



# Bacillus Calmette–Guerin intravesical instillation therapy-induced urothelial necrosis of the bladder and upper urinary tract

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## ABSTRACT

Bacillus Calmette–Guerin (BCG) intravesical instillation therapy is the most effective adjuvant therapy for bladder cancer after transurethral resection of bladder tumor (TURBT). We present the first case to our knowledge with bladder and ureteral necrosis as a severe local side effect of it.

## 1. Introduction

Bacillus Calmette–Guerin (BCG) intravesical instillation therapy is the most effective adjuvant therapy for bladder cancer after transurethral resection of bladder tumor. However, Bacillus Calmette–Guerin therapy is associated with a high risk of local and systemic side effects such as dysuria, frequent urination, hematuria, fever, and rash. We experienced a very rare case with bladder and ureteral necrosis as a severe local side effect of it.

## 2. Case presentation

A 63-year-old man was diagnosed with bladder cancer and right distal ureter cancer after reporting frequent urination and micturition pain. He suffered from hypertension, reflux esophagitis, and allergic rhinitis, and was taking oral medication for each condition. Furthermore, he had no history of tuberculosis or any diseases such as diabetes or autoimmune disorders that can result in a vascular disorder. He underwent transurethral resection of bladder tumor, including right intramural ureter resection, and was diagnosed with high-grade pT1 invasive urothelial carcinoma with carcinoma in situ. A month later, he received eight courses of weekly induction therapy with Japanese strain of BCG (Immunobladder®, Japan BCG Laboratory, Tokyo, Japan) instillations, which is one of the standard regimens as outlined by the Clinical Practice Guidelines for Bladder Cancer 2019 by the Japanese Urological Association. However, he developed a fever (38 °C),

micturition pain, and frequent urination once every 40 min as side effects. The fever was relieved with an antipyretic drug, but aseptic pyuria and frequent urination persisted. Cystoscopy at 5 months revealed that most of the right side of the bladder was covered with necrotic tissue and the right ureteral orifice could not be identified; gradually, the observations became more prominent (Fig. 1). Right hydronephrosis with encapsulated liquid storage around the distal ureter appeared at 41 months on contrast-enhanced computed tomography (Fig. 2), and biopsy of the right distal ureter under ureteroscopy and ureteral stent placement were performed. The pathological examination showed epithelioid granulomas with necrosis due to intravesical BCG therapy. Cystoscopy at 46 months revealed that necrosis had spread to the left side of the bladder, making it impossible to identify the left ureteral orifice. Finally, left hydronephrosis was also observed at 50 months, and renal function gradually worsened (serum creatinine level: 0.85 → 1.61 mg/dl). 99 mTc-MAG3 renal scintigraphy showed patterns indicative of a non-functioning right kidney. Although urinary cytology consistently revealed negative findings, it could not be denied that the mass around the right distal ureter included cancer cells. In addition, both severe frequent urination and micturition pain associated with cystitis and decreased bladder capacity persisted, which led to a decline in his quality of life, requiring surgical therapy. We performed radical cystectomy, right nephroureterectomy, and left cutaneous ureterostomy at 51 months. Histopathologic analysis of the surgical specimen (Fig. 3A) did not show any sign of cancer recurrence. However, extensive ulcer formation, inflammatory cell infiltration, and epithelioid cell

