Infect Dis Trop Med 2019; 5: e561

Disseminated BCG infection after intravesical instillation in a bladder carcinoma: an uncommon case report

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ABSTRACT:

— ***Objective:*** Bacille Calmette-Guèrin (BCG) intravesical instillation is a valid therapy for patients with non-muscle invasive bladder cancer. Although it is almost safe, uncommon cases of systemic dissemination have been reported.

— ***Case presentation:*** A 70-years-old patient with a recurrent bladder carcinoma was treated with transurethral resection of bladder tumor and BCG intravesical instillation. After the last instillation, he developed high fever, cough, nausea and vomiting, associated with shortness of breath. The patient was admitted to the Infectious Diseases Unit with a 2-point-qSOFA score. Imaging revealed interstitial infiltrates in both lungs along with hepatosplenomegaly and abdominal lymphadenopathies. Laboratory examinations showed pancytopenia and numerous acid-fast bacilli in urine whereas bone marrow biopsy showed epithelioid cells without caseous necrosis. Antituberculous treatment was started with isoniazid, rifampicin, ethambutol and moxifloxacin as well as intravenous prednisolone. The patient was discharged after 30 days with recommendation to extend 3-drugs therapy for as long as 30 days followed by a further 4 months with 2-drugs.

— ***Discussion:*** Mild complications to intravesical BCG treatment are self-limiting. On suspicion of BCG dissemination, antituberculous therapy should be promptly started. There are no official guidelines regarding treatment, however a regimen that includes isoniazid, rifampicin, ethambutol and fluoroquinolone, is usually administered for at least 6 months.

— ***Conclusions:*** Although negative smears and cultures, early recognition and prompt treatment of patients with disseminated BCG infection are essential.

— ***Keywords:*** Bacille Calmette-Guèrin,BCG intravesical instillation,bladder cancer,Disseminated BCG infection.

BACKGROUND

Bladder cancer is the most common worldwide tumor involving the urinary tract with an incidence rising with the age of patients[1]. Transurethral Resection of Bladder Tumor (TURBT) is the gold standard for non-muscle invasive bladder cancer (NMIBC), whereas muscle-invasive cancers require cystectomy[2]. Intravesical immunotherapy by BCG instillation is recommended, as an adjuvant therapy, for patients with high risk NMIBC. Compared to the TURBT alone, additional intravesical BCG significantly reduces disease recurrences and risk of progression[3].

In immunocompetent patients, BCG immunotherapy is usually well tolerated and only mild systemic symptoms are reported, such as low-grade fever and mild malaise[2].

The risk of disseminated BCG infection is increased in patients with extensive mucosal resection and in those with residual damaged mucosa, along with subjects with overt immune deficiency[4]. Although it is uncommon, BCG systemic dissemination has been reported and septic features occur in approximately 1 out of 15000 patients treated with intravesical BCG. Organ localizations such as granulomatous pneumonia or hepatitis are rare.

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Here we report an unusual and challenging BCG systemic dissemination with a clear-cut septic presentation, after intravesical immunotherapy.

CASE PRESENTATION

A 70-year-old non-smoker male was admitted to the Infectious Diseases Unit of the Civic Hospital of Syracuse (eastern Sicily) due to high fever (T max 39°C).

He had a history of superficial urinary bladder carcinoma treated with TURBT (8 months before). 5 months later, he had a cancer relapse and underwent TURBT again followed by adjuvant intravesical BCG immunotherapy, which had been administered twice monthly for five months.

After three days from the last intravesical instillation, the patient developed high fever (up to 39.5°C) together with cough, nausea, vomiting and shortness of breath. In spite of a short course of Ciprofloxacin (500 mg twice daily), symptoms persisted with high fever and worsening general conditions.

On admission, the patient was febrile (T. 39.3°C), blood pressure was 80/50 mmHg, heart rate 110 bpm, respiratory rate was 29/minute and Glasgow Coma Scale 14; qSofa score was measured as 2.

Chest clinical examination revealed bilateral inspiratory and expiratory crackles; also, the patient presented hepatosplenomegaly.

Abdominal CT scan confirmed hepatosplenomegaly associated with multiple abdominal lymphadenopathies whereas chest CT scan showed bilateral interstitial infiltrates in both lungs.

Laboratory examinations revealed leukopenia (WBC 2.900/μL, 85% neutrophils and 12% lymphocytes), anaemia (Hb 11.8 g/dL) and low platelet count (29 000/μL). Moreover, it was highlighted an increased level of γ-glutamyl-transpeptidase (249 IU/L); bilirubin (total/direct bilirubin, 1.3/0.8 mg/dL); serum glutamate pyruvate transaminase (132 mg/dL); serum glutamic pyruvic transaminase (86 mg/dL) and lactate dehydrogenase (909 mg/dL). Inflammatory markers were also high (CRP was 145 mg/L, ESR 60, Ferritin 2386 ng/ml). Coagulation markers showed elevated prothrombin time (INR was 2), partial thromboplastin time (47 seconds), low fibrinogen (1.5 g/L, with a normal range 2.0–4.0 g/L), and serum albumin 20 g/L. Arterial blood gas analysis showed hypoxaemia with respiratory alkalosis. Lactate level was 4 mmol/L.

