Bladder tuberculosis with ureteral strictures after bacillus Calmette-Guérin therapy for urinary bladder cancer: A case report

YUSUKE TOMINAGA[1*], MASANORI FUJII[2*], TAKUYA SADAHIRA[1], SATOSHI KATAYAMA[1], TAKEHIRO IWATA[1], SHINGO NISHIMURA[1], KENSUKE BEKKU[1], KOHEI EDAMURA[1], TOMOKO KOBAYASHI[1], YASUYUKI KOBAYASHI[1], KATSUYUKI KIURA[2], YOSHINOBU MAEDA[2], KOICHIRO WADA[3] and MOTOO ARAKI[1]

[1]Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences; [2]Department of Allergy and Respiratory Medicine, Okayama University Hospital, Okayama 700-8558; [3]Department of Urology, Shimane University Faculty of Medicine, Izumo, Shimane 693-8501, Japan

Received October 3, 2022; Accepted December 7, 2022

DOI: 10.3892/mco.2022.2603

Abstract. Intravesical immunotherapy using bacillus Calmette-Guérin (BCG) is recommended for patients with intermediate- to high-risk non-muscle invasive bladder cancer. Bladder tuberculosis (TB) is a rare complication of BCG therapy. The present study describes the case of a 73-year-old man who underwent intravesical BCG therapy for urothelial carcinoma in situ of the bladder. Red patches around the resection scar were first detected 1 year and 5 months after BCG treatment; these findings gradually spread to encompass more of the bladder wall. Transurethral biopsy revealed a benign lesion, but the patient developed bilateral hydronephrosis and mild voiding dysfunction. The patient was eventually diagnosed with bladder TB by mycobacterial urine culture and TB-specific polymerase chain reaction (PCR). The patient was given multidrug therapy (isoniazid, rifampicin and ethambutol) and their bladder TB was completely cured; however, their voiding dysfunction and bilateral hydronephrosis did not fully improve. Bladder TB can occur long after intravesical BCG administration and cystoscopy findings consistent with inflammation can be the key to suspecting this condition. Acid-fast examination and PCR testing of a urine sample are necessary for early diagnosis.

Correspondence to: Dr Takuya Sadahira, Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan
E-mail: t.sadahira@gmail.com

[*]Contributed equally

Key words: bladder tuberculosis, bacillus Calmette-Guérin, bladder cancer, ureteral stricture, voiding dysfunction

Introduction

Intravesical immunotherapy using bacillus Calmette-Guerin (BCG) is recommended for patients with intermediate- to high-risk non-muscle invasive bladder cancer after transurethral resection of bladder tumor (TURBT) (1,2). Carcinoma *in situ* (CIS) cannot be cured by tumor resection alone and is usually followed by intravesical BCG therapy. Induction BCG is also used to reduce the risk of intravesical recurrence and progression. Although this treatment is effective, many adverse effects have been reported and monitoring after treatment is crucial. Common adverse effects that occur shortly after BCG instillation include fever, dysuria, and hematuria due to a systemic or local immune response (3). Severe adverse effects are related to BCG infection or systemic immune reaction and can occur in any structure-one possible manifestation is Reiter syndrome-but it is rare for bladder tuberculosis (TB) to manifest several years after BCG treatment. Bladder TB is also difficult to diagnose because the symptoms are similar to those of cystitis or cancer and BCG infection cannot be proven by urinalysis or urine culture. We present our experience with a patient who had chronic cystitis due to bladder TB after BCG treatment, resulting in voiding dysfunction and hydronephrosis.

Case report

A 73-year-old man was referred to the Urology Department of Okayama University Hospital (Okayama, Japan) in March 2016 because of nocturia and a positive urine cytology. Cystoscopy showed a nonpapillary lesion on the posterior bladder wall; computed tomography (CT) revealed no evidence of metastasis or upper urinary tract tumor, and magnetic resonance imaging (MRI) showed no sign of muscle-invasive bladder cancer. TURBT pathology revealed high grade urothelial carcinoma at or above stage pT1. Second TURBT 6 weeks after the initial resection revealed CIS. The patient subsequently underwent intravesical BCG

treatment (80 mg once a week for 8 doses) without any complications.

