Disseminated *Mycobacterium bovis* Infection Complicating Intravesical BCG Instillation for the Treatment of Superficial Transitional Cell Carcinoma of the Bladder

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**ABSTRACT**

**BACKGROUND:** Intravesical instillation of Bacillus Calmette–Guérin (BCG) remains a first-line treatment for superficial transitional cell carcinoma of the bladder. Although its use is relatively safe, severe complications such as granulomatous hepatitis, osteomyelitis, pneumonitis, and sepsis occur in few patients. Complications of intravesical instillation of BCG can be local or systemic, with early or late presentation.

**CASE PRESENTATION:** Here, we report an 88-year-old man who developed fever, rigors, and episodes of syncope following fourth intravesical BCG instillation for the treatment of superficial transitional cell carcinoma of the bladder. Pancytopenia, disseminated intravascular coagulation, ground glass appearance on computerized tomography of the chest scan in addition to multiple bone marrow granulomas, suggested the diagnosis of disseminated BCG infection. All these features recovered on antituberculosis treatment.

**CONCLUSION:** Our case study highlights the importance of early recognition and prompt treatment of patients with disseminated BCG infection following intravesical instillation. Although isolation of mycobacterium is desirable to make the diagnosis, it is not unusual to have negative smears and cultures and this should not be used to dismiss the possibility of BCG infection.

**KEYWORDS:** intravesical BCG, bladder carcinoma, disseminated BCG disease

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**Introduction**

Bacillus Calmette–Guérin (BCG) vaccine, a live attenuated strain of *Mycobacterium bovis*, was first introduced in humans in 1921.¹ Intravesical BCG instillation was initially described by Marales in 1976;² it is used for the treatment of superficial transitional cell carcinoma of the bladder. However, a rare but severe complication of BCG immunotherapy is the development of disseminated BCG disease that can be manifested by features of miliary pneumonitis, sepsis, and bone marrow involvement.²³ Symptoms can present as early as a few hours or as late as several months following the BCG therapy. Its antitumor effect seems to be T-lymphocytes dependent; however, its precise mode of action is not yet fully understood.³ Although transurethral resection of bladder tumor (TURBT) can completely eradicate a tumor, recurrence rates range from 48% to 70%, and progression occurs between 7% and 40% of the time.⁴ These relatively high rates suggest the need to consider adjuvant intravesical therapy, like BCG, in many patients. The patient has given consent for publication of this report.

**Case Presentation**

An 88-year-old male patient was diagnosed with superficial transitional cell carcinoma of the bladder (T1). He underwent multiple sessions of TURBT followed by weekly intravesical BCG therapy in June 2013. Immediately following his fourth BCG session, he developed fever, rigors, respiratory distress, episodes of syncope and confusion, raised inflammatory markers, and disseminated intravascular coagulation (DIC) shortly after BCG instillation. Brain computerized tomography (CT) scan and Holter monitor were normal. An electroencephalogram (EEG) demonstrated features suggestive of moderate global cerebral dysfunction. Three days later, he developed fever of 39.5 °C associated...
with chills and rigors and received empiric intravenous antibiotics. His course was complicated by gross hematuria. His hemoglobin level (Hb) dropped from 13.8 to 7.6 g/dL. Blood and cerebrospinal fluid (CSF) culture reports were negative; CSF protein level was 0.35 g/L, white blood cell (WBC) count was 1 cell/µL, and glucose was 7.1 mmol/L. The polymerase chain reaction for *Mycobacterium tuberculosis* in sputum and CSF was also negative. Laboratory examination revealed pancytopenia with WBCs 1.8 × 10^9 cell/L, Hb 10.3 g/dL, and platelets 39 × 10^9/L. There was evidence of DIC with elevated prothrombin time 18.7, partial thromboplastin time 47, low fibrinogen 1.1 g/L (normal range 2.0–4.0 g/L), a positive D-dimer test, and serum albumin 28 g/L. Levels of bilirubin, alanine aminotransferase, and alkaline phosphatase (64 µmol/L, 320 IU/L, and 244 IU/L, respectively) were elevated. Lactate dehydrogenase level was high (1128 IU/L), and CA-125 was 88 U/mL. CT scan of the chest and abdomen was reported to show bilateral basal ground glass opacities and air space disease associated with bilateral mild pleural effusion. A ground glass nodule was seen in the (R) upper lobe (Fig. 1). Bone marrow aspirates and trephine biopsy showed multiple small granulomas (Figs. 2 and 3). Liver biopsy, on the other hand, could not be done because of the DIC. Sputum, bone marrow, CSF, and urine smear test results and cultures for mycobacteria were negative.

He received isoniazid 300 mg, rifampicin 600 mg, and ethambutol 1.2 g, together with prednisolone 60 mg once daily. One month following anti-Tuberculosis (TB) treatment, he developed skin rash and eosinophilia. Skin biopsy showed spongiform and interface dermatitis with few eosinophils consistent with drug eruption. Treatment of TB was adjusted. He continued to improve gradually with defervescence and normalization of his blood counts. His DIC was reversed, and C-reactive protein dropped from 98 mg/L to 8 mg/L. CA-125 decreased from 88 to 16 U/L. His latest blood tests showed Hb 12.9 g/dL, WBC 9 × 10^9 cell/L, platelets 364 × 10^9/L, alanine aminotransferase 13 IU/L, alkaline phosphatase 72 IU/L, and albumin 39 g/L. The patient was doing well at the time of preparation of this manuscript.

