CASE REPORT

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Renal Tuberculosis Following Intravesical Bacillus Calmette–Guérin (BCG) Immunotherapy for the Treatment of Bladder Cancer

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ABSTRACT

Introduction: Non-muscle-invasive bladder cancer (NMIBC) is usually effectively treated with transurethral resection (TUR), most often followed by intravesical instillation of bacillus Calmette-Guérin (BCG) or intravesical chemotherapy. Although the precise mechanism of BCG immunotherapy is still unclear, a local immune response is presumed. However, a number of severe side effects and complications are related to intravesical immunotherapy.
AIM: Aim of this report is to present rare case of the renal granulomatous disease in a patient previously treated with intravesical instillation of BCG immunotherapy, following TURBT. In addition, we performed review of previously reported cases of renal granulomas following intravesical BCG immunotherapy. **Case report:** A 79-year-old man was presented to Urology Clinic due to clinically verified tumor of the urinary bladder. After transurethral resection of bladder tumor, histopathological analysis revealed the diagnosis of papillary urothelial high-grade pT1 carcinoma. Intravesical BCG immunotherapy was initiated, according to protocol currently used in our institution. Upon completion of therapy with BCG, we re-examined the patient and, using ultrasound, found a change in the right kidney, resembling moth bites not seen on CT scan before TURBT. Additionally, CT-guided core-needle biopsy of the affected kidney was performed, and the specimen was sent for histopathological analysis, which revealed chronic necrotizing granulomatous inflammation. Antituberculotic therapy was initiated for 6 months. Upon completion of antituberculotic therapy, control CT-scan was performed at follow-up, indicating regression of changes on the right kidney. **Conclusion:** This case report emphasizes the importance of consistent implementation of follow-up protocol and the identification of lesions during the asymptomatic period and enables the proper treatment of the disease. To reduce the incidence of adverse effects of BCG treatment for bladder tumors, an individualized approach is needed.

Keywords: bladder cancer; immunotherapy; BCG; renal tuberculosis.

1. INTRODUCTION

Bladder cancer has become common cancer worldwide, with three to four times higher incidence in males than females (1, 2). Most bladder cancers are of urothelial origin, and a vast majority do not involve muscle wall, being categorized as non-muscle-invasive (3).

Bacillus Calmette-Guerin (BCG) is a live attenuated strain of Mycobacterium bovis, which is part of the Mycobacterium tuberculosis complex (MTBc). Intravesical immunotherapy with BCG following transurethral resection of bladder tumor (TURBT) is considered the gold standard in the treatment of intermediate and high-risk non-muscle-invasive bladder cancer (NMIBC) (4). While the precise immunological mechanism of BCG therapy is still unclear, the local immune response is presumed, requiring an intact immune system to be effective. Plausible mechanisms involve BCG attachment and internalization by the bladder cancer cells, followed by secretion of cytokines and chemokines, and presentation of BCG or cancer cell antigens by phagocytes to T helper cells. This requires a sequence of cell surface interactions, including antigen and T cell receptor, CD4, class II major histocompatibility complex (MHC) antigen, lymphocyte function antigen 1 (LFA-1), CD28, CD80, and intercellular adhesion molecule 1 (ICAM-1) (4-7).

While it is usually effective in bladder cancer treatment, several serious side effects and complications