The patient underwent routine postoperative follow-up. At 1 year and 5 months after BCG therapy, cystoscopy showed an ulcerative lesion surrounded by edematous red patches at the resection site in the bladder dome. This lesion was followed with serial cystoscopy and observed to gradually spread. The ulcerative lesion was gradually replaced with necrotic debris (Fig. 1); although this was suspicious of intravesical cancer recurrence, serial urine cytology showed no signs of malignancy. At 3 years and 8 months after BCG therapy, dysuria, pollakiuria and urge urinary incontinence occurred. Antibiotic treatment had no effect on his symptoms or cystoscopy findings. Although a repeat TURBT performed 4 years after BCG treatment revealed no malignancy, ultrasonography showed bilateral hydronephrosis (Fig. 2), and MRI revealed a postvoid urine residual volume >100 ml and bilateral distal ureteral dilation, suggesting a ureterovesical junction obstruction (Fig. 3). We placed a right ureteral stent but were unable to detect the left ureteral orifice to place a left ureteral stent.

Four years and 3 months after BCG therapy, *Mycobacterium tuberculosis* complex (MBTC) was detected by mycobacterial urine culture. The urine nitrate reduction test was negative, but urine polymerase chain reaction (PCR), which was carried out by other researchers than us who belong to the department of clinical laboratory in our hospital, was positive for *M. bovis*. Therefore, we reached a diagnosis of bladder TB caused by *M. bovis*. We placed a left ureteral stent by an antegrade approach and started antitubercular treatment with 300 mg isoniazid, 450 mg rifampicin, and 1,000 mg ethambutol daily. We initially planned to continue the regimen for 3 months; however, 2 months after treatment started, the patient experienced drug eruption over his back and both legs, which quickly spread over his entire body [grade 2 according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0]. The discoloration gradually improved after discontinuation of ethambutol. One month later, the patient developed a persistent cough productive of sputum. Chest CT revealed consolidation and a ground glass appearance in both lungs. A pulmonologist diagnosed drug-induced pneumonia after close inspection via bronchoscopy (CTACE grade 2). We then discontinued the other 2 drugs. In total, he took ethambutol for 76 days and isoniazid and rifampicin for 83 days.

Despite the interruption in TB treatment, repeat urine testing revealed no evidence of MBTC and PCR was negative. There was no evidence of intravesical cancer recurrence or metastasis. His pneumonia gradually improved with corticosteroid treatment. Six months after completing TB treatment, the patient still had voiding dysfunction, so we started clean intermittent catheterization (postvoid residual urine volume 150-180 ml). One year after TB treatment, retrograde pyelography showed improvement in his bilateral ureteral strictures (Fig. 4). After removal of both stents, he was followed up with bilateral grade 1-2 hydronephrosis and voiding dysfunction by ultrasonography.

Discussion

We present our experience with a patient who had chronic cystitis with bilateral ureteral strictures and voiding dysfunction caused by bladder TB resulting from intravesical BCG therapy for CIS 4 years prior. When the patient initially presented with continuous episodes of cystitis, we strongly suspected an intravesical carcinoma recurrence; this presumption resulted in delayed detection of his bladder TB.

Intravesical BCG instillation is standard therapy after TURBT for CIS of the bladder (4). Previous studies have shown that the therapy significantly reduces the risk of short- and long-term treatment failure compared with intravesical chemotherapy (5). Instillation of BCG for intermediate- or high-risk non-muscle invasive bladder cancer is an option to decrease the rate of recurrence (6-8). However, there are various adverse effects associated with treatment, so close follow-up is crucial.

Approximately 1% of patients develop BCG infection after bladder instillation; the median time to develop symptoms from first BCG instillation is 170 days (in our patient, it was 3 years and 8 months) (9). A contracted bladder and ureteral strictures can occur in patients with TB cystitis as a result of the granulomatous inflammation and edematous mucosa associated with infection (10,11), presumably because of thickening of the ureteral and bladder mucosae as a reaction to inflammation. Infection with BCG can cause bladder ulcers; the increased risk of this manifestation was found to be associated with male sex and certain tumor characteristics (e.g., high grade and T1 stage) (11). Bladder TB cannot be distinguished from other etiologies of cystitis using standard urinalysis and urine culture; it requires specialized testing (mycobacterial urine culture, PCR, biopsy, etc.). Clinicians should bear in mind the possibility of bladder TB during follow-up after intravesical BCG therapy, and they should remain vigilant for symptoms or cystoscopy findings suspicious for TB.

