CLINICAL CASE REPORT

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Tuberculosis Complications After BCG Treatment for Urinary Bladder Cancer

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Summary. *Bacillus Calmette-Guérin (BCG) is an attenuated strain of Mycobacterium bovis that has been effectively used in the treatment of non-muscle invasive bladder carcinoma. The complications of this treatment are uncommon, and the causes of dissemination are still discussed. We report a case of disseminated tuberculosis in a 66-year-old smoking man without a history of pulmonary diseases, who underwent immunotherapy with BCG after the initial surgical treatment of bladder cancer. After the last BCG instillation, he developed a fever. The diagnosis of sepsis was not confirmed, and miliary pulmonary tuberculosis was suspected. The diagnosis was confirmed by clinical manifestation, computed tomography of the lungs, and histological examination.*

Introduction

Bacillus Calmette-Guérin (BCG) has been effectively used in the treatment of non-muscle-invasive bladder carcinoma (stage pTa, pT1, pTis) since 1976. The instillations of attenuated strains of *Mycobacterium bovis* are used to eradicate recurrent superficial bladder cancer and are more effective than chemotherapy. It has been reported to eradicate residual tumor in more than 60% of patients with papillary disease and in more than 70% of patients with carcinoma in situ (1, 2). Several meta-analyses have confirmed the significantly reduced recurrence rates of non-muscle invasive bladder cancer when a combined treatment of transurethral resection (TUR) and BCG instillation was administered (3). Despite the good results of BCG instillation, there are publications reporting the risk of recurrent and progressing non-muscle invasive bladder cancer after a long tumor-free period. A tumor-free period of 5 years after BCG treatment is a good prognostic sign, but recurrences after more than 10 years are possible (4).

Although the majority of patients tolerate intravesical BCG treatments without significant morbidity, a number of adverse reactions such as fever, hematuria, dysuria, nausea, and malaise have been reported. More serious complications include granulomatous prostatitis, pneumonitis, and hepatitis. Most of the BCG immunotherapy-associated symptoms are a result of the immune stimulation that is required to effectively eradicate cancer cells (1). Here we report a case of disseminated pulmonary *Mycobacterium bovis* infection that developed after intravesical BCG immunotherapy.

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Case Report

In September 2010, a 66-year-old man presented with a complaint of bleeding from the bladder. Laboratory testing showed a high number of red blood cells and a moderate number of leukocytes in the urine. Abdominal ultrasonography revealed no abnormalities in the kidneys; a mass with uneven margins measuring 3 cm was identified in the bladder. An x-ray of the chest showed no abnormalities. A few years ago, a routine checkup had revealed the enlarged prostate; treatment with doxazosin at a dose of 4 mg had been administered. No other abnormalities were found. Transurethral resection of bladder tumor was performed (pathohistological examination, T1N0M0G2). After 6 months, the tumor reoccurred, and the patient underwent the repeat transurethral resection of T1N0M0 recurrent bladder tumor. Immunotherapy with intravesical BCG instillations (a course of 6 weekly instillations) was initiated in July to prevent relapse. At 5 days after the last instillation in August, the patient developed dysuria and persistent fever. He was treated with quinolone antibiotics at home. However, the fever did not respond to treatment. The patient was hospitalized to the Department of Urology with suspected urosepsis, but urine and blood cultures were negative for bacteria. During the initial examination, no acute urological pathology was found. An x-ray of the chest was performed, and lung carcinosis was suspected. For the further clarification of diagnosis, computed tomography of the chest was

