


Disseminated BCG sepsis following intravesical therapy for Bladder Carcinoma: A case report and review of literature

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ABSTRACT

Intravesical instillation of Bacillus-Calmette-Guérin (BCG), a live-attenuated-strain of *Mycobacterium bovis*, is an established treatment for superficial bladder carcinoma. Although generally well tolerated, 1/15,000 patients can develop life-threatening disseminated-BCG-infection typically soon after the procedure, a condition colloquially termed BCG-osis. Side-effects of intravesical BCG instillation including fever, chills, fatigue are common but BCG-osis is rare and severe, often-times requiring intensive care unit admission and triple anti-TB-therapy as in this case. It is therefore important for clinicians to recognize this possibility as the absence of specific signs and symptoms, coupled with the fastidious nature of the Mycobacteria, pose a diagnostic dilemma in the acute setting. Our case highlights this potential rare iatrogenic side effect of intravesical BCG treatment and the risk associated with non-treatment of BCG-osis.

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1. Introduction

Bacille Calmette Guérin (BCG) is a live-attenuated *Mycobacterium bovis* bacillus originally used for vaccination against tuberculosis. Its use in the management of vesical cancer has grown over the years after Morale et al. published the first case in 1976 [1]. BCG immunotherapy for non-invasive (superficial) bladder cancer is a standard adjuvant treatment for bladder cancer following transurethral resection of bladder tumor (TURBT) to minimize its recurrence and progression [2,3]. However, despite its effectiveness and safety, about 5% of patients still experience adverse effects such as pneumonitis, hepatitis and sepsis [4–6]. We present a patient with the rare complication of disseminated BCG sepsis following intravesical BCG therapy.

2. Case presentation

A 78-year-old man with high-grade T1 urothelial carcinoma status post-transurethral resection of bladder tumor who had been on once-weekly intravesical BCG instillation for 2 months presented to the emergency room (ER) with fever, rigors and altered mental status. He also reported shortness of breath but denied cough or chest pain. He had no urinary or gastrointestinal symptoms. He had his most recent BCG instillation done the day before the index presentation. Vital signs revealed a temperature of 102.8 F, pulse rate of 92/min, respiratory rate of 40/min and blood pressure 78/45 mmHg with oxygen saturation of 93% on ambient air.

On physical examination, he appeared toxic, dehydrated and in respiratory distress. Chest examination revealed asymmetric chest expansion with dullness to percussion, decreased tactile fremitus on the left side with reduced air entry on auscultation. The cardiovascular examination was however unremarkable.

2.1. Investigations

Complete blood count revealed marked leukocytosis with a white cell count of 27,200/microliter (Normal 4,800–12,000/microliter) and hemoglobin of 11.5 g/dL (Normal 14.0–17.5 g/dL). Lactate was markedly elevated at 7.8 meq/L (Normal 0.6–1.4 meq/L) and arterial blood gas revealed high anion gap metabolic acidosis. Basic metabolic panel revealed creatinine of 2.31 mg/dL from normal baseline (Normal 0.6–1.3 mg/dL) and blood urea nitrogen of 28 mg/dL (Normal 7–25 mg/dL). Sputum culture with gram stain showed normal oral flora. Urinary streptococcal and legionella antigens were negative. Chest X-ray on admission revealed left basilar pneumonia with small left pleural effusion. CT head showed no acute intracranial abnormalities. The preliminary blood culture result was negative for any microorganisms.

2.2. Treatment

Due to altered mental status with increased work of breathing and acute hypoxemic respiratory failure,

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patient was intubated and placed on ventilation in the medical intensive care unit. He was commenced on vasopressors and intravenous Vancomycin and Piperacillin-Tazobactam for septic shock thought to be secondary to community-acquired pneumonia and possible urinary tract infection. Despite the completion of several courses of broad-spectrum antibiotics, he continued to have low-grade pyrexia and failed to improve clinically. Suspicion for rarer etiologies such as systemic BCG dissemination began to grow and blood cultures for acid-fast bacilli initially obtained on admission returned positive for acid-fast bacilli, specifically *Mycobacteria bovis* in the two sets of samples thus confirming our suspicion. Broad-spectrum antibiotics were immediately discontinued, and he was commenced on triple therapy with Isoniazid 300 mg daily, Ethambutol 1600 mg daily and Rifampicin 30 mg daily. He improved clinically and was discharged 5 days later to complete 2 months of triple therapy with Isoniazid, Rifampicin and Ethambutol followed by 4 months of maintenance therapy with Rifampicin and Isoniazid. He was planned to return for follow up with the infectious disease team.

3. Discussion

The mechanism by which BCG exerts its antitumor property is not completely understood. However, studies suggest a local immune response to the *Mycobacterium complex* in immune-competent individuals. The inflammatory response mediated by macrophages and T-Helper cells increases pro-inflammatory cytokines and expression of adhesion molecules on the bladder tumor cells which are believed to be responsible for its antitumor effect [7]. The *Mycobacterium bacillus* is also known to attach to specialized fibronectin protein in the bladder which aids its internalization into the tumor cells, thereby producing structural changes and expression of surface molecules on tumor cells with consequent cytokines and direct cell-to-cell cytotoxicity [8].

