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CASE REPORT

Disseminated infection due to *Mycobacterium bovis* after intravesical BCG instillation

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Abstract

Intravesical bacillus Calmette-Guerin (BCG) instillation has been adopted for the treatment of patients with superficial bladder cancer. Severe adverse events due to local instillation of BCG are uncommon, with an overall rate of serious complications of less than 5%. We report the case of an immunocompetent adult patient with multi-system effects, namely pneumonitis, granulomatous hepatitis and meningitis, who responded well to standard treatment for *Mycobacterium bovis.* This case highlights the importance of a thorough assessment of this type of patient.

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Key words: Tuberculosis; *Mycobacterium bovis*; Bladder cancer; Bacillus Calmette-Guerin

Core tip: Intravesical instillation of bacillus Calmette-Guerin (BCG) is a therapeutic option in bladder cancer. Multi-system effects are a rare complication of this procedure, and certain aspects concerning its diagnosis and treatment are unclear. We report the case of a patient who developed effects on multiple organs after intravesical BCG instillations, and we review current knowledge concerning the diagnosis and management of BCG infection.

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INTRODUCTION

Intravesical administration of bacillus Calmette-Guerin (BCG) is an essential tool in the treatment of superficial bladder carcinoma in situ[1]. This approach is generally well tolerated, although it occasionally leads to severe local and/or systemic complications[2]. The most serious complications of intravesical BCG instillation are related to disseminated infection. When disseminated BCG infection occurs, antituberculous therapy with or without glucocorticoids should be administered. We report a case of disseminated infection due to intravesical BCG instillations, resulting in pneumonitis, granulomatous hepatitis and meningitis.

CASE REPORT

We present the case of a 64-year-old male patient with a

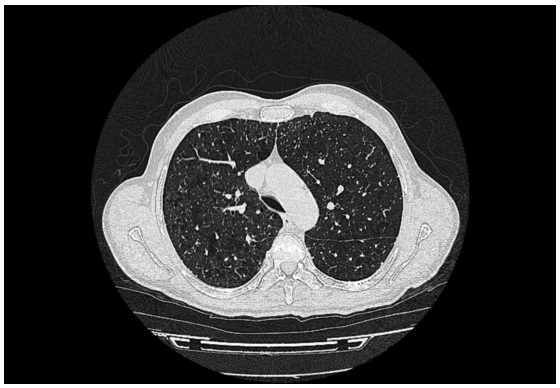

Figure 1 A thoracic computed tomography scan revealed a pulmonary micronodular pattern.

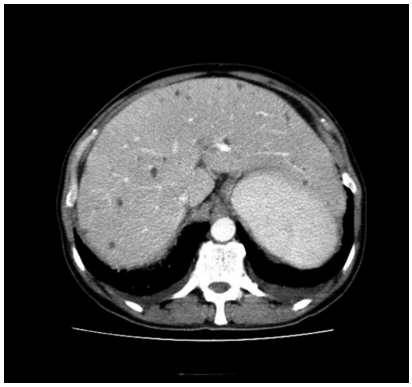

Figure 2 An abdominal computed tomography scan revealed hepatic granulomas and hepatosplenomegaly.

history of urothelial vesical neoplasm, benign prostatic hyperplasia and chronic obstructive pulmonary disease. He was being treated with tamsulosin, tiotropium bromide and salbutamol. Six months before, he had received six weekly doses of intravesical BCG instillation as an induction treatment, and one month before, he had started maintenance therapy with three doses per week. At the time of presentation, he reported weakness, weight loss and a slight fever with three weeks of evolution. Physical examination revealed hepatosplenomegaly. An analysis showed hepatic cholestasis (alkaline phosphatase 358 U/L, gamma-glutamyl transpeptidase 306 U/L), lactate dehydrogenase (LDH) 547 U/L and C-reactive protein 1.27 mg/dL. A complete blood count and urine sediment were normal. A thoracic X-ray showed multiple micronodular opacities. A thoraco-abdominal CT scan revealed a pulmonary micronodular pattern, hepatic granulomas and hepatosplenomegaly (Figures 1 and 2). Blood and urine cultures for bacteria were negative, as was a serological analysis (for HIV, HBV, HCV and *Treponema pallidum*). The urinalysis was positive for the species *Mycobacterium tuberculosis*, and *Mycobacterium bovis* (*M. bovis*) BCG grew with resistance to cycloserine and pyrazinamide. A genetic study detected the pnc A C169G (H57D) mutation, and we identified the species as *M. bovis*. The patient started treatment with isoniazid, rifampicin and ethambutol. After one week of treatment, the patient showed dizziness and instability while standing still and walking. The cerebrospinal fluid (CSF) showed red blood cells 4500/μL, leukocytes 16 μL (polymorphonuclear 25%, mononuclear 75%), proteins 82 mg/mL, glucose 67 mg/mL (capillary glycemia 144 mg/dL), LDH: 35 IU/L and adenosine deaminase 5.6 U/L (0-5). Magnetic resonance imaging of the brain (Figure 3) showed thickening and linear meningeal enhancement. Microbiological analysis of the CSF was negative. Given the meningeal involvement, anti-tuberculosis treatment was administered for one year, with good clinical and radiological responses.

