European Review for Medical and Pharmacological Sciences 2024; 28: 4290-4297

Acute tubulointerstitial nephritis induced by intravesical bacillus Calmette-Guerin: a rare case of acute kidney injury

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Abstract. – BACKGROUND: Intravesical bacillus Calmette-Guerin (IVBCG) is considered the most optimal follow-up therapy for high-risk urothelial cancers. Although side effects such as cystitis, hematuria, and low-grade fever are common, they are generally mild. Severe reactions involving the kidneys are extremely rare. Here, we present the case of a 64-year-old male who developed acute renal failure due to acute tubulointerstitial nephritis (ATIN) following the first IVBCG administration. We have also conducted a literature review concerning IVBCG-induced nephritis.

CASE REPORT: A 64-year-old male presented to the Nephrology Department with acute kidney injury indicators and hematuria. The patient was suffering from high-grade papillary urothelial carcinoma. Transurethral resection of the bladder tumor was performed twice and followed by one IVBCG administration – two days before the symptoms occurred. The latest follow-up cystoscopy excluded the recurrence of the cancer. Laboratory tests displayed hyperkalemia, decreased glomerular filtration rate (GFR = 4 ml/min/1.73 m^2), elevated C-reactive protein, and acute metabolic acidosis. Urinalysis showed proteinuria (900 mg/24 h), leukocyturia, and erythrocyturia (20,402.7 per microliter). Renal ultrasound demonstrated slight bilateral renal enlargement. The patient was identified with acute tubulointerstitial nephritis (ATIN). The treatment involved intravenous methylprednisolone (250 mg three times every two days and then 125 mg four times every two days), followed by oral methylprednisolone (24 mg and 12 mg daily alternately for a week). Piperacillin and tazobactam, probiotics, and proton pump inhibitors were also administered. Hemodialysis was conducted three times. Two weeks after the admission, a significant improvement was observed: creatinine decreased to 2.04 mg/dl, and GFR increased to 33 ml/min/1.73 m^2. The patient was discharged with a recommendation to reduce the dose of glucocorticosteroids and continued in the outpatient clinic.

CONCLUSIONS: IVBCG may lead to acute kidney injury due to ATIN. Symptoms may occur as early as after the first IVBCG, contrary to previous reports. Patients should be regularly assessed for potential complications, including creatine level measurement, after each IVBCG treatment.

Key Words:
Urothelial cancer, Bacillus Calmette-Guerin immunotherapy, Acute tubulointerstitial nephritis, Acute kidney injury.

Introduction

Transitional cell carcinoma (TCC), alternatively known as urothelial carcinoma, stands as the prevailing form of bladder cancer, with the papillary subtype being the most predominant. Intravesical bacillus Calmette-Guerin (IVBCG) serves as the premier adjuvant treatment for high-risk, non-muscle-invasive bladder cancer and is acknowledged as the gold standard for preventing recurrence or progression. It has been utilized since 1976[1] and consists of six weekly administrations conducted a few weeks after resection, followed by subsequent instillations as maintenance therapy[2]. At least three cycles of maintenance BCG are necessary to significantly lower the recurrence rate[3]. The precise mechanism underlying IVBCG remains to

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be fully comprehended. However, it is believed that IVBCG triggers a strong innate immune response lasting several weeks that results in sustained adaptive immunity. The activation of urothelial and antigen-presenting cells fosters the infiltration of granulocytes and mononuclear cells near the tumor tissue through cytokine stimulation[4,5]. Other studies[6] suggest that trained immunity might be a key mechanism in mediating BCG immunotherapy. This understanding could pave the way for enhancing personalized BCG treatment strategies for non-muscle-invasive bladder cancer[6].

Several investigations over the years aimed to increase the treatment efficiency by replacing IVBCG. A comparison[7] of intravesical Mitomycin C (MMC) chemotherapy and IVBCG showed no difference in the recurrence rates. What is more, a significant number of MMC patients experienced severe cystitis or hypersensitivity reactions. In contrast, the vast majority of the patients receiving BCG therapy had only mild or moderate side effects[7,8]. IVBCG was also revealed to be more effective intravesical immunotherapy for superficial TCC of the urinary bladder compared to interferon alpha-2b9.

