

## Intravesical bacillus Calmette-Guérin-associated *Mycobacterium tuberculosis var.bovis* infection in a patient with bladder cancer

Kazuki Maeda\*; Tatsuya Kawasaki; Shinobu Otomo; Kyoko Ego; Aki Tamaru; Mitsuhiko Inaba; Takashi Yasuda

### \*Kazuki Maeda

Clinical Laboratory Department, Matsushita Memorial Hospital, Sotojima 5-55, Moriguchi, Osaka 570-8540, Japan

Phone: +81-66992-1231, Fax: +81-66992-4845; Email: maeda.kazuki002@jp.panasonic.com

### Abstract

Intravesical infusion of bacillus Calmette-Guérin (BCG), a live attenuated strain of *Mycobacterium tuberculosis var.bovis*, has been established as adjuvant therapy for the management of bladder cancer. We report a case of BCG-associated *M. tuberculosis var.bovis* infection in the urinary tract after intravesical BCG therapy for bladder cancer. A 79-year-old man presented with hematuria and pain during urination around the fifth administration of intravesical BCG, followed by general fatigue and acute kidney injury. Acid fast bacilli were isolated from the urine, and identified as the *M. tuberculosis var.bovis* BCG Tokyo strain by polymerase chain reaction using multiple primers. Combination chemotherapy with rifampicin, isoniazid, and ethambutol was administered. The patient recovered with no recurrence of bladder cancer or *M. tuberculosis var.bovis* infection for more than 18 months after the diagnosis. Our case highlights the importance of BCG-associated *M. tuberculosis var.bovis* infection in patients with a history of intravesical BCG therapy, although this complication is considered extremely rare.

### Keywords

bacillus calmette-guerin; bladder cancer; *Mycobacterium tuberculosis var.bovis*; vesicoureteral reflux

### Introduction

Intravesical infusion of bacillus Calmette-Guérin (BCG), a live attenuated strain of *Mycobacterium bovis*, has been established as adjuvant therapy to prevent tumor recurrence in intermediate- or high-risk patients with non-muscle invasive bladder cancer [1,2]. Here, we report an extremely rare case of *M. tuberculosis var.bovis* infection after immunotherapy with intravesical BCG for bladder cancer.

## Case Presentation

A 79-year-old man was admitted because of hematuria, malaise, and acute kidney injury. The patient underwent left nephrectomy for a staghorn stone in the renal pelvis seven years ago and multiple transurethral resections for urothelial carcinoma of the bladder without complications. His last transurethral resection of the bladder tumor was performed three months before admission. Two weeks after the surgery, immunotherapy with intravesical BCG was initiated because of the frequent recurrence. *M. tuberculosis var. bovis* BCG Tokyo strain (BCG Co. Ltd., Tokyo, Japan) was scheduled for infusion into the bladder once a week for eight weeks. The patient reported that hematuria and painful urination developed around the fifth administration of BCG, followed by general fatigue. The patient had a history of diabetes and pure red cell aplasia. Medications included sodium hydrogen carbonate at 2.0 g, precipitated calcium carbonate at 3.0 g, allopurinol at 100 mg, rabeprazole at 10 mg, and voglibose at 0.6 mg.

The levels of urea nitrogen and creatinine were 83 mg/dl and 5.53 mg/dl, respectively. The white cell count was 7,300/ $\mu$ L with 66.5% neutrophils, hemoglobin was 10.5 g/dL, the platelet count was 232,000/ $\mu$ L, and C-reactive protein was 2.04 mg/dL. The liver function tests were normal, as were the lactate dehydrogenase level and electrolytes. Urinalysis revealed a specific gravity of 1.009 and a pH of 6.0, with +/- glucose, 1+ protein, + occult blood, - ketone, - bilirubin, and +/- urobilinogen. No organisms were detected by gram staining or Ziehl-Neelsen staining of the urine. Computed tomography without contrast material demonstrated dilation of the right renal pelvis, suggesting hydronephrosis due to vesicoureteral reflux. A urinary catheter and double J ureteral catheter were placed, but removed eight days later because of lack of improvement. Unexpectedly, 22 days later, acid fast bacilli were isolated from the urine from the MGIT system. Real-time polymerase chain reaction (PCR) and MPB64 [3] immunochromatographic assays revealed the *M. tuberculosis* complex. No obvious findings of pulmonary tuberculosis were noted on computed tomography of the chest, and *M. tuberculosis* was not detected by PCR of the sputum. Furthermore, *M. tuberculosis* antigen-specific interferon- $\gamma$  release assays were negative. The strain was finally identified as the *M. tuberculosis var. bovis* BCG Tokyo strain based on the PCR product patterns of *pab* [3], *mtp40* [4], *MPB64* [5], *pncA* [6], and *senX3-regX3* [7] (Table 1). Based on the multilocus variable-number tandem repeat analysis, as shown in Table 2, a diagnosis of *M. tuberculosis var. bovis* infection of the urinary tract associated with BCG immunotherapy was made.

Combination chemotherapy with rifampicin (10 mg/kg/day), isoniazid (5 mg/kg/day), and ethambutol (20 mg/kg/day) was continued for two months, followed by 10 months of rifampicin and isoniazid at the same dosages. Pyrazinamide was not prescribed as *M. tuberculosis var. bovis* is naturally resistant. The clinical course was uneventful except for a single episode of acute pyelonephritis, which was successfully treated with antibiotics. The patient was well with no recurrence of bladder cancer or *M. tuberculosis var. bovis* infection for more than 18 months after the diagnosis.