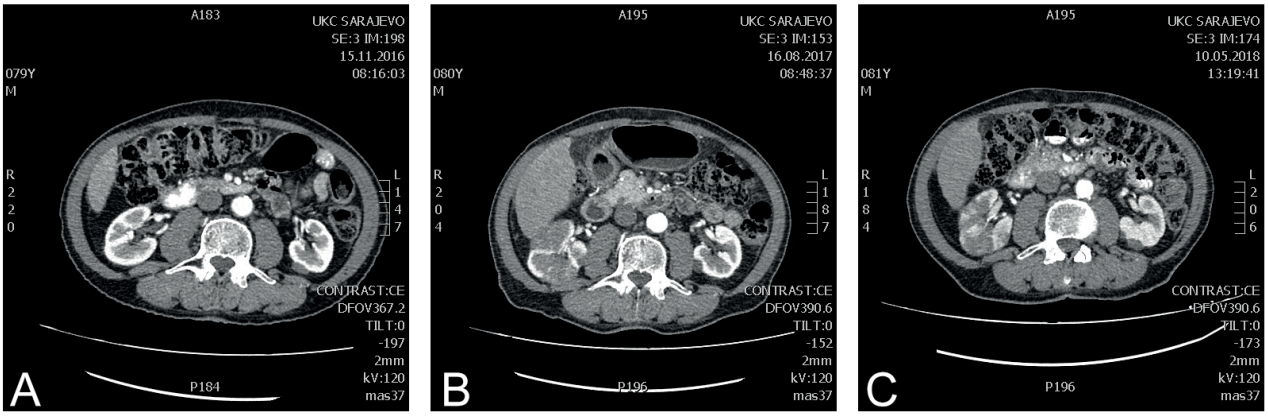

Figure 1. Radiological findings. 1a) Axial CT-scan of the upper urinary tract, before the transurethral resection (TUR) of the bladder cancer. CT scan shows healthy kidneys before BCG therapy initiation. 1b) Axial CT-scan following intravesical BCG immunotherapy, revealing granulomatosis of the right kidney. 1c) Control CT-scan of the granulomatous change of the right kidney, after antituberculous therapy, showing regression of the change of renal parenchyma.

may occur. Minor local reactions, such as lower urinary tract symptoms (LUTS), hematuria, and infection are common and generally self-limiting, occurring due to generated inflammatory response (8, 10). Approximately 30% of treated patients present with low-grade fever associated with flu-like symptoms, which usually resolve in <48 h. Severe systemic complications occur in <5% of patients and can be potentially life-threatening (8). They include persistent high-grade fever as an isolated manifestation (2.9%), pneumonitis with or without hepatitis (0.7%), and sepsis (0.4%) (9, 10).

Renal complications occur in <2% of treated patients and presentation with renal granulomatosis is extremely rare, and it occurs in 0,1% of cases (10, 16, 17). Other granulomatous complications include prostatitis (1%) and epididymitis (0,2%) and they usually require antituberculotic medications for 3–6 months (9, 10). Generally, renal granulomatosis following intravesical BCG immunotherapy may be managed with nephroureterectomy, antituberculotic medicines or a combination of both, although some incidentally found granulomas may be treated conservatively (12). Most of the cases of renal granulomatosis present with symptoms of pyelonephritis after third or fourth instillation of BCG; however, the patients may be asymptomatic, necessitating the need for follow-up imaging (13).

