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Fatal sepsis after intravesical instillation of BCG – case report

Sepse fatal após instilação intravesical de BCG – relato de caso

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ABSTRACT

Intravesical instillation of bacillus Calmette-Guérin (BCG) is the treatment of choice for carcinoma in situ and non-invasive high-grade superficial tumors of the urinary bladder. This treatment is well tolerated overall, but serious complications can occur. An elderly man with coronary disease and recurrent high-grade superficial carcinoma of the bladder underwent intravesical instillation of BCG and developed septic

shock. He received wide range antibiotics, tuberculostatic and vasoactive drugs, corticosteroids, mechanical ventilation and renal replacement therapy without improvement. He died nine days after the intravesical instillation of BCG because of multiple organ failure.

Keywords: Urinary bladder neoplasm/therapy; Immunotherapy; *Mycobacterium bovis*; BCG vaccine/adverse effects; Sepsis; Case reports

INTRODUCTION

Intensive care physicians should be able to provide appropriate care for the increasingly frequent cancer patients in intensive care units (ICUs). A recent study has shown that one out of five admissions to Brazilian ICUs involves a malignant disease patient⁽¹⁾ with encouraging survival rates. With respect to urinary bladder cancer, more than 300,000 new cases are diagnosed yearly worldwide. The Instituto Nacional do Câncer [National Cancer Institute] estimated that there were 13,110 new cases in Brazil in 2009.⁽²⁾ In 2008, 2,821 deaths were related to this type of neoplasm; 1,967 were male patients, and 854 were female patients.⁽²⁾

The initial urinary bladder cancer is superficial in about 70 to 80% of cases,⁽³⁾ with 5 to 10% of these cases being carcinoma in situ. Carcinoma in situ is a very aggressive neoplasm, with high risks of progression and death.⁽³⁾ For the initial treatment of carcinoma in situ of the urinary bladder, immunotherapy with intravesical instillation of bacillus Calmette-Guérin (BCG) is considered the therapy of choice.⁽³⁾ In addition, after transurethral resection (TUR) of high-grade, non-invasive superficial tumors, immunotherapy with intravesical BCG is considered the adjuvant therapy of choice to reduce relapse and progression risks.⁽⁴⁾ This therapy is well tolerated overall; however, severe complications are possible.

The traditional image of BCG as a beneficial vaccine agent should not deceive intensive care physicians and lead them to underestimate the risk of severe complications. This case report aims to warn intensive care professionals about the risk of septic shock and death related to intravesical BCG.

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CASE REPORT

An 82-year-old male patient with severe coronary artery disease (diffuse atheromatosis, contraindication for cystectomy) underwent transurethral resection (TUR) of a high-grade superficial urinary bladder urothelial carcinoma, followed by immunotherapy with intravesical instillation of BCG for 6 weeks for the induction phase and one monthly instillation for three months as maintenance therapy. During this therapy, the patient had occasional episodes of dysuria. He had urinary bladder carcinoma relapses, the first after nine months, which were treated with TUR. The second relapse, after fifteen months, was treated with TUR followed by intravesical mitomycin chemotherapy. After twenty three months, he had a third relapse of the high-grade superficial urothelial carcinoma and underwent TUR with complete tumor resection and was treated with another course of intravesical instillation of BCG to prevent new relapses. He underwent the first instillation of intravesical BCG (Strain Moreau – Rio de Janeiro), 80 mg, diluted in 50 mL normal saline for 2 hours, with no complications.

During the instillation of the second dose, the patient had a severe pyrogenic reaction with shivering, dyspnea and arterial hypertension. Gram-negative bacillus bacteremia or BCG cystitis was suspected. The patient was admitted to the hospital, and ciprofloxacin antibiotic therapy was started for the suspected urinary infection, although with no culture confirmation was obtained. The dyspnea persisted, and within few hours hypotension was identified, and he was referred to the ICU. Upon admission to the ICU, the patient had tachycardia, tachypnea, hypotension and oliguria. Pressure response to volume was initially achieved; however, the patient progressed into shock, requiring the use of noradrenalin. Respiratory failure developed, and mechanical ventilation was started.

The electrocardiogram showed no signs of coronary ischemia or acute myocardial infarction. The laboratory investigations revealed the following changes: leucocytosis; increased blood urea nitrogen, creatinine and bilirubin levels; increased international normalized ratio (INR); and metabolic acidosis. His APACHE II score was 19. The antibiotic schedule was changed to cefepime and vancomycin, and rifampicin, isoniazid and prednisone were started to treat the suspected BCG septic shock. Blood and urine cultures were drawn but failed to show bacterial growth. The patient progressed to multiple organ failure and died nine days after the intravesical instillation of BCG.