Despite its effectiveness, IVBCG does come with certain side effects. Dysuria and increased urinary frequency often accompany IVBCG as common side effects[10]. However, a large study[5] consisting of over 2,600 patients revealed that 95% of patients experienced no severe adverse effects. The predominant severe side effects included fever exceeding 39.5ºC (2.9%), hematuria (1.0%), granulomatous prostatitis (0.9%), granulomatous pneumonitis or hepatitis (0.7%), and arthralgia (0.5%). Additionally, extremely rare occurrences of epididymitis, severely disseminated IVBCG sepsis, rashes, ureteral obstruction, bladder contraction, and renal abscesses were reported, each with an incidence lower than 0.5%. Renal complications following IVBCG are extremely rare. However, they have been reported[11-21]. We report a 64-year-old male patient who experienced acute renal failure as a result of acute tubulointerstitial nephritis (ATIN) following the first IVBCG instillation. Among all reported cases, our case is characterized by the highest creatinine levels, nearly twice as much as the highest second one (12.14 mg/dl *vs.* 6.58 mg/dl). This underscores the severity of this patient's state and underlines the necessity of proper therapy when managing IVBCG renal complications.

Case Presentation

A 64-year-old male presented to the Nephrology Department in January 2023 with acute kidney injury indicators and hematuria. The symptoms had persisted for several days before.

The patient had a history of high-grade papillary urothelial carcinoma. As a result, transurethral resection of bladder tumor (TURBT) was performed twice (September and November 2022). Afterward, he underwent IVBCG immunotherapy. It is worth noting that it had been performed in January 2023, two days before the symptoms occurred. The latest follow-up cystoscopy excluded the recurrence of the cancer. Past medical history included hypertension, chronic ischemic heart disease, and Warthin's tumor of the parotid gland (treated surgically in 2022). The medications involved were telmisartan, nebivolol, and atorvastatin.

As shown in Table I, laboratory tests displayed hyperkalemia (6.03 mmol/l), high serum creatinine concentration, markedly decreased glomerular filtration rate (GFR = 4 ml/min/1.73 m^2), high serum urea concentration, elevated C-reactive protein, and acute metabolic acidosis. Urinalysis showed proteinuria, leukocyturia, and massive erythrocyturia (20,402.7 per microliter). Renal ultrasound demonstrated slight bilateral renal enlargement.

The patient was identified with ATIN and treated immediately. First and foremost, intravenous methylprednisolone (250 mg three times every two days and then 125 mg every two days four times) was administered. This was followed by oral methylprednisolone (24 mg and 12 mg daily alternately for a week), as Figure 1 demonstrates. Due to severe renal dysfunction, hemodialysis was required three times. The treatment also required intravenous piperacillin and tazobactam (4.5 g, 1-0-1 for 14 days), proton pump inhibitor (40 mg, 1-0-0), and probiotics. Telmisartan was replaced by lercanidipine (10 mg, 1-0-0) and doxazosin (4 mg, 0-0-1) was introduced due to increased risk of hyperkalemia and further renal suppression.

Three weeks after the admission, a significant improvement was observed: creatinine dropped to 2.04 mg/dl and GFR increased to 33 ml/min/1.73 m^2 (Figure 2). Several laboratory parameters normalized within the reference range, including potassium, C-reactive protein, and gasometry parameters. The patient was discharged with a recommendation to reduce the dose of glucocorticosteroids and continued in the outpatient

Table I. Selected patient's laboratory tests (performed during admission and three weeks after admission).

Laboratory test	Results on admission [unit]	Results 3 weeks after admission [unit]	Reference range [unit]
Potassium (serum)	6.03 [mmol/l]	4.77 [mmol/l]	3.5-5.1 [mmol/l]
Creatinine (serum)	12.14 [mg/dl]	2.04 [mg/dl]	0.7-1.2 [mg/dl]
Urea (serum)	390 [mg/dl]	55 [mg/dl]	17-50 [mg/dl]
GFR	4 [ml/min/1.73 m^2]	33 [ml/min/1.73 m^2]	>90 [ml/min/1.73 m^2]
CRP	38.9 [mg/l]	1.5 [mg/l]	<5 [mg/l]
Protein (urine)	100 [mg/dl]	15 [mg/dl]	<15 [mg/dl]
Leukocyte (urine)	570.9 [per microliter]	Absent	<13.2 [per microliter]
Erythrocyte (urine)	20,402.7 [per microliter]	Absent	<13.6 [per microliter]
pH (capillary)	7.25	7.41	7.35-7.45
$PaCO_2$ (capillary)	18.8 [mmHg]	34.8 [mmHg]	35-45 [mmHg]
Bicarbonate (capillary)	8 [mmol/l]	21.4 [mmol/l]	21-27 [mmol/l]
Base excess (capillary)	-17.7 [mEq/l]	-2.2 [mEq/l]	-2.3 to 2.3 [mEq/l]

GFR = glomerular filtration rate, CRP = C-reactive protein, $PaCO_2$ = arterial carbon dioxide pressure.

clinic. He was also advised to perform a control laboratory test a month after leaving the Nephrology Department.