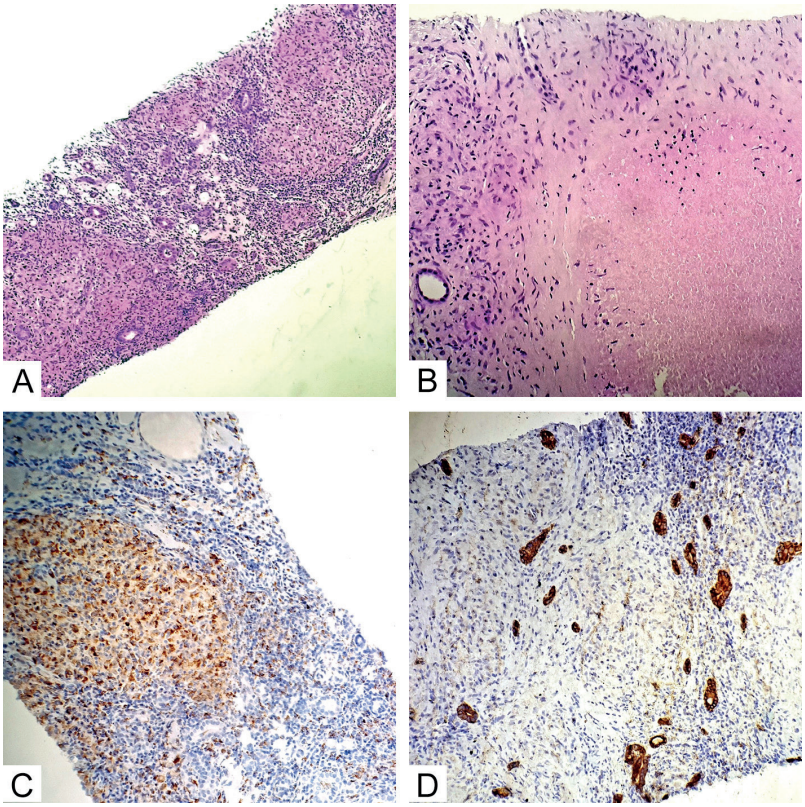

Figure 2. Histopathological findings. 2a) Kidney parenchyma containing granulomas (HEx100). 2b) Caseous necrosis of the renal tissue (HEx200). 2c) CD68 (x100) immunohistochemistry staining of epithelioid histiocytes in granuloma. 2d) Immunohistochemistry of preserved renal tubules (CKx200).

2. AIM

Aim of this report is to present rare case of the renal granulomatous disease in a patient previously treated with intravesical instillation of BCG immunotherapy, following TURBT. In addition, we performed review of previously reported cases of renal granulomas following intravesical BCG immunotherapy.

3. CASE REPORT

A 79-year-old man was first admitted to the Urology Clinic due to clinically verified tumor of the urinary bladder, when computed tomography (CT) urography revealed superficial urinary bladder tumor, near the right ureteral orifice. Transurethral resection of the tumor was performed, and the specimen was sent for histopathological analysis, which confirmed the diagnosis of papillary urothelial high-grade pT1 carcinoma. After that, intravesical BCG immunotherapy was initiated, according to protocol currently used in our institution, consisting of 6 weekly instillations in induction course of the ther-

Patients age	Symptoms of granulomatosis	Antituberculous therapy	Resolution; recurrence
68 years [12]	none	not used	complete; no recurrence
74 years [12]	none	not used	complete; no recurrence
52 years [13]	none	used	complete; no recurrence
49 years [16]	fever; chills	used	complete; no recurrence
47 years [21]	none	used	complete; no recurrence
N/A [22]	none	used	nephrectomy
67 years [23]	vomiting, flank pain	used	complete; no recurrence
67 years [24]	symptoms of glomerulonephritis	used	complete; no recurrence
68 years [25]	none	used	complete; no recurrence
77 years [26]	fever	used	complete; no recurrence
N/A [27]	none	used	complete; no recurrence
67 years [28]	fever; painful urination	used	complete; no recurrence
N/A [29]	asymptomatic	used	complete; no recurrence
79 years (our patient)	asymptomatic	used	complete; no recurrence

Table 1. Overview of published reports on patients treated with intravesical BCG immunotherapy. N/A – not applicable.

apy, followed by one-month break, and a further three instillations at monthly intervals. Upon completion of therapy with BCG, we re-examined the patient and, using ultrasound, found a change in the right kidney, resembling moth bites not seen on CT scan before TURBT (Figure 1a).

The patient was again admitted to our Clinic, for diagnostic evaluation and treatment of a newly discovered change in the right kidney (Figure 1b). Separate urine samples from each ureter for cytological analysis were obtained for three consecutive days. The presence of malignant cells was not detected in any of the specimens; however, signs of macrohematuria and inflammation were described in the cytological report. At the same time, we obtained a urine sample for mycobacterial culture on Löwenstein-Jensen medium, and additionally performed direct microscopy test with Ziehl-Neelsen stain, and they were both negative. The patient was afebrile, without any clinical signs of systemic infection, although he reported flu-like symptoms which were appearing only on therapy initiation and subsiding on symptomatic therapy. Additionally, CT-guided core-needle biopsy of the affected kidney was performed, and the specimen was sent for histopathological analysis, which revealed chronic necrotizing granulomatous inflammation. According to the histopathological findings, the diagnosis of renal tuberculosis was established (Figure 2) with signs of caseous necrosis (Figure 2b).

Antituberculotic therapy was initiated for 6 months. The initial empiric treatment was based on a 4-drug regimen: isoniazid, rifampin, pyrazinamide, and ethambutol. Upon completion of 2-month therapy, pyrazinamide and ethambutol were discontinued, and isoniazid 300 mg plus rifampin 600 mg were continued as a daily therapy for 4 more months, in addition to L-ornithine L-aspartate 150 mg, three times a day for liver protection, and ranitidine 150 mg, two times a day for the protection of gastric mucosa. Upon completion of antituberculotic therapy, control CT-scan (Figure 1c) was performed at follow-up, indicating regression of changes on the right kidney.

