CASE REPORT

Case Report: A rare case of BCGitis in a patient with bladder cancer treated with the BCG vaccine [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

The Bacillus Calmette Guérin (BCG) vaccine was initially produced as a vaccine against tuberculosis. BCG is an attenuated live strain of *Mycobacterium bovis* and has been widely used as an immunotherapy over the last years in bladder cancer. We describe a case of a 61-year-old Caucasian male with previous bladder cancer, who had been treated for the last 15 months with instillation of BCG, admitted with 3-week evolution history of fever (38°C), asthenia, anorexia and a weight loss of 6kg. The patient's condition deteriorated leading to sepsis. A liver biopsy was performed showing granulomatous dispersed through all the parenchyma. Empirical therapy for *M. bovis* was started with good response. Even though it is rare, BCGitis must be ruled out in any patient submitted to immunotherapy with BCG and prompt therapy started if disseminated disease is present, which improves the outcome.

Keywords

BCGitis, *Mycobacterium bovis*, Bladder cancer, sepsis

Open Peer Review

Approval Status

	1	2
version 1
09 Aug 2019	view	view

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2. **Marco Antonio Yamazaki-Nakashimada** , Instituto Nacional de Pediatría, Mexico City, Mexico

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: Sousa D: Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing; Antunes Silva S: Writing – Review & Editing; Jorge C: Writing – Review & Editing; Rodrigues AI: Writing – Review & Editing; Martins Fernandes R: Writing – Review & Editing; Viana Coelho M: Writing – Review & Editing; Rios E: Writing – Review & Editing; Ferro Rodrigues R: Writing – Review & Editing; Mingo A: Writing – Review & Editing

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Introduction

Most bladder carcinoma are located superficially, described as a non-muscle invasive bladder cancer, which allows a therapeutic approach with local immunotherapy¹. The Bacillus Calmette Guérin (BCG) vaccine was initially produced as a vaccine against tuberculosis. BCG is an attenuated live strain of *Mycobacterium bovis* and has been widely used as an immunotherapy over the last few years². Treatment with the BCG vaccine is well tolerated by over 95% of patients³.

The most frequent side effects of immunotherapy with the BCG vaccine are limited to the bladder – bacterial or chemical cystitis and haematuria. Although rare, systemic side effects can be mild or severe and they range from fever and influenza-like symptoms to BCG-induced lung infection, liver toxicity and BCG sepsis. Sepsis was estimated to affect 0.3% of patients treated with BCG instillation³. When a disseminated infection is present it can be described as BCGitis, with the lung and liver being the most frequently affected organs (50% and 61%, respectively)⁴.

A diagnosis of BCGitis can be validated by direct staining (Ziehl-Neelsen or auramine-rhodamine), histological observation (presence of a granulomatous pattern with or without caseous necrosis) or the results of polymerase-chain reaction (PCR) assays. However, the rentability of all options is low, leading to increasing difficulty in establishing the diagnosis^{4,5}.

We hereby report a rare case of septic BCGitis.

Case report

A 61-year-old Caucasian male with a medical history of pulmonary embolism and bladder cancer (pTaG1), who had been

treated with the BCG vaccine for the last 15-months (a total of 15 instillations) was admitted with a 3-week history of fever (38°C), asthenia, anorexia and a weight loss of 6kg.

A week prior to admission (virgula) the patient presented with dysuria and pollakiuria, justifying an empirical treatment for a urinary tract infection with ciprofloxacin (500mg bid) but without response. the urine culture requested came back negative.

The patient's general state was aggravated with persistent fever, tachycardia and increased inflammatory markers (CRP 46mg; normal range, <5mg/L), elevated liver enzymes [AST (46U/l); ALT (64U/l)], leading to hospital admission with a diagnosis of sepsis (Day 1; Table 1). An empirical broad-spectrum course of antibiotics with ceftriaxone (2gr) and gentamycin (500mg) was instituted for 5 days. A septic screen was performed, which grew no microorganisms.

After 3 days of hospital stay, the patient's status continued to deteriorate with persistent fever, hypotension and an increase in CRP to 76mg/L (Day 3; Table 1). No abnormal lymph nodes were observed. An abdominal ultrasound revealed a hyper-echoic liver lesion with preservation of length and liver contour (Figure 1). This evidence (virgula) combined with the knowledge that there had been a previous recent administration of immunotherapy with BCG 3 weeks before the onset of the presented clinical symptoms, lead physicians to perform a liver biopsy.

A liver biopsy was conducted revealing multiple small epithelial granulomas without caseous necrosis compatible with granulomatous hepatitis. Ziehl-Neelsen staining and Löwenstein-Jensen medium culture were negative. A PCR assay

Table 1. Evolution of laboratory results from hospital admission to discharge.

Haemoglobin (Hb) is expressed in grams per liter; Neutrophil cells, platelets, lymphocytes and monocytes are expressed as elements /mm³; Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (gGT), and alkaline phosphatase (ALP) are all expressed in international units per liter; Total bilirubin is expressed in milligrams per decilitre and C-reactive protein is expressed in milligrams per litre.

	Day 1 - admission	D3	D7	D15	D26 - discharged
Hb	148	147	153	149	139
Leucocytes	7000	7000	8300	9700	4300
Platelets	235.000	193000	167000	279000	217
Creatinine	1.1	1.0	1.0	0.8	0.8
AST	46	54	50	37	23
ALT	64	63	63	56	27
gGT	-	80	-	-	62
ALP	-	72	-	-	78
Total bilirubin	-	1.4	-	-	-
INR	-	1.4	-	-	1.2
CRP	45	76	189	7	4

Figure 1. Abdominal ultrasound with posterior echo attenuation and hyperechogenic liver parenchyma characteristic of liver steatosis.

for *M. tuberculosis complex* (MTB) was also negative both in the liver biopsy and urine sample.