Serological tests for viral hepatitis, Leishmania, Brucella, Toxoplasma, CMV, Rubella, EBV were negative. Furthermore, HIV1/2 antigen/antibody combo screening was performed twice and resulted negative. Antineutrophil cytoplasmic antibodies and anti-double strand DNA antibodies were negative as well. IgG, IgM and IgA levels in the serum were slightly elevated (2020, 312 and 442 mg/dL, respectively). Blood, urine and sputum cultures resulted negative.

Ziehl Neellsen stain in the urine demonstrated numerous acid-fast bacilli. Tuberculin skin test was positive whereas interferon-γ release assay (Quantiferon TB-Gold) was negative.

Due to a rapid worsening of pancytopenia (Hb: 7 g/dl; GB: 3000/mm^3, PLT: 80.000/mm^3), a bone marrow biopsy was performed showing diffuse epithelioid cell granulomas without caseous necrosis (Figure 1). Immunohistochemical staining was positive for CD68 (Figure 2).

Both PCR (GeneXpert TB for M. Tuberculosis complex and Non Tubercular Mycobacteria) and cultures (performed with use of Isolator Merck, Darmstad, Germany) on bone marrow aspirate were negative.

Oxygen therapy with nasal cannula and intravenous fluids for haemodynamic stabilisation were promptly administered. Antibiotic therapy with piperacillin/tazobactam 4.5 gr ev thrice/daily was also administered.

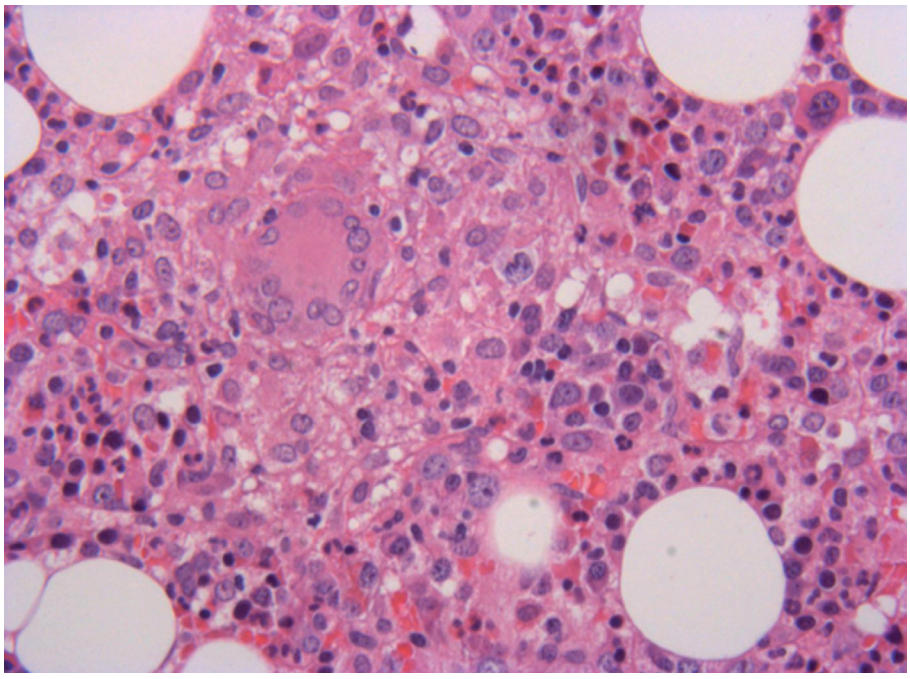

Fig. 1. Multiple granulomas on bone marrow biopsy.