4. DISCUSSION

Most patients with the intermediate and high-risk NMIBC are candidates for immunotherapy with BCG. However, based on individualized risk assessment, other intravesical treatments, or cystectomy may be recommended. Adjuvant therapy with BCG reduces the risk of recurrence in high-grade NMIBC by 70%, compared to TURBT alone (10). Accordingly, BCG failure is related to high-grade tumor recurrence. Different BCG treatment protocols exist; however, in our institution, immunotherapy with BCG commonly consists of 6 weekly instillations in induction course of the therapy, starting at least 2 weeks after TURBT.

Since Morales et al. described the first use of BCG strain in intravesical instillations as an adjuvant treatment of superficial bladder cancer in 1976, the first reports on local and systemic complications appeared (14). The precise mechanism is still not clear, and understanding of the immune responses induced by BCG is required to develop more active and less toxic immunotherapy (4). However, intravesical adjuvant BCG immunotherapy appears to be relatively safe. The incidence of severe side-effects is low, and most patients are able to successfully complete the course of therapy. In a series of 2026 patients treated with intravesical BCG, <5% had significant adverse effects, including granulomatous prostatitis, pneumonitis, hepatitis, sepsis, and hypersensitivity reactions. Additionally, this study suggested that local adverse effects, such as cystitis, fever, hematuria, and prostatitis are the most frequent complications, whereas extravesical complications are rare (15).

Pérez-Jacoiste Asín et al. followed-up patients treated with intravesical BCG in the 6-year period. Among the total of 256 patients, 11 (4.3%) developed systemic BCG infection, with miliary tuberculosis as the most common form (6 cases). In the additional pooled analysis including the total of 282 patients, disseminated (34.4%), genitourinary (23.4%), and osteomuscular (19.9%) infections were found to be the most common presentations of the disease (15).

The incidence of renal side-effects of BCG immunotherapy ranges between 0.2% to 2%, with the development of a granulomatous renal mass in <0.1% of patients (10, 16, 17). Renal disease presentation varies from asymptomatic disease, over the symptomatic pyelonephritis, to nonspecific flank pain or urinary frequency (18).

Our patient remained asymptomatic after BCG treatment; however, he reported flu-like symptoms appearing during the course of therapy, on therapy initiation.

Only a small number of studies report cases with renal masses suggestive of BCG granulomas (12, 13, 16, 21-29). Patients in reviewed reports were treated for NMIBC, and were in age range of 47-77 years. The renal masses were usually unilateral, although there was a patient with bilateral granulomatous masses (26). In almost all cases, biopsy revealed granulomatous inflammation; yet there was a patient diagnosed with renal tuberculosis analyzing histopathological specimen after radical nephrectomy for suspected renal cell carcinoma (22). Most of the patients were asymptomatic and renal masses were found accidentally (12, 13, 21, 22, 25, 27, 29); however, some patients developed symptoms, such as fever and chills (16, 26, 28), vomiting and flank pain (23), painful urination (28), and glomerulonephritis (24). These symptoms usually appeared after third or fourth instillation of BCG in described cases. According to these reports, granulomatosis occurs regardless of presence of vesicoureteral reflux, since it affected both patients with (27), and without reflux (29). Patients were treated with antituberculotic therapy for at least 3 months to a maximum 1 year, while two asymptomatic patients were followed-up, without treatment. All patients were responsive to antituberculotic therapy, showing resolution of granulomatous masses and accompanying symptoms. However, in the two asymptomatic patients managed conservatively, without antituberculotic therapy, renal lesion also showed complete resolution without any scarring after 1 year, but not using antituberculotic therapy in these cases it is questionable. This mostly depends on incidence of tuberculosis, and management of complications after BCG therapy, which is determined by national and regional guidelines of tuberculosis control.