Drug-susceptible TB is treated with a standard 6-month regimen of 4 antitubercular drugs: isoniazid, rifampicin, ethambutol, and pyrazinamide (*M. bovis* is treated in the same manner as *M. tuberculosis*) (10,12). However, short courses may be feasible for genitourinary TB. Although our patient's planned 3-month treatment period could not be completed because of treatment-related adverse effects (drug eruption and interstitial pneumonia), his mycobacterial urine culture was negative after his truncated course of treatment. He initially needed bilateral ureteral stenting for stricture, but the stents were successfully removed after TB treatment. In some patients, ureteral stricture and contracted bladder caused by TB are irreversible and require surgical repair (10,13,14). Therefore, early detection of bladder TB and proper intervention is essential.

Bladder TB can occur several years after intravesical BCG instillation. It is important to bear in mind the possibility of BCG infection when patients experience persistent cystitis with bladder ulceration after BCG instillation, even if the treatment was long ago. The essence of our report is to warn urologists not to miss the opportunity to diagnose bladder TB after BCG therapy. We believe that our findings will be

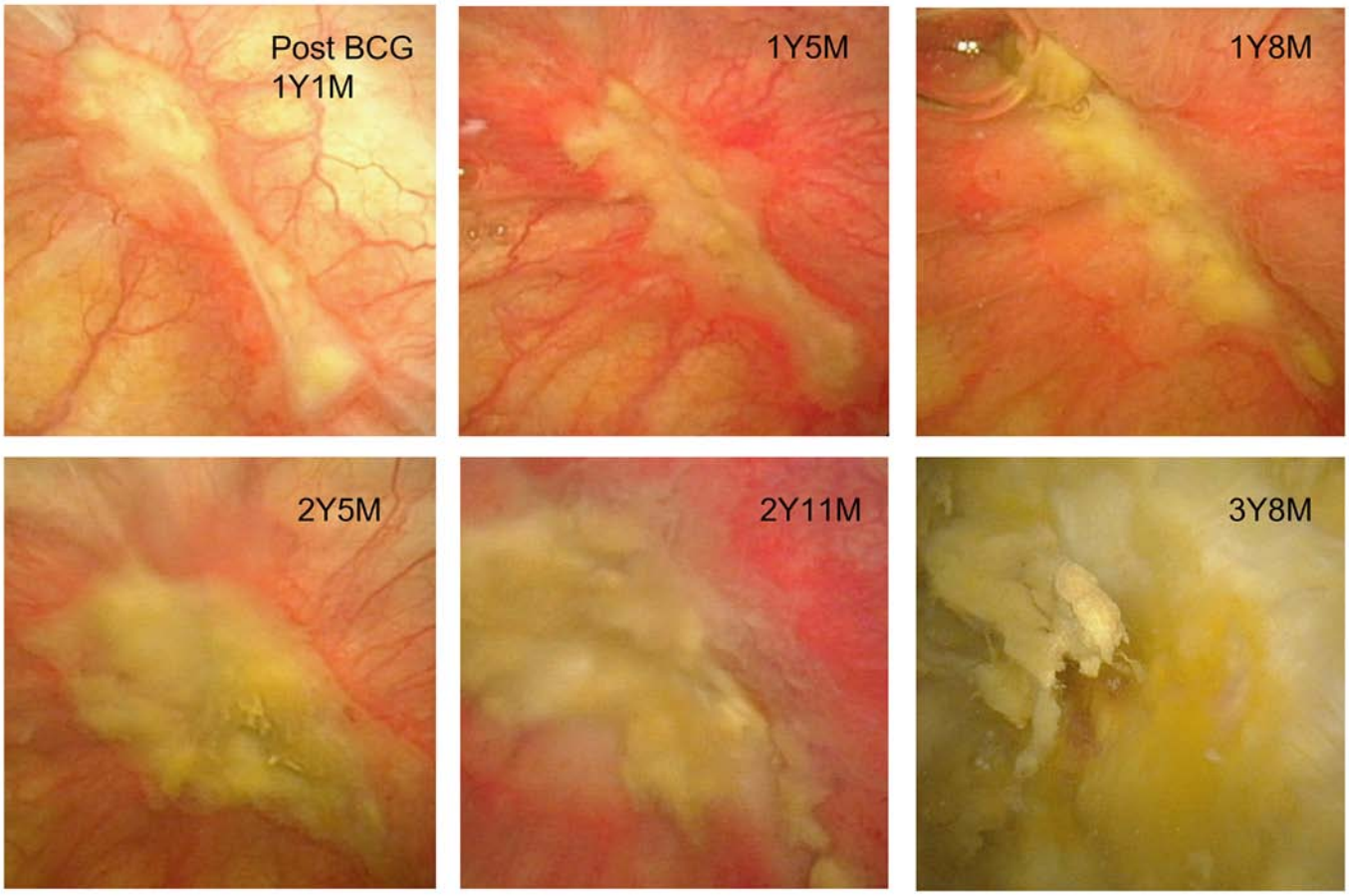

Figure 1. Sequential cystoscopy findings after BCG therapy. A bladder ulcer is seen at the dome of the bladder; the red and edematous area around the ulcer is replaced with necrotic debris over time. BCG, bacillus Calmette-Guérin; M, months; Y, years.

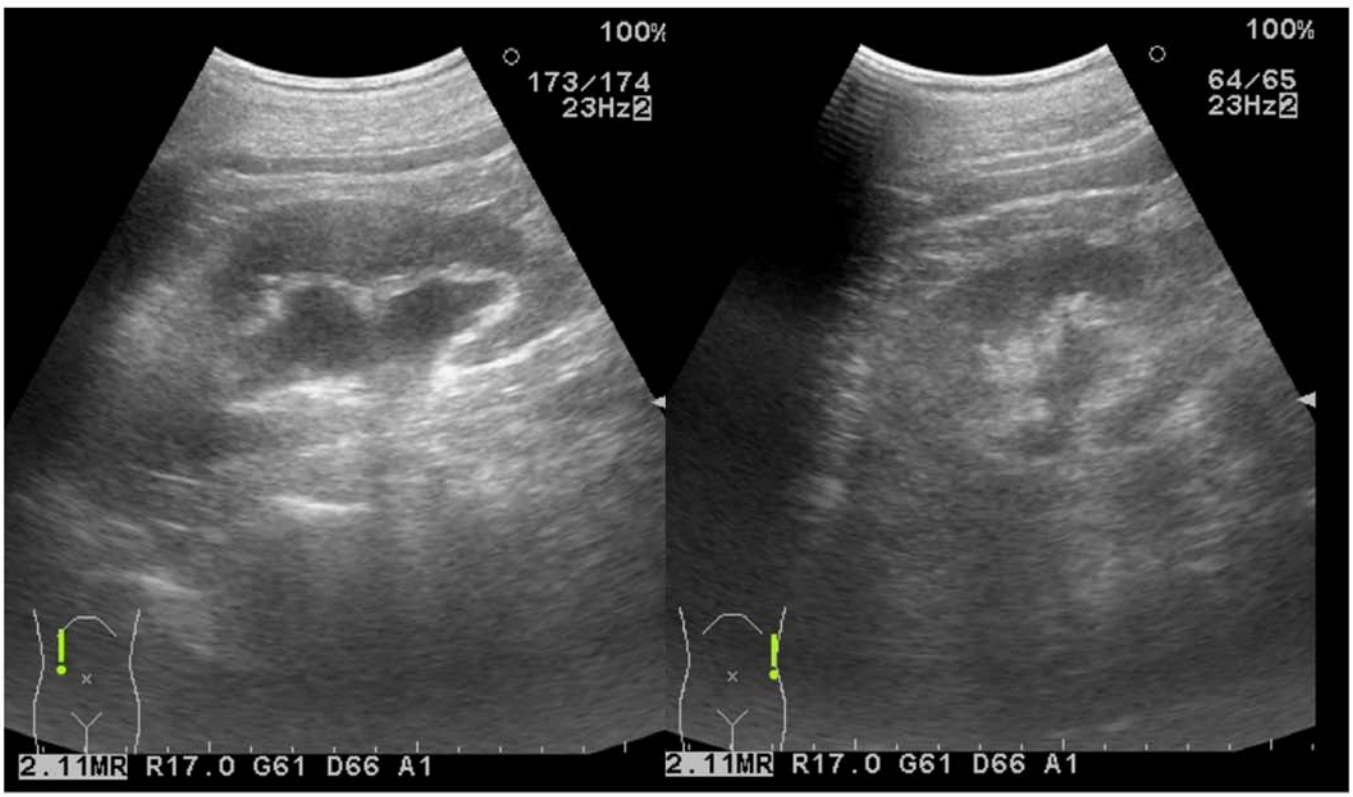

Figure 2. Ultrasonography reveals bilateral grade 2-3 hydronephrosis.