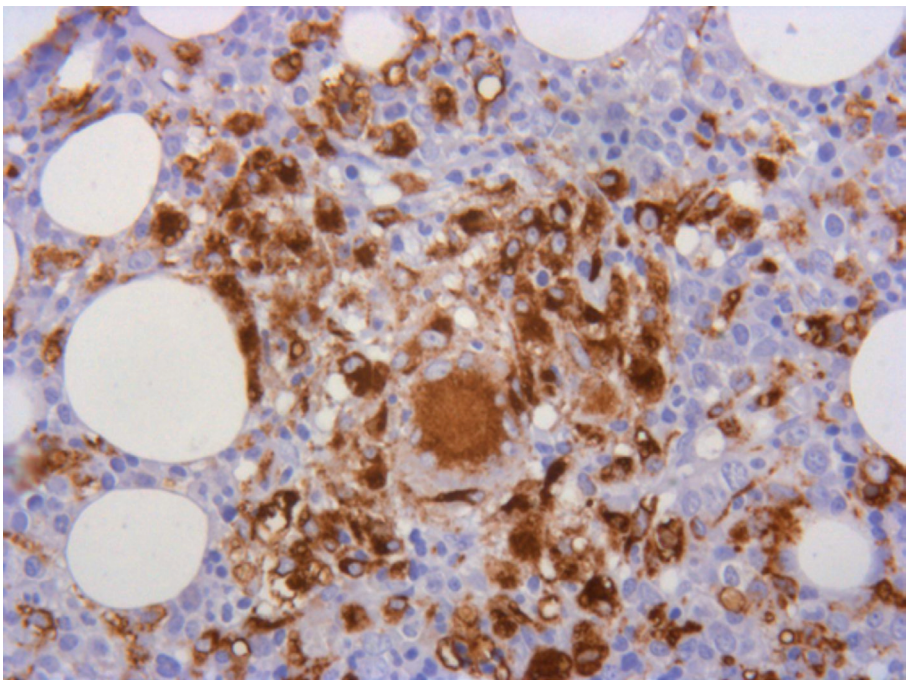

Fig. 2. Immunoistochemical staining showing CD68+ cells (macrophages) forming granulomas.

Due to the temporal proximity of BCG exposure and the high suspicion of disseminated BCG disease, antituberculous treatment was empirically started with isoniazid 5 mg/kg/day, rifampicin 10 mg/kg/day, ethambutol 20 mg/kg/ day and moxifloxacin 500 mg/day as well as intravenous prednisolone (0.5 mg/kg/day).

After a week, fever disappeared and patient's conditions improved with no need of oxygen therapy. Moreover, laboratory exams were ameliorated with reduction of inflammation. CT scan showed significant reduction of abdominal lymphadenopathy and interstitial lung infiltrates.

The patient was discharged after 30 days of treatment with recommendation to continue antibiotic therapy with isoniazid, ethambutol and rifampicin for another month. Comprehensively therapy was then prolonged with isoniazid and rifampicin for 4 further months. The patient had no complication or relapses during the 6-month treatment course and the post-treatment follow up.

DISCUSSION

BCG is a live-attenuated strain of *Mycobacterium bovis*, and its intravesical instillation showed great efficacy for treatment of non-invasive bladder carcinoma[5,6]. Systemic invasion of BCG is known to occur at a higher frequency when there is a breach in the integrity of urogenital mucosa. There are no known common comorbid conditions that would predispose to disseminated disease. An increased virulence of certain substrains could also play a role, but currently there is no evidence to support any difference in the complication rate among different BCG substrains. The spectrum of BCG-induced complications is wide. Sepsis is the most life-threatening condition associated with BCG immunotherapy, with hypotension and multisystem organ failure. This occurs in about 0.4% of cases and carries a high risk of mortality. Pancytopenia, described in 0.1% of patients[7], is also considered to be a symptom of systemic infection. This patient presented fever, pancytopenia, with clear septic features shortly after the instillation compatible with disseminated BCG infection. The mechanism by which BCG leads to the development of infectious complications is not fully understood. There is considerable debate regarding whether inflammation or infection is the predominant mechanism in the pathogenesis of BCG disease. The hypersensitivity hypothesis is based upon the presence of granulomas and the absence of recoverable organisms, as described in this case. A response to glucocorticoids, administered along with antituberculous drugs, has also supported hypersensitivity response. By contrast, other cases reports have demonstrated viable organisms in a variety of tissues, including lung, liver, pancreas, and bone marrow[8]. The fastidious growth nature of BCG in culture and a doubling time of 24 to 48 hours contribute to the difficulty in its isolation. Further compounding this controversy are several cases of delayed infection, months to even years after the original BCG administration[9]. The management of complications related to intravesical BCG treatment depends on their type and severity. Mild complications, such as low-grade fever and local lower urinary tract symptoms usually require no specific treatment and are self-limiting. On suspicion of a systemic disease due to BCG, antituberculous therapy should be initiated. There are no official guidelines regarding treatment, but as M. bovis is usually resistant to pyrazinamide, a regimen that includes isoniazid, rifampicin, ethambutol and a fluoroquinolone, such as levofloxacin, is usually administered fort at least 6 months[10]. Empirical treatment with corticosteroids was also shown to be effective in reducing symptoms[11].

In the present case, symptoms first resolved after adding prednisone, indicating a principal role for inflammation in systemic disease.

CONCLUSIONS

Our case highlights the importance of early recognition and prompt treatment of patients with disseminated BCG infection. This diagnosis should be kept in mind in spite of negative smears and cultures, although the gold standard is a positive Mycobacterium culture.

Acknowledgments:
We thank Dr. Pietro Leanza for his valuable English revision.

Availability of data and materials:
Data sharing is not applicable to this article as no datasets were generated or analysed during the current study. We used only information contained in the patient's clinical record.

Authors' contributions:
MD wrote the paper. EC, ES, PG, GS gave clinical assistance to the case. AM and BC revised the paper. All authors read and approved the final manuscript.

Consent for publication:
Written informed consent for publication of clinical details was obtained from the patient and it is.

Conflict of Interest:
The authors declare that they have no conflict of interests.

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