In cases of renal tuberculosis, urine and blood cultures are typically negative, and the diagnosis may be difficult to establish. It depends on many factors, including the number of organisms present, the handling of samples and culture technique. Siatelis et al. reported blood BCG DNA detection in 8.3% of the specimens taken 24 hours after each instillation and its amplification was associated with cases of self-limiting fever (32). Among the reviewed cases, MTBc was only isolated using PCR test in one patient (28). In our case, MTBc was not successfully isolated and identified from urine samples. However, a urine culture should be routinely performed in patients with suspected BCG infection in order to rule out the occurrence of urinary tract infection caused by conventional uropathogens, which represents a far more common cause of fever following genitourinary tract manipulation (30)

The analysis performed by Gonzales et al. revealed that BCG infections that occur after intravesical therapy could be divided into early- and late presentation of the disease. In their study, early presentation of the disease occurred in 25 of the total of 41 patients, within 3 months of the first dose, and presented with fever and generalized symptoms, and involvement of the liver and lungs, due to systemic infection by a relatively low-grade pathogen in an immunologically competent host. Generalized granulomatous response develops as a result of the proliferation of organisms introduced by repeated instillations of BCG and immunogenic response of the host. Among the 16 patients with late presentation of the disease, only 5 patients had localized symptoms involving the genitourinary tract. This late presentation is generated by the reactivation of infection after successful immunologic control of the early dissemination (20). While early-presentation disease is generally characterized by systemic manifestations, late-presentation disease is almost exclusive of genitourinary tract (21). In our case, it is impossible to determine whether it is early or late presentation of renal disease because the diagnosis was established by routine radiological examination during the asymptomatic period.

The possibility to identify MTBc in affected tissues is up to 30% of cases, especially with early presentation of the disease, supports the hypothesis that granulomas in BCG disease result from a hypersensitivity reaction, not an infection (9, 20). Nevertheless, the presence of antigens, such as live organisms or at least structural elements of dead bacteria, is required to produce a hypersensitivity reaction (20). Tuncer et al. have reported that only 9 of 126 patient samples (7.1%), analyzed by the PCR technique for detection of DNA Mycobacterium tuberculosis, were positive. These positive samples were obtained from 3 patients, who had major clinical side-effects (19). BCG immunotherapy is contraindicated in all immunocompromised patients, as well as the patients suffering an active infection. Complications of BCG immunotherapy, including renal granulomatosis cannot be predicted, although anatomical and functional variations of urinary system may contribute to higher incidence. It seems that the incidence of renal granuloma formation may be related to vesicoureteral reflux that commonly occurs after TURBT (11, 14). Ureteric stent insertion is considered to be an additional favorable factor for renal affliction. It should be noted that, in our case, the tumor was found near the right ureteral orifice.

In addition, we performed literature review for reported cases. However, the limitations of this review are a small number of published case reports on renal granulomatosis as a consequence of BCG immunotherapy for bladder cancer and unavailability of certain data in included reports.

The final treatment outcome depends on clinical, mycobacterial, environmental and pharmacological variables. In our case, a multidisciplinary approach was required, and the team included infectious disease specialists, pulmonologists, and radiologists, in addition to urologists. Antituberculous treatment was initiated immediately after receiving the biopsy report due to the high clinical suspicion for renal tuberculosis supported by the characteristic biopsy findings.

5. CONCLUSION

This case report emphasizes the importance of consistent implementation of follow-up protocol, which in-

cludes the high clinical suspicion for adverse effects of BCG treatment, and early post-BCG treatment radiological imaging. This approach guarantees the identification of lesions during the asymptomatic period and enables the proper treatment of the disease, although some asymptomatic patients may not benefit antituberculotic therapy. For that reason, further research is needed, to clarify whether antituberculotic therapy should be used in patients developing renal tuberculosis following BCG immunotherapy. Also, it is crucial to discern whether it is a primary renal or metastatic neoplastic process, to avoid unnecessary surgical interventions. However, the effect of resuming intravesical BCG immunotherapy in cases of appearance of adverse effects is still controversial. To reduce the incidence of adverse effects of BCG treatment for bladder tumors, an individualized approach is needed.