## Discussion

BCG has been exclusively used as a human vaccine against *M. tuberculosis* for almost a century [8]. The safety profile of BCG is excellent [9]; the incidence of adverse serious events, defined as beyond the

vaccination site and regional ipsilateral axillary lymph nodes, was 0.0182 cases per 100,000 vaccinations [10]. In the 1970s, intravesical BCG was first described by Morales et al. [11] for the treatment of bladder carcinoma in situ. To date, intravesical BCG has been widely applied for the management of bladder cancer [1,2,12,13]. The antitumor activity of BCG is likely associated with anti-BCG cell-mediated immunity specific to bladder cancer, such as T helper cells, activation of macrophages, and induction of cytokines [13,14]. However, attention should be paid to the administration of immunotherapy with intravesical BCG because the risk of adverse side effects from intravesical immunotherapy is higher than that from vaccination against tuberculosis [14].

The common adverse effects of intravesical BCG for bladder cancer include fever, malaise, lethargy, and abdominal pain [14], some of which were observed in this case. Serious adverse events, such as granulomatous prostatitis, epididymitis, nephritis, pneumonitis, hepatitis, ureteral obstruction, contracted bladder, cytopenia, and sepsis, occurred in approximately 5% in a review of a series of 2026 patients with bladder cancer who underwent intravesical BCG [13]. Given the components of BCG (i.e., a live attenuated strain of *M. tuberculosis var.bovis*), infection by *M. tuberculosis var.bovis* after immunotherapy with intravesical BCG for bladder cancer is not unexpected, as shown in this case. Cancer patients have been reported to be more susceptible to infectious diseases [15], probably because of changes in the immune system [16,17].

In the present case, the diagnosis of BCG-associated *M. tuberculosis var.bovis* infection in the urinary tract was confirmed by PCR analyses, but the exact site of the infection was not determined. Caution is required with regard to a diagnosis of *M. tuberculosis var.bovis* infection because BCG can remain colonized in the bladder for a long time after immunotherapy with intravesical BCG. In previous studies, *M. tuberculosis var.bovis* was detected 16.5 months and 34 months after immunotherapy with intravesical BCG [18,19]. Therefore, when *M. tuberculosis var.bovis* BCG is isolated from the urine, it is necessary to distinguish infection from colonization using the patient's symptoms and clinical course. In our case, cystoscopy was unremarkable, suggesting the upper urinary tract as an infection site. Given the relative impermeability of the bladder, direct invasion of intravesical BCG to the ureter, pelvis, or kidney is possible. This speculation is supported by the lack of organisms in blood cultures and the presence of vesicoureteral reflux in our case.

The exact incidence of BCG infection after immunotherapy with intravesical BCG remains unclear, but it is considered to be extremely rare. In a review of all reports of BCG infection from the United States and Canada from 1966 through 2002, this condition was identified in only 35 patients with sufficient clinical information [13]. The mean age of these patients was 67 years (range, 47 to 90 years), and the mean number of BCG instillations was 7.8. Of note, 20 patients had an early-onset with a mean time after the first BCG instillation of 9 weeks, whereas the remaining 15 had a late onset with a mean time after the first BCG instillation of 76 weeks. It is worth noting that early-onset disease was associated with generalized symptoms and disseminated involvement, as seen in our case, but that late-onset disease was related to localized infection with no systemic manifestations. All but one patient with early-onset disease received antituberculous therapy with a different regimen; 4 also received glucocorticosteroids. Nine of 11 patients with late-onset disease and localized infection underwent surgical resection, 3 of whom received no further

antituberculous therapy.

In conclusion, although *M. tuberculosis var.bovis* infection is not a common complication of intravesical BCG for the prevention of tumor recurrence in patients with bladder cancer, high clinical suspicion is essential for the diagnosis because its management requires antituberculous agents.

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## Tables

**Table 1:** PCR results using multiple primers

Target gene	Pab	MPB64	mtp40	pnc(7-10) <sup>a</sup>	pnc(7-11C) <sup>b</sup>	senX3 - regX3 <sup>c</sup>
<i>M. tuberculosis</i>	+	+	+	+	-	329 or 353 bp
BCG Tokyo strain	+	+	-	-	+	353 bp
The current case	+	+	-	-	+	353 bp

<sup>a</sup>*M. tuberculosis*, *M. tuberculosis var.afriacanum*, and *M. tuberculosis var.microti*. <sup>b</sup>*M. tuberculosis var.bovis* including BCG strains.

<sup>c</sup>BCG Tokyo strain: 353 bp, *M. tuberculosis var.bovis*: 406 bp.

**Table 2:** Multilocus variable-number tandem repeat analysis

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	V424	M10	V1955	V2074	Q11b	V2372	M26	V3155	M31	Q3336	Q26
BCG Tokyo strain	0	2	0	3	3	2	5	5	3	10	5
The current case	0	2	0	3	3	2	5	5	3	10	5

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**Authors Information:** Kazuki Maeda<sup>1\*</sup>; Tatsuya Kawasaki<sup>2</sup>; Shinobu Otomo<sup>1</sup>; Kyoko Ego<sup>1</sup>; Aki Tamaru<sup>3</sup>; Mitsuhiro Inaba<sup>4</sup>; Takashi Yasuda<sup>5</sup>

<sup>1</sup>Clinical Laboratory Department, Matsushita Memorial Hospital, Osaka, Japan

<sup>2</sup>Department of General Internal Medicine, Matsushita Memorial Hospital, Osaka, Japan

<sup>3</sup>Department of Microbiology, Osaka Institute of Public Health, Osaka, Japan

<sup>4</sup>Department of Urology, Matsushita Memorial Hospital, Osaka, Japan

<sup>5</sup>Department of Nephrology and Artificial Kidney, Matsushita Memorial Hospital, Osaka, Japan

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