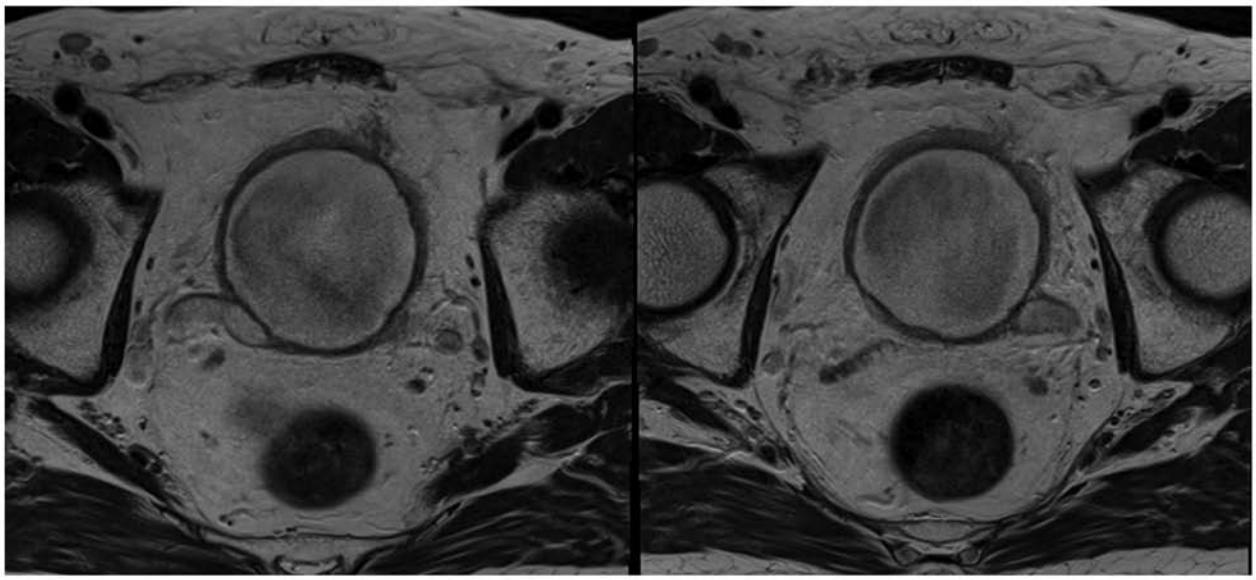

Figure 3. Magnetic resonance imaging shows moderate postvoid residual urine and bilateral distal ureteral dilation.