Discussion

Our patient was identified with ATIN as an IVBCG complication. ATIN often results in acute renal failure, and it arises from immune-mediated injury to the tubulointerstitial region. ATIN is distinguished by the infiltration of inflammatory cells and edema, impacting both the tubules and the interstitial tissues of the kidney. The predominant inflammatory cell types involved are primarily T-lymphocytes ($CD8^+$), along with mononuclear cells, macrophages, and eosinophils[22]. BCG was found[23] to be the second most common cause of ATIN among various chemotherapeutics, including ifosfamide, tyrosine kinase inhibitors, and pemetrexed.

It is the first reported case that describes severe renal nephritis following the first dose of IVBCG. The toxicity has been reported[5] to be notably correlated with the number of administrations, as severe side effects have only been noted following a few administrations. This notion is supported by our literature review (Table II) – grave compli-

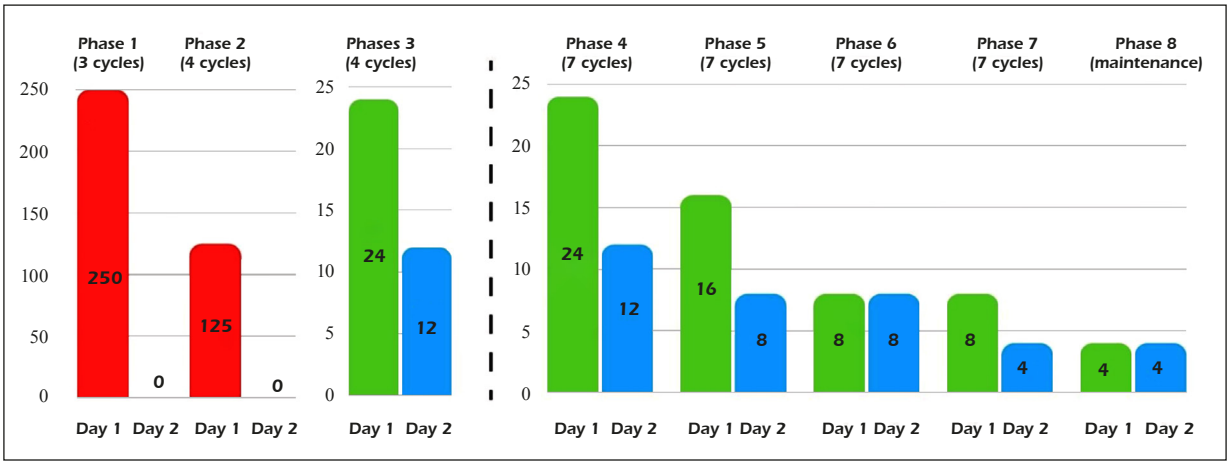

Figure 1. Steroid treatment. Red colour (Phases 1-2) represents intravenous methylprednisolone administration, while colours green and blue represent oral methylprednisolone administration. The treatment was divided into subsequent phases, each phase consisted of subsequent cycles, while each cycle consisted of 2 days. Phase 8 signifies maintenance dose. The dashed line marks the end of hospitalization. Doses are shown in miligrams. For instance, phase 4 consisted of 7 cycles and lasted 14 days, during every 'odd' day of the cycle (1., 3., 5., …) 24 mg of methylprednisolone were administered, while during every 'even' day (2., 4., 6., …) the daily dose consisted of 12 mg of methylprednisolone.

