A Rare Case of Granulomatous Pneumonitis Due to Intravesical BCG for Bladder Cancer

Um Caso Raro de Pneumonite Granulomatosa Secundária à Instilação Intravesical de BCG no Contexto de Neoplasia da Bexiga

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ABSTRACT
Granulomatous pneumonitis is a rare complication of bacillus Calmette-Guerin immunotherapy following intravesical administration of bacillus Calmette-Guerin. The authors present an unusual case of a 67-year-old man who developed mild and non-specific symptoms, following intravesical bacillus Calmette-Guerin instillations. Examinations revealed features of miliary tuberculosis and granuloma suggestive of mycobacterial infection. Anti-tuberculosis treatment resulted in a remarkable improvement in his symptoms and gradually upgrading of radiological appearance. The symptoms were less severe than some others described but this case provides evidence that, even in some cases, specific treatment may be necessary. We highlight the importance of recognizing miliary tuberculosis in patients with organ tuberculosis. Int J Dermatol. 2003;42:197-200.

RESUMO
A pneumonite granulomatosa é uma complicação rara da imunoterapia com bacillus Calmette-Guerin após administração intravesical do bacillus Calmette-Guerin. Os autores apresentam um caso incomum de um homem de 67 anos de idade que desenvolveu sintomas ligeiros e inespecíficos, após instilações de bacillus Calmette-Guerin intravesical. Os exames revelaram características da...
INTRODUCTION

Urinary bladder cancer is the most frequent urinary system malignancy, being ninth in worldwide cancer incidence.\(^1\)

Intravesical administration of bacillus Calmette-Guérin (BCG), a live attenuated strain of *Mycobacterium bovis*, is the cornerstone of adjunctive therapy for superficial bladder cancer.\(^2\)

BCG immunotherapy is typically well tolerated due to low virulence in immunocompetent patients,\(^3\) although local and systemic complications may occur. Severe adverse symptoms are uncommon. Additionally, disseminated BCG infections that present as granulomatous pneumonitis or hepatitis are quite rare.

We report a case of an immunocompetent adult patient with a history of urinary bladder cancer that presented with disseminated BCG pneumonitis, after intravesical BCG immunotherapy, with mild and non-specific symptoms, even though having a thoracic computed tomography (CT) scan with extensive bilateral miliary nodules on his primary appearance.

CASE REPORT

A 67-year-old male was diagnosed with urinary bladder carcinoma, and was placed on intravesical BCG immunotherapy. Six days after the sixth BCG instillation therapy, the patient exhibited a continuous low-grade fever, with an isolated peak of high-grade fever. He was treated with a short-term course of ciprofloxacin without improvement due to suspicion of complicated urinary tract infection. Due to the persistence of symptoms for a month, the patient was referred to the regional Pulmonology Diagnosis Center. A physical examination indicated fine inspiratory crackles in both lungs. Laboratory data were as follows: white blood cell count, 5100/μL (neutrophils, 53.4%; lymphocytes, 33.0%); haemoglobin, 12.8 g/dL; platelet count, 23.4 x 10^4/μL; C-reactive protein (PCR), 0.8 mg/dL. Chest radiography revealed bilateral diffuse reticulonodular infiltrates.

Figure 1 – Computed tomography scan showing pulmonary nodules in a miliary pattern
He was subsequently subjected to a thoracic CT that demonstrated miliary dissemination with pulmonary micronodulation (Fig. 1).

Additionally, he underwent a flexible bronchoscopy with bronchoalveolar lavage fluid (BALF) and transbronchial biopsy collection. Flow cytometric analysis of the BALF revealed a predominance of lymphocytes (53%). The Ziehl-Neelsen staining and real-time PCR performed on BALF and lung tissue specimens were negative. The lung tissue histopathological examination obtained by transbronchial biopsy revealed epithelioid granulomas in the absence of caseous necrosis and Langerhans giant cells. Furthermore, HIV1/2 antigen/antibody screening was negative. Blood, urine and sputum cultures were also negative for mycobacteria, as well as for common bacteria and fungi.

According to the patient’s history of recent intravesical BCG treatment, disseminated BCG pneumonitis was assumed and BCG immunotherapy was discontinued. Antituberculous treatment was added (isoniazid 5 mg/kg/day, rifampicin 10 mg/kg/day, ethambutol 20 mg/kg/day) as well as a short-course pf oral prednisolone (0.5 mg/kg/day). Clinical symptoms and abnormal findings on thoracic CT scan improved after 2 months of treatment. Prednisolone was tapered to complete withdrawal in a two-month period, with no clinical relapse.