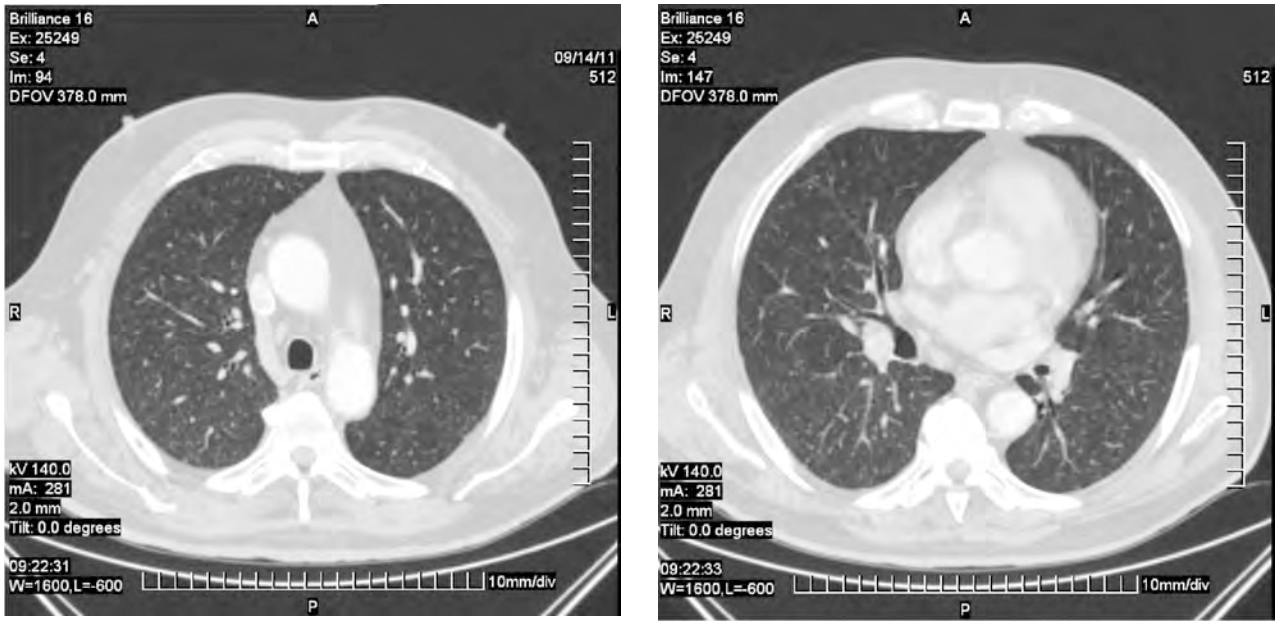

Fig. Computer tomography scans demonstrating small nodules caused by disseminated *Mycobacterium bovis* infection

performed. Lesions found in the pulmonary tissue were consistent with those observed in miliary pulmonary tuberculosis (Fig.). Hilar and mediastinal lymph nodes near the bifurcation were also enlarged. Tuberculosis bacteria were not detected in sputum. Afterwards, the diagnosis of tuberculosis was confirmed by histological investigation. Epithelioid granulomas were detected in the specimens of a transbronchial biopsy.

Treatment with rifampicin, isoniazid, ethambutol, and streptomycin was initiated. During the hospitalization, the patient developed thrombocytopenia. Treatment with rifampicin was discontinued, and thrombocytopenia disappeared. The treatment of tuberculosis was successful. If systemic adverse reactions such as miliary tuberculosis, septicemia, and polyarthritis followed by conjunctivitis occur after BCG therapy, glucocorticoids in combination with antituberculosis drugs can be prescribed (2). In our case, no glucocorticoids were prescribed.

Discussion

Immunotherapy with intravesical BCG is an effective treatment for patients with an early stage bladder carcinoma. Ultimately, the choice of treatment depends on the patient's risk of recurrence and progression (5). Preventive therapy after transurethral resection is indicated for patients with tumors at high risk of progression, for whom cystectomy has not been performed, and also for those with intermediate or high risk of recurrence and intermediate risk of progression (high grade TaT1 carcinoma or carcinoma in situ) (5). The treatment regimen most often applied is one weekly intravesical instillation of 1×10^8 or 1×10^{10} colony forming units diluted in normal saline, continuing for 6 weeks. If the desired effect is not achieved after the first induction, then treatment may be repeated.

