Disseminated Mycobacterium Sepsis with Bone Marrow, Liver, and Lung Involvement Following Intravesical Bacillus Calmette-Guerin (BCG) Therapy

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Abstract

Introduction
Bacillus Calmette-Guerin (BCG) therapy is first-line therapy for high grade non-muscle invasive bladder cancer (NMIBC).

Case Presentation
A 54-year-old male presented with fevers, rigors, and hematuria one week following intravesical BCG administration for treatment of NMIBC. He developed fever, pancytopenia, elevated liver enzymes and pulmonary infiltrates with the progression of symptoms despite broad-spectrum antimicrobial therapy. A bone marrow biopsy showed granulomatous infiltration; cultures of urine demonstrated the growth of Mycobacterium bovis. A diagnosis of disseminated BCG infection secondary to intravesical administration was made; rifampin, isoniazid, ethambutol, and high dose prednisone were initiated.

Conclusion
Adverse events associated with BCG administration have been attributed to both the primary mycobacterium infection and to hypersensitivity reactions. Timely collection of histopathology can lead to early treatment of disseminated BCG with good outcomes. Internists should have a high index of suspicion for patients presenting with organ dysfunction with an immediate or remote history of intravesical BCG administration.

RESUME

Introduction
Le Bacillus Calmette-Guerin (BCG) est le traitement de première intention du cancer de la vessie non invasif non musculaire (NMIBC) de haut grade.
Présentation de cas
Un homme de 54 ans a présenté des fièvres, des rigueurs et une hématurie une semaine après l’administration intravésicale de BCG pour le traitement du NMIBC. Il a développé de la fièvre, une pancytopenie, une élévation des enzymes hépatiques et des infiltrations pulmonaires avec la progression des symptômes malgré un traitement antimicrobien à large spectre. Une biopsie de moelle osseuse a révélé une infiltration granulomateuse ; des cultures d’urine ont démontré la croissance de Mycobacterium bovis. Un diagnostic d’infection au BCG disséminée secondaire à l’administration intravésicale a été posé ; la rifampicine, l’isoniazide, l’éthambutol et la prednisone à dose élevée ont été amorcés.

Conclusion
Les effets indésirables associés à l’administration du BCG ont été attribués à la fois à l’infection mycobactérienne primaire et aux réactions d’hypersensibilité. La collecte en temps opportun de données histopathologiques peut mener à un traitement précoce du BCG disséminé avec de bons résultats. Les internistes devraient avoir un indice élevé de suspicion chez les patients présentant un dysfonctionnement organique et des antécédents immédiats ou à distance d’administration intravésicale de BCG.

Intravesical Bacillus-Calmette-Guerin (BCG) therapy is the standard of care as adjunctive therapy for non-muscle invasive bladder cancer (NMIBC) in Canada. Therapy is generally well tolerated; however, serious adverse events can occur. We present a case of disseminated BCG infection following intravesical BCG therapy and discuss clinical, diagnostic and therapeutic aspects of relevance to clinicians who care for patients receiving BCG intravesical therapy.

Case Presentation
A 54-year-old male presented to the emergency department with persistent fever, chills, and hematuria despite receiving antimicrobials targeting a urinary tract infection as an outpatient. One week prior, he received his first intravesical administration of BCG following traumatic Foley catheter insertion for the treatment of non-muscle invasive urothelial carcinoma. He was diagnosed with urothelial carcinoma six-months prior and has undergone two transurethral resections of the bladder tumour procedures. His remaining past medical history included rectal carcinoma treated with local radiation and resection, paroxysmal atrial fibrillation, and hypertension.

On examination, his maximum temperature was 39.1°C and his heart rate was 120 beats per minute and irregular. Remaining vital signs were unremarkable. Rigors and diaphoresis were noted. The remainder of his physical exam was unremarkable. Laboratory investigations included a complete blood count, electrolytes, and renal function which were unremarkable. Liver enzymes including aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) were elevated at 104 IU/L, 138 IU/L, 256 IU/L and 353 IU/L respectively. Urinalysis was suggestive of cystitis. Urine and blood cultures were sent. His initial chest radiography (CXR) was unremarkable.

The patient was initially admitted for sepsis with a suspected urogenital source and was started on broad-spectrum antimicrobials. Despite this therapy, his fevers and diaphoresis persisted in hospital. Liver enzymes remained elevated; a work-up for infectious, autoimmune, metabolic, and structural causes of elevated liver enzymes was unremarkable. Computed tomography of the abdomen showed benign cysts and magnetic resonance imaging of the liver was normal. His condition further deteriorated as he developed hypoxemia with new bilateral infiltrates on CXR, as well as a relative pancytopenia with WBC 2.0 cell/L, Hb 100 g/dL and platelets 90 x10^9/L. A presumptive diagnosis of disseminated BCG was made. Bone marrow biopsy demonstrated non-caseating granulomas, supporting this diagnosis (Figure 1). Bone marrow and cultures for Mycobacteria were negative. Urine cultures demonstrated the growth of Mycobacterium bovis after three weeks.

The patient was managed with rifampin 600 mg oral once daily, isoniazid 300 mg oral once daily, ethambutol 1200 mg oral once daily, and prednisone 40 mg oral once daily. Ten days following the initiation of therapy, his fevers, hepatitis, and hypoxemia resolved. The pancytopenia resolved following two months of therapy. Glucocorticoids were tapered as an outpatient as tolerated. He was evaluated in follow-up by the outpatient infectious diseases specialist and was continued on his anti-tuberculosis regimen for nine months. Unfortunately,
he later developed metastatic urothelial carcinoma and died due to the progression of this illness within the following year.