The patient continued receiving anti-tuberculous therapy with no reported problems, under the supervision of his physicians that included isoniazid and rifampicin for 12 months, with a two-month intensive phase including ethambutol. The treatment period was extended for a total of 12 months, due to slow imaging improvement suggestive of active disease at nine months of treatment. Chest CT at 12-month treatment showed considerable improvement with resolution of majority of the intrapulmonary nodules and calcification of the remaining (Fig. 2).

DISCUSSION

The BCG mechanism that leads to complications is not entirely acknowledged, and neither is its mechanism in cancer as an immunotherapeutic agent. Furthermore, it is controversial whether complications associated with intravesical BCG are an active infection or a hypersensitivity reaction.

Local or systemic complications of intravesical BCG instillations can arise. Mild adverse effects such as low-grade fever, dysuria and urinary frequency, develop in 3% – 5% of patients. The most severe complications concern disseminated infection, being sepsis the most fulminant display, but organ infection can also occur. Distant organ complications are even less common and can manifest, as

Figure 2 – Axial image of repeat chest computed tomography scans performed 12 months after initiation of anti-tuberculosis medications: showing further improvement with resolution and calcification of many of the intrapulmonary nodules
hepatitis, pneumonitis, osteomyelitis and arthritis, for example. In the largest retrospective study reported to date, dissemination as pneumonitis and/or hepatitis occurred in 0.7% of over 2000 patients.

In some patients with disseminated BCG infection, pneumonitis is characterized by an interstitial or miliary nodular pattern on chest radiography and CT scanning, most frequently present in patients with sepsis. However, relatively asymptomatic patients with only mild symptoms or subclinical cases are even rarer and have been described.

Chest radiograph should not be chosen over thoracic CT scanning, since it is not adequately sensitive, leading to misdiagnosis. In fact, chest radiograph failed to reveal a miliary dissemination pattern in a quarter of the cases, recognized in a thoracic CT scanning.

The approach to complications related to intravesical BCG treatment depends on their type and severity. Relapsing fever with night sweats persisting beyond 48 hours or evidence of more acute serious systemic symptoms, are usually signs of BCG infection that requires antituberculous therapy. M. bovis is susceptible to most of the anti-tuberculous therapy with the exception of pyrazinamide and cycloserine, to which it is typically resistant. M. bovis is quite sensitive to later-generation fluoroquinolone antibiotics. A regimen that includes isoniazid, rifampicin, ethambutol and a fluoroquinolone can be typically used for six months, but there is limited evidence to support standard recommendations for the treatment of human disease due to M. Bovis.

This period may be extended due to symptoms relapse or refractory disease. Adjunctive therapy with corticosteroids has shown to be effective in decreasing symptoms in cases with suspected hypersensitivity, with attentiveness during tapering due to high risk of symptom relapse and formation of granuloma.

Several studies have been done to demonstrate effective measures in preventing the occurrence of disseminated BCG infection, such as fluoroquinolone short prophylaxis use after each BCG administration. A multicenter, randomized and prospective study showed that ofloxacin reduced the incidence of severe local reactions and the use of anti-tuberculosis treatment. However, no cases of BCG sepsis were reported and the ability of ofloxacin to prevent more severe complications was not evaluated. Fluoroquinolone prophylaxis might reduce the antitumor activity of BCG, but no clear evidence has been found to recommend routine fluoroquinolone prophylaxis. Another study using prulifloxacin reported very comparable findings.

It can be discussed that in this report, the patient’s symptoms were caused by a hypersensitivity reaction instead of disseminated BCG, due to the absence of acid-fast bacilli on direct microscopy and negative culture results. Nevertheless, the presence of formed granuloma in transbronchial biopsy, added to anti-tuberculous treatment that led to clinical and radiological improvement supports disseminated BCG infection as a more probable diagnosis. Additionally, the lack of identification of M. bovis may be related to several modifying factors, such as culture techniques, the number of organisms, and its low virulence in an immunocompetent host. The patient presented in this case had some atypical features, for instance mild non-specific symptoms as low-grade fever, despite extensive pulmonary involvement; and only anti-tuberculous treatment with corticosteroids led to clinical and radiological improvement despite a slow image upgrading.

In conclusion, we report a rare complication of intravesical BCG instillation presenting as disseminated BCG pneumonitis. This case highpoints the importance of identifying disseminated mycobacterial infection as a complication in any patient receiving intravesical BCG instillation even if there are mild and non-specific symptoms.

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PROTECTION OF HUMANS AND ANIMALS
The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY
The authors declare having followed the protocols in use at their working center regarding patients’ data publication.

PATIENT CONSENT
Obtained.

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