Disseminated Bacillus Calmette-Guérin (BCG) infection presenting with fever and pancytopenia

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Consent Statement
Written informed consent was obtained from the patient to publish this report in accordance with the journal’s patient consent policy

ABSTRACT

Intravesical instillation of bacillus Calmette-Guérin (BCG) an attenuated live strain of Mycobacterium bovis has been used in the treatment of superficial urothelial carcinoma of the bladder. Although well tolerated, it can cause local and systemic complications. We report the case of an adult male treated for carcinoma in situ of the bladder with this immunotherapy, who presented, one year later, with fever and progressive pancytopenia. After an extensive workup, the bone marrow biopsy showed non-caseating granulomas and cultures grew Mycobacterium bovis. He had a favorable response to the standard therapy for M. bovis infection. Disseminated BCG infection is a rare complication and often implies a challenging diagnostic workup. This case highlights the importance of early recognition of this serious complication in patients with BCG exposure for proper treatment.

KEYWORDS
Intravesical instillation; bacillus Calmette-Guérin; disseminated BCG infection; pancytopenia.

INTRODUCTION

Bacillus Calmette-Guérin (BCG) is a live attenuated strain of Mycobacterium bovis, a member of the Mycobacterium tuberculosis complex. Since its approval by Food and Drug Administration, in 1990, intravesical BCG instillation has become a first-line adjuvant immunotherapy for the treatment of superficial urothelial carcinoma of the bladder after transurethral resection (TUR). It has shown a decrease in the recurrence rates, delay of disease progression and prolonged survival compared to TUR as monotherapy. Although well tolerated without significant morbidity, BCG instillation can cause local and systemic side effects. The...
The most serious complication is systemic infection and progressive multisystemic organ failure [3]. We report a case of culture proven BCG infection with bone marrow involvement presenting with fever and pancytopenia.

**CASE DESCRIPTION**

A 69-year-old man was admitted with intermittent fever (maximum of 39°C), weight loss of 10 Kg, anorexia and malaise in the previous month. He denied any respiratory, genitourinary or gastrointestinal symptoms. He had a medical history of superficial urothelial carcinoma of the bladder treated with transurethral resection (TUR) followed by intravesical BCG instillations every 6 weeks, completed 1 year earlier, with no evidence of cancer recurrence.

Upon admission, he was febrile (auricular temperature of 38°C) but the rest of his physical examination was normal. Laboratory blood tests showed progressive pancytopenia (nadir values: hemoglobin of 8.3 g/dL, 1950 leukocytes, 74000 platelets); hepatic cholestasis (alkaline phosphatase of 286 UI/L, gamma-glutamyl transpeptidase of 514 UI/L); lactate dehydrogenase of 249 UI/L and C-reactive protein of 44.7 mg/L. Repeated blood and urine cultures were sterile. M. tuberculosis DNA in urine was negative. Serological tests for HIV, cytomegalovirus, epstein-barr, hepatitis B and C, bartonellosis, brucellosis, Q fever were also negative as was a rheumatological antibody panel. A thoraco-abdomino-pelvic CT scan only revealed hepatosplenomegaly. An echocardiogram showed no vegetations. A bone marrow biopsy was performed and revealed non-caseating granulomas (Figure 1) with negative acid-fast bacillus (AFB) and fungal stains. The *Mycobacterium tuberculosis complex* PCR was negative. Despite a negative PCR and a pending AFB culture, the medical team made a presumptive diagnosis of disseminated BCG infection considering the history of intravesical BCG therapy and the histological findings in the bone marrow. The patient started on isoniazid 300mg id, rifampin 600mg id and ethambutol 1200mg id with clinical and analytical improvement, and was discharged one week later. After 45 days of incubation, the AFB culture from the bone marrow aspiration grew *Mycobacterium bovis* thus confirming the clinical diagnosis. The patient presented full recovery after 12 months therapy.

**DISCUSSION**

Intravesical instillation of BCG remains the most adequate therapy for superficial urothelial carcinoma of the bladder, ensuring cure rates of up to 80%. It is thought that BCG produce a local immune response which results in the production of proinflammatory cytokines and influx of leucocytes, ultimately result to lysis of tumor cells. Its side effects may include urinary frequency (71%), cystitis (67%), fever (25%) and hematuria (23%), that in most cases resolve spontaneously within 48h and can be managed symptomatically [4]. Other more serious side effects may be granulomatous hepatitis and pneumonitis occurring in 0.7% of the cases, sepsis in 0.4%, arthralgias in 0.5% and cytopenias in 0.1%. Less than 1% of the patients evolved with disseminated BCG infection [5]. The exact pathogenesis underlying the systemic infection occurring after instillation of intravesicular BCG is not fully understood. It is thought that local inflammatory process results in disruption of the uroepithelial bladder cells thereby allowing organisms to disseminate hematogenously or via the lymphatic system. It has also been reported that BCG can persist in the bladder and spread hours to months, and even years, following the completion of the therapy [6]. Until the date, was not possible to identified risk factors associated to disseminated BCG infection, including the time from TUR, the number of BCG instillations or associated immunosuppression [7]. Disseminated BCG should be suspected in every patient with previous intravesical BCG therapy that presents with fever and/or organ disfunction, with or without symptoms in the genitourinary tract. However, establishing the diagnosis is difficult: regardless of a history of BCG exposure, all other causes of fever must be excluded, although, clinical improvement after treatment initiation reinforces the diagnosis. Histologic examination of biopsies of different possible involved organ usually demonstrates granulomatous inflammation but only the microbiologic tests confirm the diagnosis [7]. Disseminated BCG infection should be treated with antituberculosis therapy. The most common regimen consisted of isoniazid, rifampin and ethambutol. Corticosteroid use is not consensual and is usually reserved for severe cases that evolve with respiratory failure [7].

**CONCLUSIONS**
The authors report a rare complication and the challenging diagnostic workup in a patient with minimal symptoms and unspecific analytical changes. An early suspicion and thorough assessment are key to a prompt treatment but other infections, inflammatory and neoplastic conditions must first be ruled out. In this case, the clinical suspicion was supported by bone marrow histology and good clinical and laboratorial response upon institution of therapy.

**AUTHOR CONTRIBUTIONS**

Author 1: Involved in patient care, data and information collection and main author of the manuscript.

Author 2: Involved in patient care and manuscript review.

Author 3: Involved in patient care and manuscript review.

Author 4: Involved in patient care and manuscript review.

Author 5: Involved in patient care and manuscript review.

Author 6: Involved in manuscript review.

Author 7: Involved in manuscript review.

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**ETHICAL APPROVAL**

The authors have no ethical conflicts to disclose.

**CONSENT**

Informed consent was obtained for publication of this case report.

**REFERENCES**