Intravesical BCG treatment is relatively safe but not without occasional complications. Local complications are by far more common and account for about 62.8% of cases, with BCG-induced cystitis being the commonest [9]. Frequency and dysuria, macroscopic hematuria, bladder contracture, ureteral obstruction, prostatitis and epididymo-orchitis can all occur [10]. Rarely, serious systemic complications can arise in the form of sepsis, pneumonitis, granulomatous hepatitis, reactive arthritis and even death from disseminated BCG can arise in less than 5% of cases [5,11]. These complications may be classified as early or late depending on the timing from intravesical instillation. Early complications present within 3 months while late complications occur after 3 months [12].

The risk of BCG sepsis increases in the presence of traumatic catheterization, macroscopic hematuria, urinary tract infection, instillation within 30 days of TURBT, and concomitant use of immunosuppressive therapy [10,13]. The majority of these factors represent a breach of the urothelial barrier enhancing hematogenous spread and dissemination of the *Mycobacteria*. BCG sepsis can occur acutely following intravesical instillation but more commonly are cases of sepsis several weeks to months where suspicion of BCG as the culprit is less likely and this tends to delay diagnosis. This is unsurprising as studies have shown the persistence of acid fast *Mycobacteria* in urine and bladder of patients up to 16.5 months after completing intravesical instillations of BCG [14]. Typical symptoms of BCG sepsis are not different from sepsis due to other causes. High-grade pyrexia, chills and rigors, altered mental state, respiratory distress, hypotension, coagulopathy and jaundice can be seen in these patients [15]. Although no standard guidelines exist for the management of BCG sepsis, the trial of antimycobacterial therapy should be initiated once it is suspected and should be continued for 3–6 months. It is also reasonable to suspend further courses of intra-vesical BCG therapy. Systemic steroid therapy has shown to be of benefit and should be used in conjunction with antituberculosis therapy followed by gradual tapering [16].

4. Learning points

- High index of suspicion is required for the diagnosis of BCG related sepsis.
- Negative blood cultures should not be used to exclude diagnosis since this is only positive in about 41% of cases.
- Anti-mycobacterial therapy should be commenced as soon as the diagnosis is suspected.

Disclosure statement

The authors declare no conflicts of interest.

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References

- [1] Morales A, Eiding D, Bruce A. Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. *J Urol.* 1976;116(2):180–182.
- [2] Sylvester RJ, van der MEIJDEN AP, Witjes JA, et al. 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.* 2005;174(1):86–91.

- [3] Hussain MH, Wood DP, Bajorin DF, et al. Bladder cancer: narrowing the gap between evidence and practice. *J clin oncol*. 2009;27(34):5680.
- [4] To U, Kim J, Chia D. Disseminated BCG: complications of intravesical bladder cancer treatment. *Case Rep Med*. 2014;2014:1–3.
- [5] Naudžiūnas A, Juškaitė R, Žiaugrytė I, et al. Tuberculosis complications after BCG treatment for urinary bladder cancer. *Medicina (B Aires)*. 2012;48(11):82.
- [6] Ziegler J, Ho J, Gibson IW, et al. Disseminated Mycobacterium bovis infection post-kidney transplant following remote intravesical BCG therapy for bladder cancer. *Transplant Infect Dis*. 2018;20(5):e12931.
- [7] Prescott S, Jackson AM, Hawkyard SJ, et al. Mechanisms of action of intravesical bacille Calmette-Guerin: local immune mechanisms. *Clin Infect Dis*. 2000;31(Supplement_3):S91–S93.
- [8] Zhao W, Schorey JS, Bong-Mastek M, et al. Role of a bacillus calmette-guérin fibronectin attachment protein in BCG-induced antitumor activity. *Int J Cancer*. 2000;86(1):83–88.
- [9] Brausi M, Oddens J, Sylvester R, 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*. 2014;65(1):69–76.
- [10] Decaestecker K, Oosterlinck W. Managing the adverse events of intravesical bacillus Calmette–Guérin therapy. *Res Rep Urol*. 2015;7:157.
- [11] Hogarth M, Thomas S, Seifert M, et al. Reiter's syndrome following intravesical BCG immunotherapy. *Postgrad. Med J*. 2000 December;1:76.
- [12] Lukacs S, Tschobotko B, Szabo N, et al. Systemic BCG-osis as a rare side effect of intravesical BCG treatment for superficial bladder cancer. *Case Rep Urol*. 2013;2013:1–3.
- [13] Viana L, Oliveira e Castro, PdTd, Almeida, RDS, and Silva, RSPd, *Sepse fatal após instilação intravesical de BCG: relato de caso*. *Rev Bras Ter Intensiva*. 2011;23(1):104–107.
- [14] Bowyer L, Hall R, Reading J, et al. The persistence of bacille Calmette-Guérin in the bladder after intravesical treatment for bladder cancer. *Br J Urol*. 1995;75(2):188–192.
- [15] Figueiredo C, Póvoas D, Alves C, et al. Septic shock after intravesical BCG instillation—A case report. *Adv Infect Dis*. 2013;3(4):243–247.
- [16] Liaw F, Tan YY, Hendry D. Systemic BCG-osis following intravesical BCG instillation for bladder carcinoma. *Clin Case Rep*. 2017;5(10):1569.