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ID CASE

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), derived from *Mycobacterium bovis*, has been used to treat bladder neoplasms [1]. Although it is generally safe, pleural effusion following BCG immunotherapy for bladder cancer is a rare complication [2, 3]. Here, we describe a patient who presented with a pleural effusion 6 years after initial BCG immunotherapy.

PRESENTATION

A 77-year-old retired male steelworker was diagnosed with urothelial carcinoma in 2008. His medical history was significant for congestive heart failure, hypertension, coronary artery disease status after coronary artery bypass graft, and repair of an abdominal aortic aneurysm. In 2009, he began treatment for bladder cancer with transurethral resection of bladder tumor procedures and intravesical BCG. Within hours of his first treatment, complicated by a traumatic catheterization and bleeding, he developed chills and sweats. Subsequent infusions led to continued sweats, profound fatigue, and weight loss. His last BCG treatment was in 2012; his systemic symptoms resolved thereafter. Risk factors for pulmonary disease included occupational dust and asbestos exposures as well as a previous 24-year smoking history. For nearly 3 years, the patient's subsequent cystoscopies demonstrated no recurrence of malignancy.

In the summer of 2014, the patient developed right-sided pleuritic chest pain, which he attributed to a fall from a ladder. In early 2015, he experienced increasing chest pain, fatigue, intermittent night sweats, and hematuria. He developed dyspnea and productive cough in May 2015; his symptoms improved with antibiotics, although his right-sided chest pain persisted.

The patient was evaluated in the pulmonary clinic for persistent right-sided chest pain. Aspiration of a right chest subcutaneous nodule yielded scant fluid positive for *M. bovis* by nucleic acid amplification testing and culture (Figure 1). The Cepheid GeneXpert assay confirmed infection with *Mycobacterium tuberculosis* complex. Although it is possible that this was a new infection unrelated to the patient's prior BCG therapy, the low prevalence of tuberculosis in Utah and the isolate's resistance to pyrazinamide strongly suggest that this infection was caused by subspecies Bovis.

Chest computed tomography (CT) revealed bilateral pleural effusions with right-sided loculations. Although the patient's fevers and night sweats resolved after starting isoniazid, ethambutol, and rifampin, his chest pain persisted, moving posteriorly. A repeat chest CT showed a right posterior extrapleural phlegmon (Figure 2). Interventional radiology performed a CT-guided biopsy of the right pleura; pathology revealed necrotizing granulomata with acid-fast bacilli without evidence of malignant cells. The patient's pain improved after the addition of prednisone. He completed a 9-month course of antimycobacterial therapy, including a prednisone taper, and his symptoms resolved. Imaging performed 1 year later did not show significant changes in the areas of bilateral pleural thickening; the complex pleural effusions persisted but did have slightly decreased enhancement from previous CT chest imaging. Unfortunately, while receiving therapy for his BCG infection, the patient developed tumor recurrence that was treated with radiation therapy.

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

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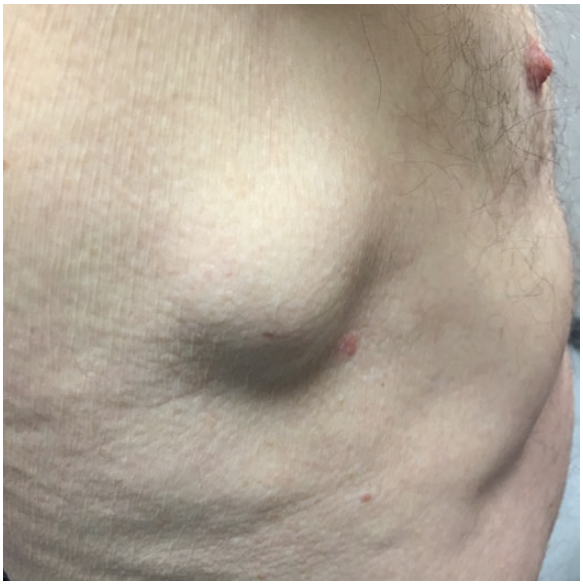

Figure 1. Subcutaneous nodule on the right lateral chest. Aspiration yielded *Mycobacterium bovis* organisms.

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

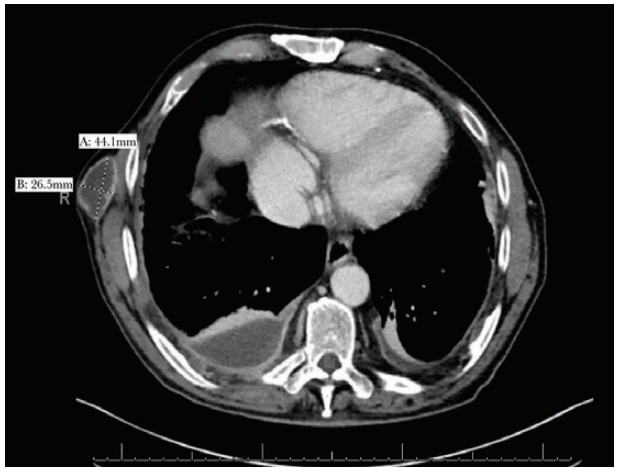

Figure 2. Computed tomography chest with intravenous contrast shows a complex pleural effusion, as well as radiographic visualization of the subcutaneous nodule. A, The anterior–posterior dimensions of the subcutaneous chest wall nodule. B, The medial–lateral dimensions of the subcutaneous chest wall nodule.

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 as 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-Jacoiste 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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