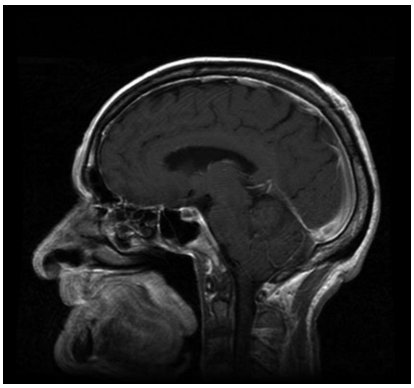

Figure 3 Magnetic resonance imaging showed thickening and linear meningeal enhancement.

DISCUSSION

The adverse effects of intravesical BCG instillations can appear early or several years after the treatment. Although there are certain common local effects, such as cystitis (91%)[3] (this condition can be difficult to differentiate from other urinary tract infections), systemic complications are rare. The frequency of appearance ranges from 2.9% in cases with fever to 0.3% in cases with skin exanthema[4]. The most severe symptoms are pneumonitis, hepatitis, sepsis and pancytopenia. No differences in the incidence of complications were observed when comparing different BCG preparations or doses[5]. The spreading mechanism is not exhaustively known. Certain authors think that hematogenous spread occurs from the bladder[3], whereas others believe that the spread is due to a type IV hypersensitivity-related mechanism[6]. The response to glucocorticoids administered along with antituberculous drugs has also supported the notion of a hypersensitivity response. There are no established effective measures to prevent a disseminated infection with BCG[7], although the risk increases when instillations are temporally close to surgery or to traumatic catheterization[8]. The genetic study of the urine sample of our patient allowed us to identify *M. bovis* and to confirm its classic resistance profile. Given the meningeal involvement in the patient in our case, the treatment was extended for one year, with combination with corticoids in the first weeks.

In conclusion, intravesical BCG instillation can induce disseminated infection. Molecular techniques can help in early diagnosis because a delay in management can be lethal. In our patient, standard triple therapy with steroids led to complete recovery.

COMMENTS

Case characteristics

A 64-year-old male patient with an urothelial-vesical neoplasm treated by intravesical bacillus Calmette-Guerin (BCG) instillations.

Clinical diagnosis

Hepatosplenomegaly and later dizziness and instability.

Differential diagnosis

Neoplasm and central nervous system infection.

Laboratory diagnosis

Alkaline phosphatase 358 U/L, gamma-glutamyl transpeptidase 306 U/L, lactate dehydrogenase 547 U/L and C-reactive protein 1.27 mg/dL. A complete blood count and urine sediment were normal.

Imaging diagnosis

A thoracic X-ray showed multiple micronodular opacities. A thoraco-abdominal computed tomography scan revealed a pulmonary micronodular pattern, hepatic granulomas and hepatosplenomegaly. Magnetic resonance imaging of the brain showed thickening and linear meningeal enhancement.

Pathological diagnosis

A urinalysis was positive for *Mycobacterium bovis*.

Treatment

Anti-tuberculosis treatment was administered for one year.

Related reports

Severe adverse events due to local instillation of BCG are uncommon, and disseminated BCG infection can simulate several diseases.

Term explanation

BGG is a low-virulence mycobacterium that originates from successive cultures of *Mycobacterium bovis*. Pnc A is a gene encoding the mycobacterial enzyme pyrazinamidase.

Experiences and lessons

BCG can induce disseminated disease with multi-system failure.

Peer review

This paper reports the case of serious complications in a variety of organs after intravesical BCG instillation. The manuscript is basically well written.

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