBT	Transurethral resection of the bladder tumor
UC	Urothelial carcinoma
Cis	Carcinoma in situ
CS	Cystoscopy
CT	Computed tomography
PNS	Percutaneous nephrostomy
PCR	Polymerase chain reaction
<i>M. tuberculosis</i>	<i>Mycobacterium tuberculosis</i>
<i>E. coli</i>	<i>Escherichia coli</i>
ICU	Intensive care unit
DRPM	Doripenem
FRPM	Faropenem
RFP	Rifampicin
INH	Isoniazid

EB	Ethambutol
AE	Adverse event
MMC	Mitomycin C

Introduction

Intravesical bacillus Calmette–Guérin (BCG) therapy is useful for adjuvant treatment of patients with high- and intermediate-risk non-muscle-invasive bladder cancer (NMIBC) [1–3]. The European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines recommend that patients with high- and intermediate-risk NMIBC should be offered BCG therapy [4, 5]. The EAU guideline states that the optimal BCG schedule for induction BCG instillation is once weekly for 6 weeks.

For optimal efficacy, BCG must be given on a maintenance schedule. However, intravesical BCG treatment, despite its efficacy for tumor control, has a high frequency rate of adverse events (AEs). The most common AEs are cystitis, hematuria and fever, whereas a severe systemic adverse reaction that requires anti-tuberculosis chemotherapy and intensive care is rare [1, 6, 7]. Here, we report the case of a patient who had bilateral ureteral obstruction and sepsis induced by bladder perforation following intravesical BCG instillation who was successfully treated with an

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antituberculous agent, antimicrobial chemotherapy and percutaneous urine drainage.

Case report

A 56-year-old man was newly diagnosed with a bladder tumor at another department of urology in 2015. He underwent transurethral resection of the bladder tumor (TURBT) in December 2015 and the pathological diagnosis was confirmed to be urothelial carcinoma (UC), G3, pTa with carcinoma in situ (Cis). The details of location of TURBT were left side and posterior wall of urinary bladder. The location of random biopsies were performed on the anterior wall, retro trigone, triangle, right side wall, apical and neck of urinary bladder. He was referred to our department for treatment of the bladder cancer in January 2016. Cystoscopy (CS) showed no apparent residual tumor. He was diagnosed with high-risk NMIBC.

We decided to treat him with intravesical BCG instillation according to the recommendations of several guidelines for high-risk NMIBC [4, 5]. He had no personal or family history of tuberculosis. He started intravesical BCG 80 mg weekly from February 2016. Intermittent urination pain, hematuria, and fever were observed between 1st and 5th intravesical BCG. Fever, fatigue and lower abdominal pain persisted at the 6th scheduled time. Just before the 6th course of treatment with BCG, fatty tissues were revealed in urine examination obtained by atraumatic urethral catheterization. We therefore, decided to skip the 6th intravesical BCG treatment. At 8 h after urethral catheterization, he had a high fever (a temperature of 38° or more) and pyuria. His white blood cell count and the concentrations of CRP were 12,000/ μ L and 24.05 mg/dl, respectively. Computed tomography (CT) showed a fluctuant perivesical abscess and bilateral hydroureteronephrosis due to the abscess (Fig. 1a–c). He underwent successful placement of bilateral percutaneous nephrostomies (PNSs), a urethral catheter and a drainage tube for perivesical fluid. Purulent fluid was discharged from the PNSs and drainage tube. We carried out culture and polymerase chain reactions (PCRs) for blood, urine and perivesical fluid to test for *Mycobacterium tuberculosis* (*M. tuberculosis*) complex. Although his blood cultures were negative, *Escherichia coli* (*E. coli*) was isolated from a urine sample. Using a PCR test we found that the perivesical fluid was positive for *M. tuberculosis*. According to these examinations, we diagnosed his condition as bladder perforation due to intravesical BCG treatment.