Due to continuous clinical worsening of the patient's condition until day 7 and aggravated sepsis with persistent fever, hypotension and increased CRP to 186mg/dL under broad-spectrum antibiotics, an empirical regimen with isoniazid 300mg, rifabutin 300mg and ethambutol 1200mg was started for 3 months. Given its interaction with rivaroxaban, rifampicin was switched to rifabutin. In a matter of days, the clinical outcome with resolution of the fever and normalized the inflammation markers at day seven from admission (Table 1). Moreover, within one week of therapy, CRP, AST and ALT revealed a notorious decrease, with a complete normalization within 11 days upon treatment institution.

The patient's therapeutic regimen included isoniazid 300mg, rifabutin 300mg and ethambutol 1200mg for the first 3 months and the subsequent 3 months with isoniazid and rifabutin with good adherence and physiological tolerance. After 2 years of treatment, the patient remains in remission.

Discussion

Our case highlights the rare but dangerous systemic secondary side effects of BCG instillations that characterize (singular) BCGitis. Evolution to a multisystemic disease deserves attention because its diagnosis can be a challenge to any physician – unspecified symptoms could also be present in acute infection, autoimmune disorders, evolution of malignancy or drug toxicity.

The pathophysiology of BCGitis is not yet well understood. Previous studies have suggested that it is the result from

hypersensitivity, with a diffuse granulomatous reaction without isolation of *M. bovis*, while others consider it a disseminated disease of *M. bovis*⁴.

The identification of *Mycobacterium* requires a combination of tests because there is a poor reliability of PCR for MTB, Ziehl-Neelsen or auramine-rhodamine stains and also with Löwenstein–Jensen medium culture^{4,6}. The histological finding of granulomatous lesions remains the main support to the diagnosis when it is not possible to identify *Mycobacteria*, as we describe in this case. However, the steatotic liver pattern presented in Figure 1 supports the presence of liver inflammation and the need of a liver biopsy.

In sensitive strains, the use of empirical antibiotherapy with fluoroquinolone could decrease the accuracy of Ziehl-Neelsen stain, Löwenstein–Jensen medium culture and PCR for MTB.

Options for treatment regimens and duration of therapy also remain under discussion; however, treatment options that have been accepted vary from 6–9 months^{4,5}. Our patient was treated for 6 months, which proved to be adequate for treatment of BCGitis. The interaction of rivaroxaban with rifampicin forced a switch to rifabutin.

Corticosteroids should only be used in severe cases, due to the lack of evidence in mild and moderate presentations⁴.

Finally, the present case confirms the good clinical and laboratorial response upon institution of empirical therapy, with complete recovery. Moreover, two years after BCGitis, the patient is stable but remains under surveillance.

Conclusions

We describe in detail a very rare case of sepsis secondary to immunotherapy with BCG for a non-muscle invasive bladder cancer. Most frequently, patients have local manifestations, however systemic infection may also occur. The diagnosis can be challenging as other infections and malignancies must be first ruled out. Nonetheless, physicians ought to be familiar with bcgitis and upon diagnosis, prompt therapy must be started.

Consent

Written informed consent for the publication of this case report and any associated images was obtained from the patient.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Grant information

The author(s) declared that no grants were involved in supporting this work.

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Marco Antonio Yamazaki-Nakashimada

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The authors report a patient presenting an uncommon complication of BCG immunotherapy to treat bladder cancer. It is a very interesting case, with the peculiarity that the patient presented important radiological and histopathological liver involvement without jaundice or very elevated transaminases. Some authors suggest to reserve the term of BCGitis to local, regional BCG induced disease, and BCGosis to a distant or disseminated BCG induced disease, like in this case.

I believe that the manuscript would be more valuable if the authors review all the cases of intravesical BCG treatment complicated with BCGosis involving the liver (Desmet *et al.*, 2012¹, Bodurtha *et al.*, 1974², Kaklamanos *et al.*, 2011³ etc.) and compare them to the present case. A table would be useful. Could you explain why corticosteroids were not used in this case since it presented in a severe fashion? Okano *et al.* (2019⁴), reported a patient who was considered to have a hypersensitivity reaction to the liver after intravesical BCG who responded only to corticosteroids, and this study can be added and discussed.

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Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical Immunology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 20 December 2019

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André Lencastre

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The authors report on a case of iatrogenic sepsis induced by BCG immunotherapy to treat bladder cancer. The final diagnosis was made with clinical history, ultrasound imagery and histology of the liver revealing a granulomatous hepatitis. No confirmation was possible testing for M. Bovis but the patient improved under specific treatment.

The overall structure and language of the document is elegantly built. I would suggest a more thorough review of cases of BCG induced sepsis or hematogenous spread to other organs, and its treatment.

Please review some of the language namely: 1) there are (*virgula*) spread all over the text; 2) there are units of concentration lacking or improperly written; 3) the phrase "*In a matter of days, the clinical outcome with resolution of the fever and normalized the inflammation markers at day seven from admission.*" has no verb; 4) (*singular*) is written somewhere in the text and makes little sense

to me.

I am kindly cited in the references but my name is not correct.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Dermatology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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