Following intravesical instillation, live mycobacteria attach to the urothelial lining; the process is facilitated by fibronectin, a component of the extracellular matrix. This process leaves bacterial cell surface glycoproteins attached to epithelial cell membranes, and this antigen is thought to mediate the immune response. Tumor cell motility is also thought to be inhibited by BCG through a mechanism involving the BCG-fibronectin-tumor cell interaction. Biopsies of the bladder following BCG administration show an increased expression of human leukocyte antigen (HLA)-DR on tumor cells and infiltration of tumor and stroma with lymphocytes, predominantly T-helper cells and macrophages (6).

Despite the high efficacy of BCG immunotherapy, the potential complications of treatment are possible. It should be noted that more than 95% of patients tolerate BCG without significant morbidity (1). BCG should not be administered during the first 2 weeks after TUR, in patients with urinary tract infections or macroscopic hematuria, or after traumatic catheterization. Moreover, it should not be used in immunocompromised patients (immunosuppression, human immunodeficiency virus) (5, 7).

Adverse reactions that occur may be grouped into 2 categories: infectious and noninfectious (inflammatory). The latter reactions are most common. They include abacterial cystitis and dysuria, occurring in 80% of patients, hematuria (40%),

and low-grade fever (30%) (6). These adverse reactions are usually benign and resolve within 48 hours without intensive treatment (6). On the other hand, concurring cystitis may predispose the dissemination of BCG. During the inflammatory process, microlesions may occur in the bladder mucosa through which BCG may spread into surrounding tissue or blood.

Our patient had no obvious risk factors or immunosuppression, no traumatic catheterization was reported, and the treatment was initiated 4 months after the surgery. Malignant disease, smoking, and age were considered as potential risk factors in our patient. Because the patient had dysuria, we suspected that cystitis could be the cause of dissemination. The prevalence of dangerous complications after BCG immunotherapy, such as systemic sepsis or hypersensitivity reactions, was reported to be 0.4% (1).

A study performed by Lamm et al. in 1992 reported systemic reactions to BCG to be very rare. Of the 2602 patients who received BCG immunotherapy, only 5% had systemic complications, including fever (2.9%), granulomatous prostatitis (0.9%), pneumonitis and/or hepatitis (0.7%), arthralgia (0.5%), rash (0.3%), renal abscess (0.1%), sepsis (0.4%), and cytopenia (0.1%) (1, 7). Miliary tuberculosis is extremely rare, and only a small number of clinical cases have been reported, but physicians should be aware how to diagnose and treat BCG-induced complications.

There is a controversy as to whether the clinical presentation of miliary tuberculosis is caused by the actual dissemination of *Mycobacterium bovis* in the pulmonary tissue or if it is a secondary hypersensitivity reaction (8). The most reliable diagnostic method of tuberculosis, of course, is the detection of tuberculosis bacteria. Findings of microscopic or bacteriological tests confirm the disease in 40% to 50% of patients (9). Some data show that in the investigated specimens even when DNA and RNA amplification techniques are employed, sometimes *Mycobacterium tuberculosis, Mycobacterium bovis,* and other strains are difficult to detect, especially when pathogens spread through the blood stream. In describing the similar cases, mycobacterial infection is most commonly confirmed by pathological findings, but bacteria responsible for the disease are not detected (10).

Mycobacterium bovis in blood and bronchial aspirate may also be identified by a polymerase chain reaction technique. It is a rapid diagnostic method with a high sensitivity (11). Unfortunately, it was not possible to perform it in our laboratory.

Conclusions

Systemic complications such as miliary tuberculosis after BCG immunotherapy are not common, but are associated with high mortality. Early diagnosis and treatment are essential. In this case presented, the diagnosis of tuberculosis was confirmed by clinical manifestation, computed tomography of the lungs, and histological examination. The polymerase chain reaction technique is helpful to identify bacteremic BCG cases. A careful selection of patients for BCG therapy and the assessment of risk factors following the guidelines will help avoid such dangerous complications.

Statement of Conflict of Interest

The authors state no conflict of interest.

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