During admission, he developed septic shock and was treated in the intensive care unit (ICU). Doripenem (DRPM) was administered for 11 days and faropenem (FRPM) for 14 days. We started anti-tuberculosis treatment with rifampicin (RFP), isoniazid (INH) and ethambutol (EB) for

systemic BCG infection. These treatments resulted in the resolution of his condition and he was discharged from the ICU after 3 days of treatment. Two months after his diagnosis, cystography and nephrostography showed persistent bladder leakage from the site of perforation and bilateral ureteral obstruction (Fig. 1d, e). The location of perforation was presumed to be the retro trigone by the cystoscope and cystography. We removed the urethral catheter at this time because his urine was completely drained through the bilateral PNSs. EB was discontinued after 2 months because of fear of disturbance of vision. RFP and INH were administered for 9 months.

In October 2016, 8 months after the bladder perforation, cystography and nephrostography showed no bladder leakage or ureteral obstruction (Fig. 1f, g). He was freed from the PNSs and drainage tube at this time. He had no residual urine. In December 2017, the patient was still free from recurrence of NMIBC and BCG infection 21 months after the treatment of the bladder perforation.

Discussion

In general, BCG treatment-related AEs are tolerated, about 8% of patients stop BCG treatments because of AEs. Sepsis is observed in about 0.3% of these patients [6–8]. Notably, our patient had sepsis because of bladder perforation induced by intravesical BCG treatment and the bladder perforation developed into a fluctuant perivesical abscess and bilateral ureteral obstruction. Some reports have revealed the causes of bladder perforation, including TURBT, interstitial cystitis, neurogenic bladder, radiation cystitis, bladder cancer and an indwelling urethral catheter [9–11]. Recently, bladder perforation associated with instillation of intravesical mitomycin C (MMC) after TURBT was reported [12, 13]. However, there have been no reports of bladder perforation associated with intravesical instillation of BCG. The mechanism of the bladder perforation induced by BCG is unclear. In our patient, since cystoscopy before the 1st treatment with BCG revealed no apparent cause of perforation, bladder perforation was not suspected at the 1st BCG treatment. Inflammatory changes induced by BCG treatment in the area of the TURBT might cause ischemic changes leading to the development of bladder perforation similar to MMC [12, 13].

We treated our patient with an antituberculous agent, antimicrobial chemotherapy, percutaneous urine drainage and drainage of the abscess for the systemic *M. tuberculosis* infection, bladder perforation and perivesical abscess, respectively. The EAU guidelines for the management of BCG sepsis recommend RFP, INH and EB for 6 months and consideration of an empirical antibiotic to cover Gram-negative bacteria and/or Enterococcus [4]. There have been

Fig. 1 Computed tomography (CT). Fluctuant perivesical abscess and bilateral hydro-ureteronephrosis at the initial examination (**a–c**), 2 months after diagnosis, cystography and nephrostography showed persistent bladder leakage from perforation and ureteral obstruction (**d, e**). Ten months after diagnosis, cystography and nephrostography showed no bladder leakage or ureteral obstruction (**f, g**)

some reports of BCG infection following intravesical BCG treatment [8, 14, 15]. Pérez-Jacoiste et al. reported that a

three-drug regime (RFP, INH and EB for 2 months, followed by INH and RFP for 4 months or more) should be used in

cases with either local or systemic BCG infection and considered surgical treatment in the presence of an abscess [8]. Our patient underwent antituberculous treatment for RFP, INH and EB for 2 months and we added INH and RFP for 7 months according to the WHO: Treatment of Tuberculosis Guidelines [16].

The management of bladder perforation is determined by the site and etiology of the perforation. Catheter drainage alone is recommended for minimal iatrogenic injury. Surgical repair with absorbable sutures is the standard of care, avoiding failure of the catheter to provide adequate drainage [17]. Delayed surgical repair is associated with worse outcomes of repairs of bladder fistulae [18]. However, in our case, we successfully treated the bladder perforation without surgical suture of the bladder fistula via management with bilateral PNS and perivesical drainage without a urethral catheter.

Here, we report the case of a patient who had bilateral ureteral obstruction and sepsis induced by bladder perforation following intravesical BCG that was successfully treated with an antituberculous agent, antimicrobial chemotherapy and percutaneous urine drainage.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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