Scientific Research Publishing

Advances in Infectious Diseases, 2022, 12, 563-567
https://www.scirp.org/journal/aid
ISSN Online: 2164-2656
ISSN Print: 2164-2648

Genitourinary Bacillus Calmette-Guerin Infection after BCG Intravesical Administration in a Patient under Hemodialysis—What Can We Do Better?

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How to cite this paper: Dias, L.R., Almeida, C., Nogueira, F., Soares, R., Soares, S.G., Costa, M.L., Boncoraglio, M.T. and Ceia, F. (2022) Genitourinary Bacillus Calmette-Guerin Infection after BCG Intravesical Administration in a Patient under Hemodialysis—What Can We Do Better? *Advances in Infectious Diseases*, **12**, 563-567.
https://doi.org/10.4236/aid.2022.123041

Received: August 20, 2022
Accepted: September 18, 2022
Published: September 21, 2022

Abstract

A 74-year-old man with terminal chronic kidney disease, under hemodialysis and with residual diuresis, was admitted due to myalgia, arthralgia, fever and pyuria in the previous 10 days. The patient had a recent diagnosis of high-grade non-invasive bladder cancer and was doing weekly BCG intravesical administrations. The symptoms started three days before the fifth administration. He had done cefixime as an outpatient and started piperacillin-tazobactam on hospital admission, but the fever persisted, and there was no bacterial isolation in urine or blood culture. On the tenth and seventeenth day after the last BCG intravesical administration Mycobacterium bovis was still isolated in the urine culture. The diagnosis of BCGitis was made and treatment was started, with a good response. Forty days after the last administration and under treatment, the culture remained positive for Mycobacterium bovis in the urine. We raise the question about the safety of BCG administration in patients with residual diuresis.

Keywords

BCGitis, Mycobacterium Bovis, Hemodialysis, Non-Tuberculosis Mycobacterium, Bladder Cancer

1. Background

Bacillus Calmette-Guérin (BCG) was initially produced as a vaccine against tu-

berculosis. However, in the last decades, its immunologic components have been explored. Intravesical administration of *Bacillus Calmette-Guérin* (BCG) is increasingly used as an adjunctive treatment for non-muscle invasive bladder cancer, as the treatment of choice [1]. Complications from this procedure may arise, and localized or disseminated BCG infection (BCGitis) has been reported, although being relatively rare [2] [3]. It is more common in patients with primary or secondary immunodepression.

In this case, the authors wonder about the safety of the procedure in patients with residual diuresis, such as patients on hemodialysis, since there is no physiological removal of the bacillus from the bladder, which could allow its growth and potential complications.

Currently, there are no recommendations or guidelines for patients with low or absence diuresis.

2. Clinical Case

A 74-year-old Portuguese man presented with a ten-day history of myalgia, arthralgia, fever (T 38˚C) and pyuria. The patient had a medical history of hypertension, end-stage renal disease (ESRD), undergoing a regular hemodialysis program with residual diuresis, and bladder cancer (high grade non-invasive), for which he underwent transurethral resection. He was medicated with transdermal fentanyl and had been treated in the previous month with BCG intravesical administrations, having already undergone five administrations. The last one had been three days after the onset of symptoms.

He had already received seven days of cefixime in the outpatient setting due to a presumptive urinary infection, with no clinical improvement.

On admission, the patient was febrile (T 38.2˚C), confused and disoriented. The physical examination showed suprapubic pain. The arteriovenous fistula had no inflammatory signs and was working properly. Blood examinations showed a hemoglobin level of 8.3 g/dl (normochromic normocytic anemia, with iron 16 ug/dl, transferrin saturation 13%, ferritin 898 ng/ml), a white blood cell count of 9920 cells/mm^3 (79.9% neutrophils, 10.5% lymphocytes) and a platelet count of 286,000 cells/mm. C-reactive protein was 370.2 mg/dl, and erythrocyte sedimentation rate 128 mm/hr. Blood and urine cultures were negative.

The patient was hospitalized and initiated antibiotic therapy with piperacillin-tazobactam.

During hospitalization, the patient's general state was worsened with persistent fever and high inflammatory markers. Four days after admission, he had aggravated arthralgia, now with additive polyarthritis, causing intense pain, mainly on the wrists, knees and ankles.

