Bacillus Calmette-Guérin pneumonitis after intravesical instillation: Report of two cases and a review of the literature

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Objective. Intravesical administration of bacillus Calmette-Guérin is standard adjuvant treatment of non-muscle invasive bladder cancer. In spite of the fact that this immunotherapy is locoregional, there are still risk of some complications.
Methods. We describe two cases of systemic BCG infection after intravesical administration of BCG vaccine in patients with early stage of bladder cancer.
Results. Both patients suffered from systemic BCG infection manifesting as BCG pneumonitis. After standard therapy with antituberculotic agents, both of them fully recovered.
Conclusion. BCG infection can occur as a rare but potentially serious complication of this treatment procedure. Gravity of this side effect and its specific therapy require prompt and right diagnosis.

Key words: bacillus Calmette-Guérin, bladder cancer, intravesical therapy

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INTRODUCTION

Immunotherapy currently represents a therapeutic modality used across a spectrum of solid tumors. Using manipulation of the immune system in the management of cancer dates back to the late 19th century. The current renaissance of immunotherapy is due to the advent of immune checkpoint inhibitors[1]. Active non-specific immunotherapy has been used for decades before the era of immune checkpoint inhibitors with variable success, and most therapeutic regimens using these agents are now considered obsolete. The intravesical administration of bacillus Calmette-Guérin (BCG) is one notable exception to this trend, and intravesical BCG remains standard adjuvant therapy in patients with intermediate and high-risk non-muscle invasive urinary bladder cancer[2,3]. Because of the locoregional nature of intravesical therapy, systemic complications are rare[4]. One obvious potential complication mechanism is related to the fact that live bacteria are administered. Although BCG is a strain with reduced virulence, it may cause infection in subjects with attenuated immunity. Systemic BCG infection has been documented as a rare, but potentially serious complication of intravesical administration of this mycobacterial strain[4]. Here we report two new cases and present a review of the literature on this rare complication.

CASE DESCRIPTION

CASE 1

A 74-year old man was diagnosed in May 2021 with urinary bladder tumor. The patient was a non-smoker, had history of ischemic heart disease treated with coronary bypass surgery in September 2012, arterial hypertension, hyperlipidemia and diabetes mellitus controlled by diet.

The patient underwent transurethral resection of bladder tumor (TURBT) in May 2021. The histological examination revealed high grade T1 urothelial carcinoma, without evidence of carcinoma in situ. According to guidelines recommendation, transurethral re-resection of the scar was performed in June 2021 with histological findings of carcinoma in situ.

The patient was offered radical cystectomy with ureteroileostomy, but after in-depth discussion, he preferred adjuvant intravesical administration of BCG. During

September and October 2021, the patient received a total of 6 doses of intravesical BCG as an induction course. The follow-up cystoscopy with both target and random bladder biopsies in November 2021 did not reveal any evidence of tumor recurrence. The 7th dose of vaccine was administered on January 26, 2022.

In February 2022, (i.e. 5 months after BCG treatment initiation) the patient was admitted for fever (38.8 °C) accompanied by chills, dyspnea, cough and anorexia with weight loss (4 kg during the preceding 14 days). On examination the patient was afebrile, oxygen saturation was 94%, 16 breaths per minute, blood pressure 120/80 mm Hg, heart rate 76 beats per minute (bpm). Alveolar breathing was noted without added sounds. Because of epidemiological situation testing for SARS/COVID-19 was performed with negative result. Chest X-ray examination was inconspicuous and computed angiography (CT) of the chest excluded pulmonary embolism.

Laboratory tests showed a high level of C-reactive protein (44.6 mg/dL). Because of suspected incipient pneumonia the patient was treated with empirical antibiotic therapy comprising amoxicillin/clavulonic acid and clarithromycine. Bronchoscopy with bronchoalveolar lavage and transbronchial biopsy from the left lower lobe was performed. Tuberculin skin test was negative, microscopic examination of the BAL smears for acid-resistant rods and interferon-gamma releasing assays (both T-spot and Quantiferon) were also negative. However, PCR for Mycobacterium tuberculosis complex from the biopsy was borderline positive. The CT scan in February 2022 revealed multiple small nodules with pathological content (Fig. 1), up to 9 mm in size, but without lymphadenopathy.

The treatment with combination of rifampicin 600 mg daily (in the morning), isoniazide 300 mg daily (in the morning), and ethambutol 1200 mg daily (in the evening) was initiated in February 2022. Because of hepatopathy the medication was interrupted for a week in early March, 2022, and resumed in reduced dose. Ofloxacin was added in March 2022. The patient was discharged from the hospital in April 2022 and continued the therapy (planned treatment duration of 9 months). A recurrence of bladder carcinoma was detected in June, 2022, and treated with TURBT. Cystectomy was considered, but chemoradiation was started instead as a definitive local treatment in October, 2022, because of internal comorbidities.