**Discussion**

Most bladder cancer patients initially present with superficial disease. Intravesical BCG instillation has been shown to delay the time to the first recurrence after TURBT and to reduce the risk of progression to muscle invasive disease. Also, intravesical BCG treatments have been shown to eradicate residual tumors in some patients with papillary carcinoma and carcinoma in situ and to improve overall survival. Rare but severe complications can occur, which can be local or systemic, with early or late presentation.

We here report a patient with disseminated BCG infection following intravesical instillation for superficial bladder carcinoma. He presented with fever, rigors, respiratory distress, raised inflammatory markers, and DIC shortly after the instillation; features compatible with disseminated BCG infection. This acute presentation is probably due to high levels of cytokines released directly into the bloodstream as a part of the hypersensitivity response rather than mycobacterium dissemination. There is still controversy relating to whether the clinical presentation of BCG systemic disease is caused by actual dissemination of *M. bovis* in the involved tissues or is secondary to hypersensitivity reaction. The isolation of viable

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**Figure 1.** CT scan of chest showing bilateral ground glass and air space opacities and a ground glass nodule seen in the right upper lobe.

**Figure 2.** Bone marrow trephine biopsy shows granulomas.

**Figure 3.** Immunohistochemical stain using CD68 highlights the clustering of epithelioid histocytes in the granulomas.
mycobacteria from involved tissues suggests an ongoing active infection. The presence of granulomas in the absence of isolated mycobacteria in other cases, however, favors a hypersensitivity response. Moreover, response to corticosteroids in addition to antitubercular drugs further supports a hypersensitivity etiology.

This patient presentation fits into early presentation of the disease that typically occurs within three months of BCG instillation. In a series of 41 patients with BCG infections, patients with early disease developed an illness characterized by fever, generalized symptoms, and evidence of systemic infection with involvement of the liver and lungs in nearly all cases.8 Although systemic sepsis and even death have been reported in cases with early BCG infection, intravesical treatment with BCG appears to be relatively safe. In a study of 1200 patients who received BCG immunotherapy, only 2.9% incidence of high fever (>39 °C), 1.0% major hemorrhia, 0.9% granulomatous prostatitis, 0.7% granulomatous pneumonia/ hepatitis, 0.5% arthritis or arthralgia, 0.4% epididymo-orchitis, 0.4% life-threatening BCG sepsis, 0.3% urethral obstruction, and 0.1% cytopenias were reported.8 Previous reports have speculated as to the mechanism of BCG dissemination. One accepted risk factor is recent urological trauma.10 Our patient had an episode of severe hematuria, possibly secondary to trauma and warfarin therapy.

Like many reported cases in the literature, the search for acid-fast bacilli performed on bone marrow, sputum, urine, and CSF returned negative. This inability to identify M. bovis in affected tissues is not entirely unexpected. Some authorities use the negative culture results to support their hypothesis that the granulomas in BCG disease result from a hypersensitivity reaction and not an infection.11

There have been no randomized trials to assess the optimal therapy for BCG infection. Currently, due to the lack of randomized trials on the side effects of intravesical BCG, minimal recommendations are available, and severe complications are usually described in case reports only.12 The suggested first-line treatment is the combination of isoniazid, rifampicin, and ethambutol. M. bovis is intrinsically resistant to pyrazinamide, and low-level isoniazid resistance has been described in some strains.13

BCG-related dermatitis have been previously reported; however, the development of the rash in the setting of improved inflammatory biomarkers and the skin biopsy changes are more consistent of a drug rash.14

Pancytopenia, abnormal liver function tests, DIC, and raised C-reactive protein have all reverted to normal. Interestingly, the CA-125 declined from 88 to 16 U/mL (normal range 0–35 U/mL). There are few reports on increased CA-125 in M. bovis infection. On the other hand, many studies have documented the utility of CA-125 in patients with M. tuberculosis infection. Serum CA-125 levels in patients with TB peritonitis are as high as seen in ovarian cancer associated with peritoneal infiltration. These high levels fall after adequate treatment and are considered as a useful marker in the diagnosis and follow-up of patients with TB peritonitis.15 Although our case is not the first case report on such a severe complication as similar cases were previously reported in the literature,6,7,16 it adds to previous reports and reinforces the recommendation that all patients should be made full aware of the potential systemic and delayed complications of BCG immunotherapy.

Conclusion
Our study highlights the importance of early recognition and prompt treatment of patients with disseminated BCG infection following intravesical instillation. Although isolation of mycobacterium is desirable to make the diagnosis, it is not unusual to have negative smears and cultures, and this should not be used to dismiss the possibility of BCG infection.

Author Contributions
Conceived and designed the experiments: FE, GE. Analyzed the data: NA, MS, NE. Wrote the first draft of the manuscript: FE, AA, MS, NE. Contributed to the writing of the manuscript: NA, GE. Agree with manuscript results and conclusions: FE, GE, MS, NE. Jointly developed the structure and arguments for the paper: NA, AA. Made critical revisions and approved final version: GE, FE. All authors reviewed and approved of the final manuscript.

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