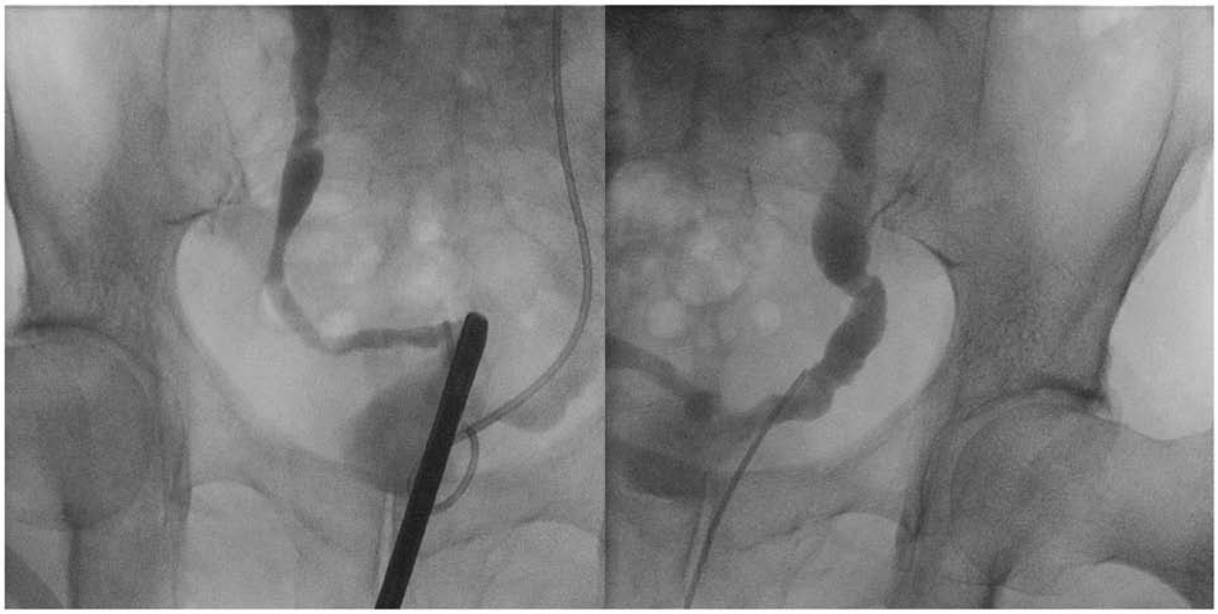

Figure 4. Retrograde pyelography shows no evidence of the bilateral ureteral strictures.

beneficial to detect bladder TB at an early stage and reduce complications.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YT and MF wrote the manuscript (equally contributed). TS was a major contributor to the conception and design of the study. YT, MF and KW performed the patient's examination. TS, SK, TI and SN confirm the authenticity of all the raw data. YT, KB, KE, TK, YK, KW and MA performed the patient's surgery and acquired the data. YT, MF, KK, YM and MA analyzed and interpreted the data. SK, TI, SN, KB, KE, TK, YK, KK, YM, KW and MA critically revised the manuscript for intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publications

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

The author declare that they have no competing interests.

References

1. Flaig TW, Spiess PE, Agarwal N, Bangs R, Boorjian SA, Buyyounouski MK, Chang S, Downs TM, Efstathiou JA, Friedlander T, *et al*: Bladder cancer, version 3.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 18: 329-354, 2020.
2. Babjuk M, Burger M, Capoun O, Cohen D, Compérat EM, Dominguez Escrig JL, Gontero P, Liedberg F, Masson-Lecomte A, Mostafid AH, *et al*: European association of urology guidelines on non-muscle-invasive bladder cancer (Ta, T1, and carcinoma in situ). Eur Urol 81: 75-94, 2022.
3. Green DB, Kawashima A, Menias CO, Tanaka T, Redelman-Sidi G, Bhalla S, Shah R and King BF: Complications of intravesical BCG immunotherapy for bladder cancer. Radiographics 39: 80-94, 2019.
4. Takenaka A, Yamada Y, Miyake H, Hara I and Fujisawa M: Clinical outcomes of bacillus Calmette-Guérin instillation therapy for carcinoma in situ of urinary bladder. Int J Urol 15: 309-313, 2008.
5. Sylvester RJ, van der Meijden AP, Witjes JA and Kurth K: Bacillus calmette-guerin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: A meta-analysis of the published results of randomized clinical trials. J Urol 174: 86-92, 2005.
6. Malmström PU, Sylvester RJ, Crawford DE, Friedrich M, Krege S, Rintala E, Solsona E, Di Stasi SM and Witjes JA: An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guérin for non-muscle-invasive bladder cancer. Eur Urol 56: 247-256, 2009.
7. Böhle A and Bock PR: Intravesical bacille Calmette-Guérin versus mitomycin C in superficial bladder cancer: Formal meta-analysis of comparative studies on tumor progression. Urology 63: 682-687, 2004.
8. Sylvester RJ, van der Meijden AP and Lamm DL: Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: A meta-analysis of the published results of randomized clinical trials. J Urol 168: 1964-1970, 2002.
9. Larsen ES, Nordholm AC, Lillebaek T, Holden IK and Johansen IS: The epidemiology of bacille Calmette-Guérin infections after bladder instillation from 2002 through 2017: A nationwide retrospective cohort study. BJU Int 124: 910-916, 2019.
10. Muneer A, Macrae B, Krishnamoorthy S and Zumla A: Urogenital tuberculosis-epidemiology, pathogenesis and clinical features. Nat Rev Urol 16: 573-598, 2019.
11. Liu Y, Lu J, Huang Y and Ma L: Clinical spectrum of complications induced by intravesical immunotherapy of bacillus Calmette-Guérin for bladder cancer. J Oncol 2019: 6230409, 2019.
12. WHO: Treatment of Tuberculosis: Guidelines. 4th edition. World Health Organization, Geneva, pp95-99, 2010.
13. Kulchavenya E: Urogenital tuberculosis: Definition and classification. Ther Adv Infect Dis 2: 117-122, 2014.
14. Handmer MM, Winter M, Lee WG and Louie-Johnsun M: Unexpected tuberculosis causing ureteral stricture. ANZ J Surg 87: 515-516, 2017.