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- **Conflict of interest**: None declared.
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REFERENCES

1. Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. Eur Urol. 2017 Jan; 71(1): 96-108.
2. Dobruch J, Daneshmand S, Fisch M, Lotan Y, Noon AP, Resnick MJ. Gender and Bladder Cancer: A Collaborative Review of Etiology, Biology, and Outcomes. Eur Urol. 2016 Feb; 69(2): 300-310.
3. Woldu SL, Bagrodia A, Lotan Y. Guideline of guidelines: non-muscle-invasive bladder cancer. BJU Int. 2017 Mar; 119(3): 371-380.
4. Alexandroff AB, Nicholson S, Patel PM, Jackson AM. Recent advances in bacillus Calmette-Guerin immunotherapy in bladder cancer. Immunotherapy. 2010; 2: 551-560.
5. Herr HW. Intravesical bacillus Calmette-Guérin outcomes in patients with bladder cancer and asymptomatic bacteriuria. J Urol. 2012; 187(2): 435-437.
6. Redelman-Sidi G, Glickman MS, Bochner BH. The mechanism of action of BCG therapy for bladder cancer–a current perspective. Nat Rev Urol. 2014; 11: 153-162.
7. Prescott S, Jackson AM, Hawkyard SJ, Alexandroff AB, James K. Mechanisms of action of intravesical bacille Calmette-Guérin: local immune mechanisms. Clin Infect Dis. 2000 Sep; 31 Suppl 3: S91-93.
8. Saluja, M, Gilling, P., Intravesical bacillus Calmette–Guérin instillation in non-muscle-invasive bladder cancer: A review. Int. J Urol. 2018; 25: 18-24.
9. Brausi M, Oddens J, Sylvester R, Bono A, Van de Beek C, Van Andel G, et al. Side effects of Bacillus Calmette-Guerin (BCG) in the treatment of intermediate and high-risk Ta, T1 papillary carcinoma of the bladder: results of the EORTC genito-urinary cancers group randomised phase 3 study comparing one-third dose with full dose and 1 year with 3 years of maintenance BCG. Eur Urol. 2018; 65: 69-76.
10. Lamm DL. Complications of Bacillus Calmette-Guerin immunotherapy. Urol Clin North Am. 1992; 19: 565-672.
11. Mazeman E, Gilliot P. Vesicorenal reflux and intravesical chemotherapy. Prog Clin Biol Res 1989; 303: 517-522.
12. Al-Qaoud T, Brimo F, Aprikian AG, Andonian S. BCG-related renal granulomas managed conservatively: A case series. Can Urol Assoc J. 2015 Mar-Apr; 9(3-4): E200-E203.
13. Bhat S, Srinivasa Y, Paul F. Asymptomatic renal BCG granulomatosis: An unusual complication of intravesical BCG therapy for carcinoma of urinary bladder. Indian J Urol. 2015 Jul-Sep; 31(3): 259-261.
14. Morales A, Eidenger D, Bruce AW. Intracavitary Bacillus Calmette Guerin in the treatment of superficial bladder tumors. Journal of Urology. 1992; 116: 180-183.
15. Perez-Jacoiste Asin MA, Fernandez-Ruiz M, Lopez-Medrano F, Lumbreras C, Tejido A, San Juan R, et al. Bacillus Calmette-Guerin (BCG) infection following intravesical BCG administration as adjunctive therapy for bladder cancer: incidence, risk factors, and outcome in a single-institution series and review of the literature. Medicine. 2014; 93(17): 236-254.
16. Tran-Harding K, Nair RT, Ganesh H. Renal Granulomatosis Post Intravesical Bacillus Calmette–Guerin Therapy for Non-muscle-invasive Bladder Cancer. J Clin Imaging Sci. 2018; 8: 18.
17. Poletajew S, Zapała P, Radziszewski P. Safety and Efficacy of Intravesical Bacillus Calmette-Guérin Immunotherapy in Patients with Non-Muscle-Invasive Bladder Cancer Presenting with Asymptomatic Bacteriuria: A Systematic Review. Urol Int. 2017; 99: 1-5.