DISCUSSION

The history of BCG begins in 1902, when Edmond Nocard, a French veterinarian and microbiologist, isolated a very virulent *Mycobacterium bovis* bacillus strain from a heifer with tuberculous mastitis.⁽⁵⁾ From this material, a sample was provided to Albert Calmette, who obtained an accidental mutation. His assistant, Camille Guérin, cultured this strain for 13 years, noticing a gradual reduction in the virulence of the bacillus while maintaining its immunogenicity. This strain was named BCG – Bacillus Calmette-Guérin – and was first used to vaccinate cows to prevent tuberculous disease. Next, vaccination was successfully tried in humans. In 1924, the Pasteur Institute in Lille, France, started massive BCG vaccine production, with worldwide distribution. Several sub-strains were provided to several countries in different manners, leading to variants with biochemical, morphological and immunological differences. One of these samples reached Brazil in 1925 by the hands of the Uruguayan physician Julio E. Moreau, who in turn provided samples to Dr. Arlindo de Assis in Rio de Janeiro. The latter named this strain “BCG Moreau Rio de Janeiro”.⁽⁵⁾

The history of the antitumor effects of BCG is long.⁽⁶⁾ In 1929, Pearl observed a lower incidence of cancer in tuberculosis patients in a series of autopsies and concluded that there is an antagonism between the two diseases.⁽⁶⁾ Old et al., in 1959, showed that BCG-infected rats were resistant to transplantable tumors, with increased immunological reactivity.⁽⁷⁾ In 1971, Zbar et al. observed that tumor growth was inhibited by live BCG injection, ascribing this effect to an immunological late hypersensitivity reaction.⁽⁸⁾ The progression of both clinical and experimental studies led deKernion in 1975 to successfully treat an isolated urinary bladder melanoma with cystoscopic BCG injection.⁽⁹⁾ In 1976, Morales et al. published a report of the first intravesical BCG administration for the treatment of superficial urinary bladder cancer.⁽¹⁰⁾ Repeated studies have confirmed that intravesical BCG eliminates in situ urinary bladder carcinoma, delays the disease progression, improves the survival of high-grade superficial cancer patients, and is more effective than intravesical chemotherapy.⁽¹¹⁾ There are several BCG strains; however, even after so many years of culturing in different laboratories, the genetic changes in bacterial immunogenicity that have accumulated do not pose significant challenges as demonstrated by the consistently favorable results of studies worldwide.⁽¹¹⁾

BCG Moreau Rio de Janeiro has been produced as frozen dried product since 1973. According to the Fundação Atauilpho de Paiva (Brazil), the manufacturer of ImunoBCG, a vial for intravesical use contains 40 mg frozen dried bacteria, corresponding to more than 2×10^6 living colony-forming units, which can be fatal if administered intravenously.⁽¹²⁾ Viable mycobacteria are essential for the therapeutic effect.⁽¹³⁾ After intravesical instillation, intensive reticuloendothelial system stimulation, with development of cell immunity versus tuberculosis and neoplasms, is seen.⁽¹⁴⁾ Intravesical BCG therapy remains the standard of care for high-grade, non-invasive urinary bladder cancer.⁽¹¹⁾ Given the high incidence of urinary bladder cancer and the positive results reported in the oncologic literature, BCG continues to be widely used, and intensive care physicians must be aware of the risks and complications of intravesical immunotherapy.

When intravesical BCG is instilled, a portion of the bacilli adhere to the bladder wall,⁽¹⁵⁾ leading to an intensive immune response with inflammatory cell infiltration, initially polymorphonuclear leucocytes, which produce large amounts of cytokines, which are eliminated in the urine. After new instillations, the polymorphonuclear cells are replaced by mononuclear cells such as monocytes, macrophages, CD4 and CD8 T cells and natural killer lymphocytes, leading to tumor destruction. Biopsies after BCG instillation have shown intensive granulomatous reactions, characterized by multinuclear giant cells, mononuclear cells and histiocytes, and necrotic areas.⁽¹¹⁾

Several intravesical BCG instillation therapeutic regimens have been tested, and currently the most frequently used schedule has both induction and maintenance phases. The use of maintenance therapy has shown statistically significantly improved survival versus only induction.⁽⁴⁾

