Pleural Effusion Caused by Bacillus Calmette-Guérin Immunotherapy for Bladder Cancer

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Intravesical bacillus Calmette Guérin (BCG) instillation has been used as immunotherapy for early stage bladder cancer for >40 years. Complications from this therapy are rare but may result in a spectrum of infectious sequelae. Here we describe the case of an elderly man who presented with a pleural effusion and subcutaneous nodule several years after treatment with BCG.

Keywords. bacillus Calmette Guérin; bladder cancer; pleural effusion.

Since the 1960s, bacillus Calmette-Guérin (BCG) instillation has been used as immunotherapy for early stage bladder cancer for >40 years. Complications from this therapy are rare but may result in a spectrum of infectious sequelae. Here we describe the case of an elderly man who presented with a pleural effusion and subcutaneous nodule several years after treatment with BCG.

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DISCUSSION

Infectious complications of BCG administration have been referred to as “BCGitis” and “BCGosis” [4, 5]. Mycobacterium bovis’s vaccine potential was discovered nearly a century ago; neonates and infants in countries with a high prevalence of tuberculosis now receive the vaccination for protection against meningitis and disseminated tuberculosis [1]. A weakened
but live strain of mycobacterium commonly found in cows, *M. bovis*, serves as the source of the vaccination [1].

The immunomodulatory, antitumor effects of BCG were first recognized >40 years ago [6]. Since that time, it has been widely used in non-muscle-invasive bladder cancers. It is thought that BCG leads to a local immune activation involving a multitude of cytokines, as well as T cells, NK cells, dendritic cells, and polymorphonuclear cells [7, 8]. Bacillus Calmette Guérin infusions for bladder carcinoma are generally safe; Lamm and colleagues reported that among a cohort of 2602 patients, only 5% sustained serious side effects [9]. Infectious complications may occur, rarely leading to sepsis, usually shortly after intravesicular instillation of BCG [10]. The onset of complications is variable, ranging from immediate onset of symptoms to years later [3]. Risk factors for infection include immunodeficiency, occupational lung disease and traumatic catheterization; the latter two risk factors were present in our patient [2, 3]. Prior history of or exposure to pulmonary tuberculosis may put patients at risk for BCG infection after intravesicular instillation [11]. There have been several cases of prosthetic and device infections reported as well [12–14].

In a pooled analysis of case reports and their patients, Perez-Jacoste Asin and colleagues reported the most frequent manifestations of tuberculosis following BCG immunotherapy were disseminated, genitourinary, and osteoarticular disease [2]. At their institution, 11 of 256 patients (4.3%) developed infection. Pulmonary complications accounted for 2 of 282 (0.7%) analyzed patients. Another retrospective review from Spain revealed an incidence rate of 1.3% of patients receiving intravesicular BCG [15].

There is uncertainty about whether systemic BCGosis represents an infectious process among uniquely susceptible hosts, a hypersensitivity immune response to a minimally pathogenic organism, or a combination of both. A murine model of systemic BCG exposure demonstrated aspects of both processes and identified a survival advantage with systemic glucocorticoids in mice challenged with repeated systemic exposure to BCG [16]. Several individual case reports of BCGosis have described clinical resolution with systemic glucocorticoids [17, 18]. A retrospective review of 8 cases identified improvement with glucocorticoids among patients presenting with clinical signs of hypersensitivity, including pneumonitis and hepatitis [3].

The delayed presentation of pleural infection after BCG infusion makes this case particularly interesting. However, another group of authors from Belgium recently published a report describing systemic BCG infection in a patient 9 years after intravesical BCG [19]. Although *M. bovis* can also be contracted from contaminated dairy products or between persons, the rarity of this and the systemic symptoms associated with intravesical infusions strongly suggest that this infection was due to BCG instillation. This case illustrates that intravesicular instillation of BCG can result in extravesical complications years after initial exposure.

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