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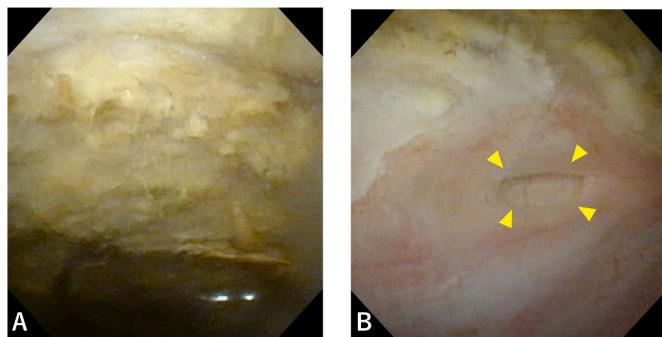
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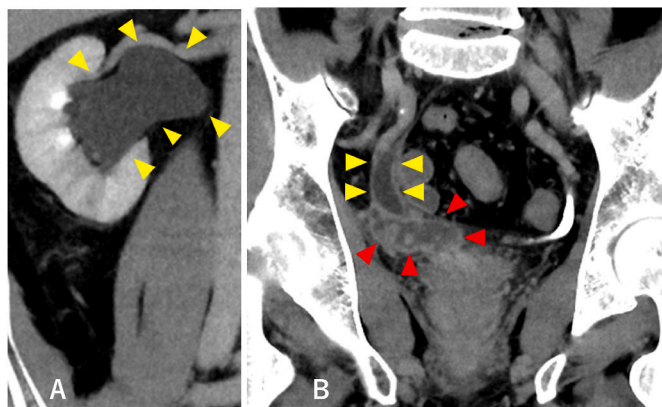
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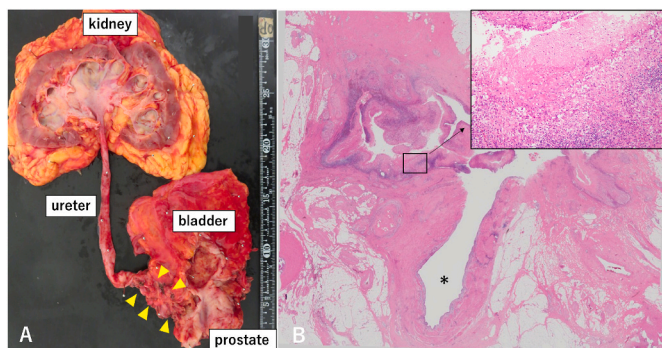
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**Fig. 1.** Cystoscopy of the patient's bladder at 40 months. (A) Necrotic tissue covering almost the entire right side of the bladder. (B) A left ureteral orifice was identified.



**Fig. 2.** Contrast-enhanced computed tomography findings at 41 months. (A) Coronal image demonstrating right hydronephrosis (yellow arrows). (B) Coronal image demonstrating the hydroureter (yellow arrows) and encapsulated liquid storage around the distal ureter (red arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)



**Fig. 3.** (A) Macroscopic observation of the cystectomy and right nephroureterectomy specimen. Necrosis and atrophic changes were observed in the bladder and right distal ureter. Inflammatory mass lesion around the right distal ureter caused by urinary extravasation due to minor leak of the ureter was observed (yellow arrows). (B) Microscopic observation of the cystectomy specimen. The asterisk indicates the lumen of the ureter. Granulomatous lesions with infiltration of epithelioid cells and lymphocytes were found around the ureteral wall, mainly with extensive necrosis. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

granulomas with extensive necrosis were observed. In other words, the patient had severe inflammation with epithelioid cell granulomas and no remnant carcinoma (Fig. 3B).

### 3. Informed consent was obtained from the patient for the publication of this case

**DISCUSSION:** BCG intravesical instillation therapy has been often reported to result in frequent local and systemic side effects.<sup>1</sup> It has been suggested that local side effects result from the inflammatory response to intravesical administration, and systemic effects result from BCG infection.<sup>1</sup> In our case, chemical cystitis with frequent urination and micturition pain were observed as local side effects, and fever was observed as a systemic side effect several hours after BCG administration. Local side effects of BCG are common and are generally not serious<sup>1</sup>; however, in our case, the local response gradually exacerbated over several years, and strong inflammation led to necrosis and rupture of the urothelium of bladder and ureter. It was assumed that resection of the right ureteral orifice in the transurethral resection of bladder tumor caused vesicoureteral reflux and promoted BCG regurgitation into the ureter. Kisbenedek et al. reported that vesicoureteral reflux occurred in 11 of 33 (33%) patients who underwent TUR of the ureteral orifice.<sup>2</sup> Krönig et al. reported BCG-induced necrosis of the entire bladder urothelium in 2015.<sup>3</sup> To our knowledge, this is the first report on BCG intravesical instillation therapy-induced urothelium necrosis of both the bladder and upper urinary tract. Although there were no obvious recurrences, surgical treatment alleviated severe symptoms and progressive postrenal failure and improved the patient's quality of life. Despite long clinical experiences with BCG, the full mechanisms of its therapeutic effects have not yet been elucidated.<sup>4,5</sup> Therefore, it is important to further investigate the immunological mechanism of the series of processes that have progressed over several years and to establish treatment and prevention methods for it.

### 4. Conclusion

To our knowledge, this is the first report of BCG intravesical instillation therapy-induced severe local side effects not only in the bladder but also in the upper urinary tract over several years.

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### Author contributions

TT and AA conceived the idea of this case report and contributed the interpretation of the clinical course. TK drafted the original manuscript. KA contributed the pathological interpretation. All authors approved the final version of the manuscript to be published.

### Declaration of competing interest

None.

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