BCG intravesical administration is well tolerated overall.^(12,16) Low fever and cystitis are common after intravesical instillation and are even considered signs of a good therapeutic response.⁽¹⁶⁾ However, several complications are possible, such as high fever, granulomatous prostatitis, granulomatous orchiepididymitis, granulomatous hepatitis, pneumonitis, allergic reactions, urethral obstruction, contracted bladder and other less common complications. However, the worst complication is BCG sepsis.^(12,16) The probable pathophysiological mechanisms for sepsis are mycobacteria absorption and hematogenic dissemination^(12,16) and the hypersensitivity reaction.^(12,16) Risk factors for BCG sepsis are related to the following intravesical instillation of BCG contraindications: 1)

instillation less than 30 days after the TUR; 2) traumatic vesical catheterization; 3) macroscopic hematuria; 4) urinary infections; and 5) concomitant immunosuppressive drug use.^(16,17) The above conditions would predispose a patient to mycobacterial absorption. High fever, shivering, and sepsis signs following intravesical BCG are indicative of a severe complication.^(12,16)

In 1992, Lamm et al. reported an incidence of 0.4% of this BCG sepsis in a group of more than 2,400 patients.^(12,16) This study is the largest series in the literature evaluating BCG complications and remains a reference for other papers.⁽¹⁶⁾ It is estimated that one death will occur for each 15,000 intravesical BCG patients.⁽¹⁶⁾ In Brazil, Barbosa et al. reported one fatal case of granulomatous hepatitis in 1999.⁽¹⁷⁾ The above described case experienced a fast installation septic shock. The cultures failed to show bacterial growth, as reported in similar cases in the literature.⁽¹²⁾ Sepsis from a gram-negative urinary focus could be speculated; however, BCG sepsis must be considered due to the temporal relationship with intravesical instillation of BCG and the lack of any other infectious site.⁽¹²⁾ It is, therefore, a diagnosis of exclusion.

Among the intravesical BCG sepsis cases described, BCG did not manifest after the first contact but after several instillations.⁽¹⁸⁾ In addition, an experimental trial in rats has shown that severe cases were seen in BCG rechallenge toxicity experiments, suggesting hypersensitivity.⁽¹⁸⁾ In this experiment, the best animal survival rate was seen in the rats treated with rifampicin, isoniazid and prednisone.⁽¹⁸⁾

In a clinically suspected case, in addition to the usual intensive support, the studies recommend immediate start of fluoroquinolone therapy⁽¹⁹⁾ aiming to treat eventual gram-negative urinary sepsis; this treatment is effective against BCG.⁽¹³⁾ Tuberculostatics (rifampicin 600 mg/day; isoniazid 300 mg/day; ethambutol 1,200 mg/day)^(19,20) and prednisone (40 mg/day) should be added to this therapy as well.⁽¹²⁾ The effect of tuberculostatics on BCG starts later than the effects of quinolones. It is noteworthy to remember that BCG is resistant to pyrazinamide. The use of a corticoid is related to the possible hypersensitivity reaction developed after the start of BCG therapy.^(12,18-20)

In summary, BCG sepsis is a rare but severe complication that can occur after intravesical immunotherapy. Several BCG sepsis reports are available in the literature, and not all cases have been fatal.⁽²¹⁻²⁴⁾ It is necessary to verify the temporal association between the intravesical instillation and the septic shock to reach the appropriate diagnosis and to start therapy as early as possible.⁽¹²⁾

RESUMO

A instilação intravesical do bacilo de Calmette-Guérin (BCG) é o tratamento de escolha para carcinoma de bexiga *in situ* ou tumores superficiais de bexiga de alto grau não invasivos. Este tratamento geralmente é bem tolerado, mas podem ocorrer complicações graves. Paciente idoso, coronariopata, portador de carcinoma superficial de bexiga de alto grau recidivado foi submetido à instilação intravesical de

BCG, evoluindo com choque séptico. Recebeu antibioticoterapia de amplo espectro, tuberculostáticos, corticóide, aminas vasoativas, suporte ventilatório e tratamento hemodialítico, sem melhora. Faleceu nove dias após a instilação intravesical de BCG por insuficiência de múltiplos órgãos.

Descritores: Neoplasias da bexiga urinária/terapia; Imunoterapia; *Mycobacterium bovis*; Vacina BCG/efeitos adversos; Sepsis; Relatos de casos

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