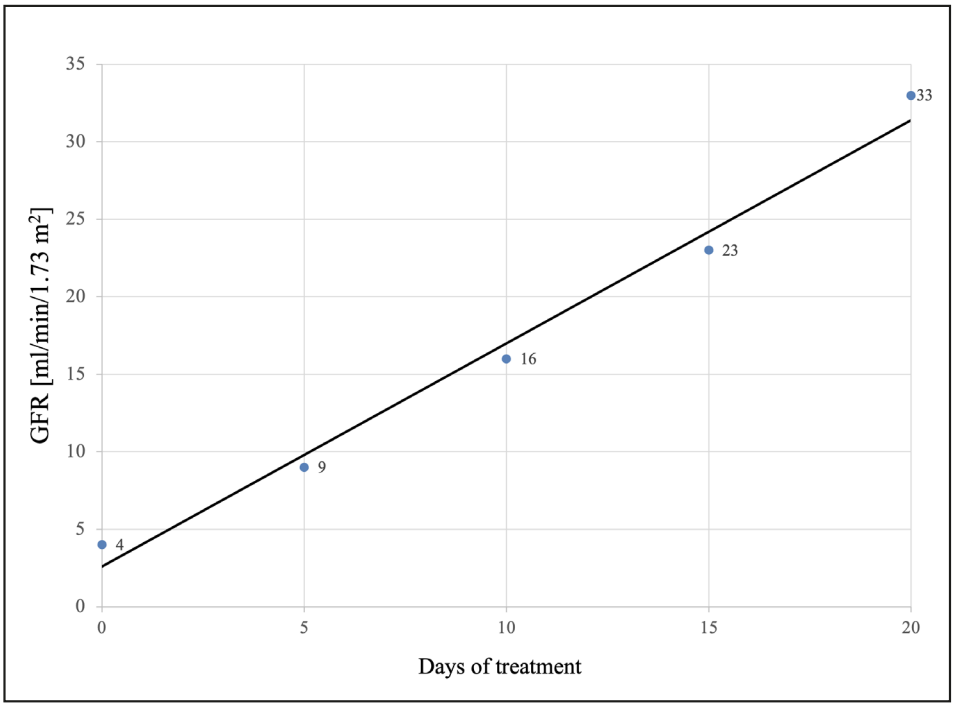

Figure 2. Changes in glomerular filtration rate (GFR) during treatment.

Table II. Literature review concerning renal inflammation incidents following IVBCG.

Reference	Age	Sex	Renal histology	No. BCG administration	Therapy	Creatinine before treatment (mg/dL)	Creatinine after treatment (mg/dL)
Modesto et al[11]	70	M	Epithelioid granulomas with giant cells	11	ATT (I) + P	3	1.8
Modesto et al[11]	70	M	Interstitial fibrosis with diffuse mononuclear infiltrates without granulomas, mesangial IgM and C3 deposits	18	ATT (I + E; 8 months) + P (single course), HD (2 months)	5.4	NAa
Modesto et al[11]	48	M	Diffused mesangial proliferation with moderate interstitial fibrosis, without granulomas, subendothelial IgG and C3 deposits	3	ATT (I+R; 6 months)	1.3	NA
Fry et al[12]	72	M	Acute tubulointerstitial nephritis without granulomas; 30% of glomeruli were abnormal, with focal segmental mesangial proliferation without necrosis	3	ATT (I+R), P	6.31	1.97

Continued

Table II *(Continued)*. Literature review concerning renal inflammation incidents following IVBCG.

Reference	Age	Sex	Renal histology	No. BCG administration	Therapy	Creatinine before treatment (mg/dL)	Creatinine after treatment (mg/dL)
Kennedy et al[13]	72	F	Diffuse tubulointerstitial nephritis, patchy inflammatory infiltrate included lymphocytes, plasma cells, histiocytes and a moderate number of eosinophils, tubular degeneration, intramural lymhocytes, non-necrotizing granulomas present, mild interstitial fibrosis, mesangial deposits of IgM and C3	5	P	3.13	1.7
Jose Manzanera Escribano et al[14]	76	M	Acute interstitial nephritis, diffuse interstitial cellular infiltrate of lymphocytes, plasma cells, and eosinophils, without granulomas	4	MP (3 days), P	6.58	3.5
Mohammed et al[15]	73	F	Interstitial inflammation with moderate lymphocytic infiltration, eosinophils and a non-caseating granuloma	16	P	4.04	NA
Soda et al[16]	67	F	Granulomatous nephritis contai multinucleated giant cells and central necrosis	4	ATT (PY + I + E + R)	NA	NA
Singh et al[17]	54	M	Membranous glomerulonephritis, diffuse thickening of basement membrane without significant proliferative activity, capillary wall and glomerular deposits of IgM, C3, and IgG	6	P	NA	NA
Tamzali et al[18]	79	M	No renalbiopsy	2	ATT (I + E + R)	4.38	NA
Tsukada et al[19]	80	M	Crescentic and fibrinoid necrotizing glomerulonephritis in 20% of glomeruli, IgA deposits mainly in the mesangium	4	MP (3 days), P, 3 plasmapheresis sessions, HD	3.6	3.6
Garcia et al[20]	70	M	No biopsy, pyelonephritis	5	I (3 months)	NA	NA
Bijol et al[21]	76	M	IgA nephropathy, extensive necrotizing granulomatous inflammation	NA	NA	NA	NA

ATT = anti-tuberculosis treatment, I = isoniazid, PY = pyrazinamide, E = ethambutol, HD = hemodialysis, P = prednisone, MP = methylprednisolone, NA = not available.

cations usually arise between the third and fifth course – it has never been reported after the first administration. Since the complication may occur so soon, it is especially important to be aware of possible renal complications of IVBCG. We recommend conducting regular follow-up appointments after each IVBCG instillation. Patients ought to be examined alongside basic laboratory tests, including serum creatinine levels.