18. Ma W, Kang SK, Hricak H, Gerst SR, Zhang J. Imaging appearance of granulomatous disease after intravesical bacille Calmette-Guerin (BCG) treatment of bladder carcinoma. AJR Am J Roentgenol. 2009; 192: 1494-1500.
19. Tuncer S, Tekin MI, Ozen H, Bilen C, Unal S and Remzi D. Detection of Bacillus Calmette-Guerin in the Blood by the Polymerase Chain Reaction Method of Treated Bladder Cancer Patients. Journal of Urology. 1997; 158: 2109-2112.
20. Gonzalez OY, Musher DM, Brar I, et al. Spectrum of Bacille Calmette-Guérin (BCG) infection after intravesical BCG immunotherapy. Clin Infect Dis. 2003; 36: 140-148.
21. Sihra N, Diasuke N, Thurairaja R, Khan MS, Malde S. Renal Tuberculosis Following Intravesical Bacillus Calmette-Guérin for High-grade Non-muscle-invasive Bladder Cancer. Urology. 2017 Sep; 107: e3-e4. doi: 10.1016/j.urology.2017.05.035.
22. Wada Y, Sugiyama Y, Kikukawa H, Kuwahara T, Takahashi W, Takamiya T, Ueda S. Isolated renal tuberculosis following intravesical Bacillus Calmette-Guérin therapy for bladder cancer. Urol Int. 2004; 72(3): 257-260.
23. Senés AT, Badet L, Lyonnet D, Rouvière O. Granulomatous renal masses following intravesical bacillus Calmette Guérin therapy: the central unaffected calyx sign. Br J Radiol. 2007 Oct; 80(958): e230-3.
24. Selmi Y, Kheder-Elfekih R, Jebali H, Fatma LB, Smaoui W, Krid M, Beji S, Rais L, Zouaghi MK. A case of renal granulomatosis with polyangiitis following intravesical bacillus Calmette-Guérin therapy. Saudi J Kidney Dis Transpl. 2018 Jan-Feb; 29(1): 185-188. doi: 10.4103/1319-2442.225178.
25. Kuramoto T, Nishikawa T, Nanpou Y. A Case Report of Granulomatous Renal Masses Following Intravesical Instillation of Bacillus Calmette-Guérin Therapy. Hinyokika Kiyo. 2018 May; 64(5): 225-230. doi: 10.14989/ActaUrolJap_64_5_225.
26. Higashioka K, Miyake N, Nishida R, Chong Y, Shimoda S, Shimono N. Bilateral Granulomatous Renal Masses after Intravesical BCG Therapy for Non-muscle-invasive Bladder Cancer and Carcinoma in Situ of the Upper Urinary Tract: A Case Study. Kansenshogaku Zasshi. 2015 Jul; 89(4): 481-484.
27. De Boisgisson P, Roussel F, Leclerc D, Picquenot JM. Granulomatous renal mass during endovesical BCG therapy for bladder carcinoma Diagnosis by fine-needle aspiration. Urology. 1991 Jun; 37(6): 557-560.
28. Numao N, Goto S, Suzuki S. A case of renal tuberculosis following bacillus Calmette-Guerin instillation therapy for bladder cancer. Acta urologica Japonica. 2000 Mar; 46(2): 109-111.
29. Mody GN, Tran V, Landman J. BCGosis: Case Report of Intravesicular Bacille Calmette-Guérin Causing Upper Tract Granulomas Simulating a Renal Mass Without Evidence of Ipsilateral Vesicoureteral Reflux. Urology. 2009 Feb; 73(2): 444. e9-444.e10
30. Rodriguez F, Palou J, Martinez R, et al. Practical guideline for the management of adverse events associated with BCG installations. Arch Esp Urol. 2008; 61: 591-596.
31. Nascimento L, Linhas A, Duarte R. Disseminated Bacille Calmette-Guérin disease in immunocompetent adult patients. Braz J Infect Dis. 2016; 20(4): 408-409.
32. Siatelis A, Houhoula DP, Papaparaskevas J, Delakas D, Tsakris A. Detection of Bacillus Calmette-Guerin (Mycobacterium bovis BCG) DNA in Urine and Blood Specimens after Intravesical Immunotherapy for Bladder Carcinoma. Journal Clinical Microbiology. 2011; 49: 1206-1208.