Discussion
BCG is a live, attenuated strain of *Mycobacterium bovis*. The intravesical administration of BCG has been approved as first-line therapy for non-muscle invasive urothelial carcinoma within North America. The Canadian Urology Association’s 2015 guidelines suggest high-grade NMIBC should be treated with intravesical BCG immunotherapy, which has been shown to reduce tumour recurrence, progression, and mortality in this population. Treatment courses often last three years.

The Canadian Cancer Society estimate there will be 206,200 new cases of cancer in 2017. Since bladder cancer accounts for 4% of all new cancer diagnosis in Canada per year, there will be an estimated 8248 new cases of bladder cancer in 2017. Non-muscle invasive bladder cancer typically accounts for 75–80% of bladder cancer cases. Based on the Canadian Urology Association’s 2015 guidelines, BCG immunotherapy will be offered as first-line therapy for thousands of patients within Canada annually.

The adverse events associated with BCG may occur immediately or months after administration, and range from local inflammation to serious systemic effects. A local inflammatory response is often seen and may manifest as a self-limited cystitis. Severe local adverse effects are uncommon and include prostatitis, epididymo-orchitis, ureteric obstruction, and renal abscess. Disseminated infection may also lead to multi-organ dysfunction including reactive arthritis, osteomyelitis, nephritis, and large vessel vasculitis. Fever is the most common, occurring in 2.9% of patients. Cytopenias are present in about 0.1% of patients. Severe complications usually occur at first instillation but are not dependent on the number of instillations. The rate of death directly attributable to BCG intravesical treatment is difficult to estimate and current literature has estimated it to be <1:12500.

The disseminated infection in our case initially presented with fever and sepsis, followed by the development of hepatitis, pneumonitis, and finally cytopenias.

Factors that increase the risk of adverse events following intravesical BCG instillation have been studied. A recent case series retrospectively analyzed 256 patients who received BCG instillation for NMIBC at a single centre over 6 years and were unable to identify any factors associated with disseminated infection; however, only 11 cases of BCG infection occurred which severely limits power to detect this rare complication. However, traumatic Foley catheter insertion and urinary tract infections at the time of BCG instillation have been identified as risk factors for BCG infection. The magnitude of risk associated with these factors, or host factors such as previous surgical bladder mucosal manipulation or immunosuppression, remain poorly quantified. Nevertheless, prudent procedural guidelines for the administration of intravesical BCG exist. Contraindications to administration include recent (7–14 days) urothelial procedure or injury, evidence of fever, urinary tract infection, or gross hematuria, and patients who are immunosuppressed, have active tuberculosis infection, or had previous adverse events secondary to BCG. The patient in our case suffered traumatic Foley catheter insertion prior to BCG instillation.

Suspicion of disseminated infection secondary to intravesical BCG is primarily clinical, however, the diagnosis may be supported by specific investigations. Following clinical suspicion, microbiological and histopathological specimens should be obtained promptly, ideally prior to treatment. Patients should have microbiological samples drawn from the blood and any potentially infected sources, and sent for mycobacterial culture and acid-fast bacilli staining. In a case review of 282 patients diagnosed with disseminated BCG, 242 patients were evaluated with microbiological investigations. Positive results were present in 25.3% of acid-fast bacilli stains, 40.9% of mycobacterial cultures of any source, and 41.8% of PCR assays. It is important to note that mycobacterial cultures of urine suffer from false positives in this setting, due to >10^8 live organisms per 50 mL being instilled. Given the low sensitivity of microbiological evaluation and the possibility for false positives from a urinary source, histopathological diagnosis is key. In the previously discussed case review, histopathological evaluation revealed granulomatous inflammation in 86.3% of tissues biopsied. The most common tissues included lung (21%), liver (20%), and bone marrow (20%). Therefore, patients with suspected disseminated BCG should receive a thorough evaluation for possible organ infiltration, with specific attention to less invasive tests (e.g., Bone marrow biopsy), to obtain histopathological confirmation. Negative microbiological and histopathological investigations...
do not rule out a diagnosis of disseminated BCG and should not delay initiation of therapy.

Patients with multi-organ and/or septic complications from disseminated BCG often respond well to treatment with antimycobacterial agents and corticosteroids.9–11 Rifampin, isoniazid, and ethambutol are preferred agents. *Mycobacterium bovis* is intrinsically resistant to pyrazinamide.10 Systemic glucocorticoids have been employed in many cases as adjunctive therapy to help diminish the hypersensitivity reaction associated with mycobacterium dissemination, especially in cases of miliary disease or pneumonitis. Most patients diagnosed and treated early in this way do make an eventual recovery.7

**Conclusion**

BCG instillation is the standard of care for certain types of urothelial carcinoma in Canada. This case helps illustrate the spectrum of serious adverse events associated with this therapy. Early diagnosis and treatment can lead to good outcomes. Timely collection of histopathology in the appropriate clinical context is paramount for diagnosis. Internists should have a high index of suspicion for any patient presenting with organ dysfunction with an immediate or remote history of intravesical BCG administration.

**References**