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Disseminated BCG Infection after Intravesical Instillation in Bladder Cancer: Early Recognition and Prompt Treatment

Marco Distefano*

Department of Infectious Diseases Umberto I° Hospital, ASP 8 Siracusa via Testaferrata, 196100 Siracusa, Italy

***Corresponding author:** Marco Distefano, Department of Infectious Diseases, Umberto I° Hospital, ASP 8 Siracusa via Testaferrata, 196100 Siracusa, Italy, Tel: 00-39-0931-724213, Fax: 00-39-0931-724108; E-mail: erdis@tin.it

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Abstract

Intravesical administration of Bacillus Calmette-Guérin delay tumor progression, decrease the need for cystectomy, and improve overall survival of non-muscle invasive bladder cancer.

In immunocompetent patients, iBCG is usually well tolerated; but uncommonly, severe local and systemic complications can occur. Definitive diagnosis of BCG infection requires *M. bovis* BCG culture (of bodily fluids or tissue from involved sites) but the fastidious growth nature of BCG in culture and a doubling time of 24 to 48 hours contribute to the difficulty in its isolation.

On suspicion of a systemic disease due to BCG, antituberculous therapy should be initiated. There are no clinical trials and no official guidelines regarding treatment, but as *M. bovis* is usually resistant to pyrazinamide and cycloserine, a regimen that includes isoniazid, rifampicin, ethambutol and a fluoroquinolone, such as levofloxacin, is usually administered for at least 6 months.

In the setting of extensive miliary involvement and/or respiratory failure, the concomitant administration of glucocorticoids given the potential role of hypersensitivity in the pathogenesis of the disease, has been associated with clinical improvement in case reports.

Keywords: BCG; Bladder cancer; M. bovis; Sepsis

Description

Bladder cancer (BC) is the most common malignancy involving the urinary system. Urothelial (transitional cell) carcinoma is the predominant histologic type (90% of all bladder cancers). The spectrum of BC includes non-muscle invasive (NMIBC), muscle-invasive, and metastatic disease. Each cancer has different clinical behavior, biology, prognosis, and treatment [1].

Cystoscopy is the gold standard for the diagnosis and staging of bladder cancer. Any visible tumor or suspicious lesion seen should be biopsied or resected transurethrally to determine the histology and depth of invasion into the submucosa and muscle layers of the bladder. For patients with documented high-risk disease confirmed on a diagnostic transurethral resection of bladder tumor (TURBT), repeat resection may be indicated to eliminate the risk of understaging.

Stage is the most important independent prognostic variable for progression and overall survival for invasive bladder cancer. The eighth edition (2017) of the tumor, node, metastasis (TNM) system is used to stage bladder cancer. For patients with non-muscle invasive cancer (Ta, T1, Tis), TURBT and bladder biopsies determine the stage.

BCG is a live attenuated strain of Mycobacterium bovis that was initially investigated as a vaccine against tuberculosis. In NMIBC iBCG induce local immune activation, leading to death of tumor cells.

Intravesical administration of Bacillus Calmette-Guérin (iBCG) has been shown to delay tumor progression, decrease the need for cystectomy, and improve overall survival of NMIBC. TURBT plus iBCG rather than immediate cystectomy is the treatment of choice for the initial NMIBC management (similar survival rate: 70 to 86 percent) [1]. Although late relapses are observed, iBCG significantly reduces recurrences. In immunocompetent patients, iBCG is usually well tolerated; uncommonly, severe local and systemic complications can occur [2].

The spectrum of iBCG-induced complications is wide. Acute toxicities (fever, malaise, dysuria, or mild hematuria) are the most common complications (up to 85 percent of patients) [3]. Analgesics and/or anti-inflammatory drugs resolve symptoms within 48 hours (reflecting a hypersensitivity reaction) and iBCG may be resumed. In addition to acute toxicities, both localized and systemic infectious complications can occur after iBCG (1%-5% of cases).

Systemic disease occurs when BCG disseminates outside the genitourinary tract *via* the bloodstream to other sites [4]. Organ localizations such as granulomatous pneumonia or hepatitis are rare.The risk of systemic invasion of BCG is increased with extensive resection and when there is a breach in the integrity of urogenital mucosa. Currently there is no evidence to support any difference in the complication rate among different BCG substrains.

Complications associated with BCG immunotherapy may represent a hypersensitivity reaction, active infection, or both. The hypersensitivity reaction hypothesis is based upon the presence of granulomas and the absence of recoverable organisms and favorable

clinical response to administration of systemic corticosteroids. By contrast, demonstration of viable organisms in a variety of tissues, including lung, liver, pancreas, and bone marrow supports active infection. The fastidious growth nature in culture and a doubling time of 24 to 48 hours contribute to the difficulty of BCG isolation. Further compounding this controversy are several cases of delayed infection, months to even years after the original BCG administration.

Definitive diagnosis of BCG infection requires *M. bovis* BCG culture (of bodily fluids or tissue from involved sites). A presumptive diagnosis may be made in the setting of positive acid-fast bacilli (AFB) smear, histopathology demonstrating granulomas, and/or positive nucleic acid amplification (NAA) test on fluid or tissue, in the appropriate clinical and epidemiologic setting and no alternative etiology. The sensitivity of AFB smear, mycobacterial culture, and molecular testing is limited. Microbiologic diagnosis was established more frequently among patients with localized BCG infection (53 versus 38 percent). Histopathology demonstrated granulomatous inflammation in 86 percent of cases; the highest yield biopsy sites were lung, bone marrow, and liver. Caseous necrosis is typically absent [5]. NAA tests cannot differentiate between members of the Mycobacterium tuberculosis complex. The differential diagnosis of infectious complications associated with iBCG includes: mild post-instillation symptoms, bacterial infection , fungal infection , alternative mycobacterial infection .

Early recognition and prompt treatment of patients with disseminated BCG infection are essential. Suspicion should be high even when smears and cultures are negative.

The treatment of infectious complications associated with iBCG depends on clinical presentation (type and severity) [6]. Mild complications 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 clinical trials and no official guidelines regarding treatment, but as *M. bovis* is usually resistant to pyrazinamide and cycloserine, a regimen that includes isoniazid, rifampicin, ethambutol and a fluoroquinolone, such as levofloxacin, is usually administered for at least 6 months.

In the setting of extensive miliary involvement and/or respiratory failure, the concomitant administration of glucocorticoids given the potential role of hypersensitivity in the pathogenesis of the disease, has been associated with clinical improvement in case reports [7,8]. There is no standard regimen for administration of adjunctive glucocorticoids; a reasonable strategy consists of prednisone 40 to 60 mg orally daily for 3 to 5 days, followed by a gradual taper over a few weeks.

Conclusion

Even if iBCG is a safe procedure rare severe complications can occur. High grade of suspicion should be kept for early recognition of disseminated BCG infection. Prompt treatment of disseminated infection is essential and requires a long course of antibiotics and sometimes steroids.

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