Ten days after admission, the patient still had little improvement and was then transferred to the Infectious Diseases Department. Of the study that was done, blood and urine culture remained negative and a lumbar puncture was performed with a negative microbiological study. At this point, abundant bacilli

were found in the direct exam of the urine. A presumptive diagnosis of localized genitourinary BCGitis was then admitted and treatment with rifampicin, isoniazid and ethambutol was initiated. The additive polyarthritis had no microbiological evidence of localized BCGitis or other infection, and a diagnosis of reactive arthritis was made. Other causes of arthritis were excluded, such as gout flares, Lyme arthritis and arthritis linked to inflammatory bowel diseases. The patient was positive for HLA-B27. Prednisolone was initially given, with little improvement, with 20 up to 30 mg a day. After the exclusion of upper gastrointestinal hemorrhage or predisposing condition, non-steroid anti-inflammatory drugs were initiated, with a great clinical response.

Twenty-two days after admission, the patient presented with testicular asymmetry and a diagnosis of orchiepididymitis was assumed, due to the patient's symptoms. No biopsy was done due to the risk of fistulization.

After isoniazid, rifampicin and ethambutol were initiated the patient gradually improved. At ten, thirteen, fifteen and forty days after the last BCG intravesical administration *Mycobacterium bovis* BCG strain was isolated from urine culture, confirming the diagnosis.

Gradually, fewer bacilli were found in the direct exam. Two months after the beginning of antituberculosis therapy, the urine culture was negative for *Mycobacterium bovis*.

In short, we present a patient with genitourinary BCGitis (cystitis and presumable orchiepididymitis) and reactive arthritis due to BCG intravesical administrations, who had chronic kidney disease on hemodialysis, with residual diuresis. The diagnosis and treatment of this patient was a challenge, with a lot of complications and raised the question about the safety of the procedure without a dose adjustment or procedure adaptations.

3. Discussion

Our case highlights a gap in knowledge in the treatment with intravesical administration of BCG. There are currently no guidelines or clinical cases described in the literature on how to proceed in patients with low or no residual diuresis. The procedure is only contraindicated in patients with visible hematuria, after traumatic catheterization or with symptomatic urinary tract infection. Localized and systemic symptoms, such as the ones reported in our case, have been associated with intravesical BCG administration, although severe complications are uncommon [4].

The authors hypothesize about the theoretical greatest risk of BCGitis in patients with low or no residual diuresis due to longer intravesical stay of BCG. In fact, a reduced dose of intravesical BCG has been related to a lower potential for toxicity. In a randomized prospective study, 500 patients with superficial bladder cancer were randomly assigned to be treated with intravesical BCG after transurethral resection, 252 with the standard dose (81 mg) and 247 with the reduced dose (27 mg), with similar outcomes for recurrence and progression of cancer

but significantly less toxicity in the reduced dose. Although when analyzed for severe systemic toxicity there was no significant difference in the standard dose (3.6%) and reduced dose (4.4%) [5]. In another study, a systematic review and meta-analysis on the low-dose versus standard-dose of intravesical BCG, showed in the low-dose a significantly lower incidence of overall side effects (RR = 0.75; P = 0.01), systemic side effects (RR = 0.57; P = 0.04), severe side effects (RR = 0.52; P = 0.0003), and withdrawal due to BCG toxicity (RR = 0.49; P = 0.02). On the other hand, local side effects were comparable (RR = 0.89; P = 0.24) [6].

To mitigate the possibility of BCGitis in patients with low or no residual diuresis the authors suggest the use of a lower dose of BCG or even the use of the second line of treatment, such as intravesical instillation of mitomycin or gemcitabine. The authors also suggest emptying or/and bladder irrigation after the instillation of BCG, in order to mimic the treatment in a patient with diuresis, but more studies are needed in this population.

The absence of isolation of the bacillus in products other than urine was a limitation in our case.

4. Conclusion

This paper focus on possible complications of BCG intravesical treatment, particularly in patients with no or residual diuresis, describing a case followed and treated by the authors. It draws attention to the importance of a timely diagnosis.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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