IVBCG-induced ATIN also seems to occur more frequently in the elderly (69.35 ± 8.65 years). This corresponds well with the literature data as the prevalence of ATIN in general has risen in recent years, particularly among seniors. This increase is likely linked to a higher incidence of drug-induced ATIN[24]. However, our review suggests increased frequency in males (77%). At the same time, available epidemiological findings[24,25] concerning ATIN, in general, indicate either no significant difference in incidence between males and females or a slight female preference. More investigations are required to determine the cause of this phenomenon.

There is a discernible cause-and-effect association between the administration of IVBCG therapy in our case and the onset of ATIN. The patient displayed typical acute kidney indicators (decreased urine production, edema, confusion, lethargy) for two days following IVBCG administration. While ATIN typically arises in patients who have been exposed to a variety of medications[26], no correlation has been reported between the use of telmisartan/nebivolol/atorvastatin and the development of ATIN. ATIN can also occur from infections, autoimmune and systemic diseases, environmental exposures, and some idiopathic causes[22]. However, the fact that the symptoms followed the first IVBCG administration in a short period of time makes this explanation highly unlikely in our case.

The renal function gradually improved after steroid administration. Although there was some variability in the dosage and duration of steroid therapy, the standard ATIN treatment regimen involves intravenous methylprednisolone followed by oral prednisone[22]. This regularity is confirmed by our literature review – in the majority of cases, prednisone or methylprednisone (or both) are involved. It has been documented[23] that steroid use seemed to improve outcomes in ATIN, compared to conservative treatment. Another aspect is the use of anti-tuberculosis treatment in such cases: it has been introduced in 6 of 13 reported nephritis cases[11-21]. Our case lacked notable systemic signs and involvement of other organs and showed no evidence of mycobacterial infection. Therefore, we decided not to administer an anti-tubercular regimen. As mentioned above, it is unclear whether tuberculostatic drugs should be administered to patients with similar cases. However, observational studies[27,28] report that administering isoniazid prophylactically during IVBCG does not result in a reduction in severe side effects of IVBCG.

Conclusions

IVBCG, a renowned urothelial carcinoma treatment method, may induce severe acute renal failure due to ATIN. Symptoms may occur as soon as after the first IVBCG, as in our case, contrary to the previous reports. This highlights the need for regular assessment of potential complications, including renal complications, after each IVBCG. This ATIN subtype appears to have a higher incidence in males and elderly people. In the case of IVBCG-induced ATIN, the treatment should consist of steroids: intravenous methylprednisolone followed by oral prednisolone. As long as there are no signs of notable systemic signs, involvement of other organs, or mycobacterial infection evidence, there are no recommendations for anti-tuberculotic treatment.

Conflict of Interest
The authors declare that they have no conflict of interest to disclose.

Ethics Approval
Not applicable.

Informed Consent
The patient provided written informed consent for permission to publish this case report.

Funding
This research received no external funding.

Authors' Contribution
Conceptualization: Piotr Tyburski and Jędrzej Sikora. Investigation: Piotr Tyburski and Jędrzej Sikora. Re-sources: Zofia Niemir. Writing (original draft preparation): Piotr Tyburski and Jędrzej Sikora. Writing (review and ed-

iting) Miłosz Miedziaszczyk, Zofia Niemir and Ilona Idasiak-Piechocka. Visualization: Piotr Tyburski and Jędrzej Sikora. Supervision: Ilona Idasiak-Piechocka. Project administration: Miłosz Miedziaszczyk. All authors have read and agreed to the published version of the manuscript.

AI Disclosure

No form of generative artificial intelligence (AI) for writing the manuscript has been used.

Acknowledgments

We thank the patient for sharing his time and medical data for this article's purposes.

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Data Availability

Data is available on request from the authors.

Congress Presentation

The results of our case report were presented at the 17th Antwerp Medical Students' Congress (AMSC), which was held from September 11 to 14, 2023, in Antwerp, Belgium, where our abstract was previously accepted.

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