

# Fatal Outcome Due to Sepsis by Mycobacterium Bovis Six Years After BCG Intravesical Instillations

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## Abstract

Bacillus Calmette-Guerin (BCG) in intravesical instillations is the reference treatment for urothelial carcinoma with a high risk of progression. Morbidity secondary to intravesical BCG may present both locally and systemically. Most patients suffer a self-limited irritative voiding syndrome. Prevention of these complications requires implementing rules of good practice for the instillations. The undesirable side effects should be recognized early. Their treatment should be rapid and adapted to the patient. Besides the commonly seen side effects of intravesical BCG instillations, very rare complications have been reported. In some patients, infection appears early (within 3 months after instillation) and is characterized by generalized symptoms, with pneumonitis and hepatitis. Late-presentation disease occurs more than 1 year after the first BCG treatment and usually involves focal infection of the genitourinary tract (the site at which bacteria were introduced) and/or other sites that are typical for reactivation of mycobacterial disease, such as the vertebral spine or the retroperitoneal tissues. Non caseating granulomas are found in the majority of cases, whether early or late. Most patients respond to treatment with antituberculous drugs; in early-presentation disease, when features of hypersensitivity predominate, glucocorticosteroids are sometimes added. Late localized infection often requires surgical resection.

**Keywords:** Bacillus Calmette-Guerin; Instillations; Transitional cell carcinoma; Septicaemia

## Introduction

Bacillus Calmette-Guerin (BCG) is a live attenuated strain of Mycobacterium bovis that has been used to treat transitional-cell carcinoma since 1976 [1] and has been reported to eradicate disease in more than 70% of patients with in situ and stage I disease [2]. Intravesical therapy with BCG is generally considered safe, however, serious complications including hematuria, granulomatous pneumonitis, suppurative lymphadenitis, distant intramuscular and bone abscesses, hepatitis, and life-threatening BCG sepsis are well known [3], although late bacteriuria and sepsis due to BCG instillations, have not been described yet. The reported incidence of other than minor complications is under 5% [4]. Recommended treatment for disseminated BCG disease includes a combination of antituberculous medications (with the exception of pyrazinamide, to which BCG is typically resistant) and a tapering course of steroids [5].

These complications are an absolute contraindication for further BCG instillations. Despite its toxicity, the risk-benefit ratio favors the use of BCG in patients who have moderate and high risk tumors [2]. There are not differences of toxicity between Connaught and Pasteur strain in intravesical BCG-therapy of superficial bladder tumors [6].

Compliance with this treatment is altered by its potentially serious locoregional or general side effects. Prevention of these complications requires implementing rules of good practice for the instillations. The undesirable side effects should be recognized early. Their treatment should be rapid and adapted to the patient. In order to prevent complications from BCG immunotherapy, a French study showed that side effects were significantly reduced by administration of ofloxacin after each instillation of BCG. The number of side effects requiring antitubercular treatment was also reduced in the patients in this study who had received ofloxacin [7]. Puigvert Foundation in Spain developed a practical guideline for the management of the complications followed BCG instillations [8].

Although fatal sepsis has been described before [9-11], in a search of PubMed we did not find any fatal sepsis as late complication of BCG instillations. What we report, to our

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knowledge, is the first case of disseminated BCG infection causing septicemia and death 6 years after intravesical treatment with BCG therapy for bladder cancer.

## Case Report

An 83-year-old man was hospitalized with a 2-week history of fever, malaise, anorexia and bleeding from a back drainage. The patient had previously undergone two trans-urethral resections receiving 12 intravesical bacillus Calmette-Guerin instillations without any complications for a high grade transitional cell carcinoma of the bladder. Due to tumor progression he was performed a radical cystoprostatectomy 5 years earlier of this admission. He also had an endovascular stent-graft repair of an infrarenal abdominal aortic aneurysm. Six months before this new admission, he was diagnosed from multiple retroperitoneal abscesses in which mycobacterium bovis grew. Since then, the patient received a combination of antitubercular medication.

Physical examination revealed an ill-appearing man. Pulmonary and cardiac examinations were unremarkable. He complained of abdominal pain in the right flank. Laboratory tests revealed abnormal liver function tests, anemia, renal insufficiency, leukocytosis and signs of coagulation disorder. A computed tomography (CT) scan of the abdomen showed a diffused and enlarged left psoas muscle. High doses of corticosteroids were associated to the antitubercular treatment. The patient developed a severe sepsis. Blood cultures were positive for acid-fast bacilli stains. Despite partial improvement, the course was complicated with a multiple organ failure, and the patient died two weeks after admission.

## Discussion

Permanent increase in neoplasm incidence including bladder neoplasm makes physicians to search for new forms and methods of treatment that prevents either appearance and/or progression of the disease. Application of new preparations entails in many cases appearance of side effects which sometimes are difficult to manage and thus must be monitored constantly. To avoid complications which in case of BCG application are very burdensome and sometimes dangerous for patient, it is necessary to intervene in due time.

The BCG therapy has been effectively used in the management of superficial bladder cancers. It is especially useful as an adjuvant therapy following bladder surgery for cancer. For instance, Demkow et al [2], in a recent study, reported that nearly 66% of the patients who received intravesical BCG therapy following complete transurethral resection of a bladder tumor were cancer free after a median follow-up of 45 months.

Adverse events following intravesical BCG therapy are

related to strain virulence, allergic reactions or to nosocomial urinary tract infections. BCG is a potent immunostimulator that exerts its urological effects by inducing a strong immune response and by causing cell cycle arrest at the G1/S transition phase [12, 13]. A multicenter reviewed and studied complications on 1,278 patients after bacillus Calmette-Guerin therapy for bladder cancer [14]. Cystitis occurred in 91% of the patients. Complications identified included fever in 50 patients (3.9%), granulomatous prostatitis in 17 (1.3%), bacillus Calmette-Guerin pneumonitis or hepatitis in 12 (0.9%), arthritis or arthralgia in 6 (0.5%), hematuria requiring catheterization or transfusion in 6 (0.5%), skin rash in 5 (0.4%), skin abscess in 5 (0.4%), ureteral obstruction in 4 (0.3%), epididymo-orchitis in 2 (0.2%), bladder contracture in 2 (0.2%), hypotension in 1 (0.1%), and cytopenia in 1 (0.1%). Deaths due to BCG sepsis and the high frequency of BCG-induced cystitis have compromised the use of BCG. However, with increased experience in applying BCG, the side-effects now appear to be less prominent. Serious side-effects are encountered in fewer than 5% [15]. Major complications can appear after systemic absorption of the drug, therefore BCG should not be administered during the first 2 weeks after transurethral resection, in patients with hematuria and after traumatic catheterization. Morbidity secondary to intravesical BCG may present both locally and systemically. Most patients suffer a self-limited irritative voiding syndrome. Prevention of these complications requires implementing rules of good practice for the instillations. The undesirable side effects should be recognized early. Their treatment should be rapid and adapted to the patient. Besides the commonly seen side effects of intravesical BCG instillations, very rare complications have been reported.

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