CASE 2

A 42-year old man had a history of urothelial carcinoma of the urinary bladder treated by TURBT in November 2017 (grade 1, pT1N0M0). After the primary TURBT, the patient was treated with six doses of intravesical BCG vaccine between February and April 2018 (induction course). In April 2018, the patient presented to the emergency service with chills, fever of 39.3 °C and dry cough. Small nodules in both lungs were detected on a CT scan (Fig. 2) and the patient was treated with antibiotics followed by a regression of the radiological findings. Bladder tumor recurrence was detected during cystoscopy, and in May 2018, the patient underwent repeat TURBT with histological finding of another pTa low grade papillary urothelial carcinoma. Intravesical BCG therapy was continued. After 9 doses of intravesical BCG administration re-TURBT was performed in October 2018 with a histological finding of low-grade urothelial neoplasia. Intravesical BCG therapy was continued up to a total of 15 doses, with the last dose administered in April 2019. A follow-up cystoscopy in May 2019 revealed no evidence of tumor, and the patient was followed regularly with cystoscopy and cytology performed in 3-months intervals.

In August 2021, a chest X-ray revealed a lesion in the right lower lobe of 50 mm in diameter. Biopsy obtained during bronchoscopy confirmed a metastasis of urothelial carcinoma. Positron emission tomography/CT confirmed fluorodeoxyglucose uptake in the lung tumor with no other suspected lesions. The patient underwent right lower lobectomy in November 2021. Histology confirmed metastatic urothelial carcinoma. Numerous small granulomas with epitheloid lining and central necrosis were also noted. PCR confirmed the presence of Mycobacterium tuberculosis complex DNA.

The patient was admitted for the treatment of BCG infection in early December 2021. On admission he was

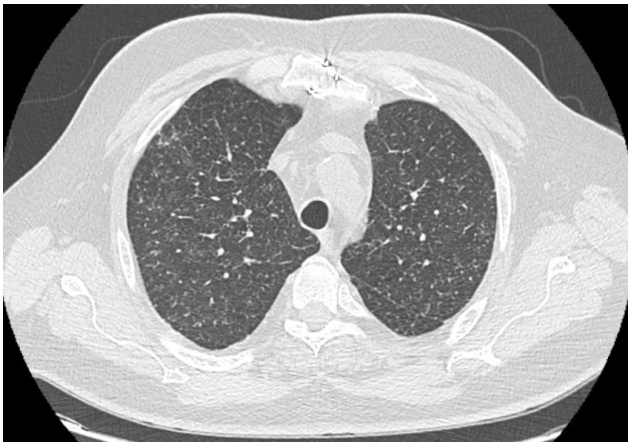

Fig. 1. Chest CT scan: multiple small nodules in the lungs.

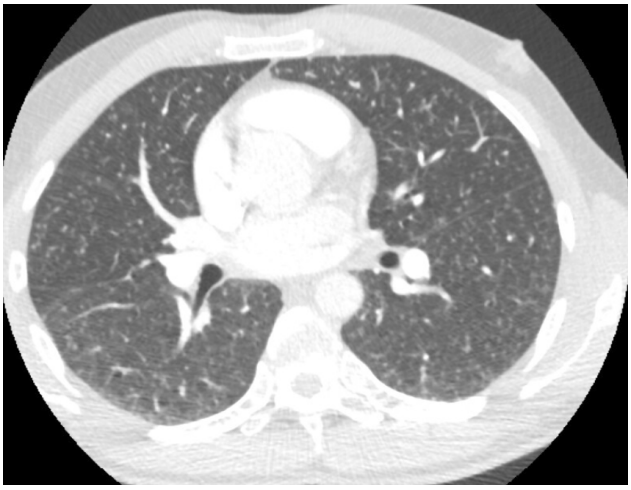

Fig. 2. Chest CT scan: multiple pulmonary nodules.

Table 1. Comparison of patient characteristics.

	Patient 1	Patient 2
Age at the time of BCG complication (years)	73	37
Sex	male	male
Initial stage of bladder cancer	pT1 (high grade)	pT1 (low grade)
Time from BCG therapy initiation (months) to BCG complication onset	4	3
Time from BCG therapy to diagnosis of BCG complication (months)	4	45
Number of BCG instilation	7	15
BCG treatment duration (months)	4	14
Type of toxicity	pneumonitis	pneumonitis
Number of involved organs	1	1
Genitourinary complication	no	no
Symptoms	fever, chills, cough, dyspnoe, weight loss	fever, chills, dry cough
Need for surgery	no	no
Antimycobacterial therapy duration (months)	9	9
Full recovery	yes	yes
Relapse of bladder cancer	yes	no
Time to relapse of bladder cancer (months)	13	NA
Death due to BCG complication	no	no

asymptomatic, with no history of weight loss, fever, dyspnea or other respiratory symptoms. Tuberculin skin test was negative, microscopic examination of the BAL smears for acid-resistant rods and interferon-gamma releasing assays (both T-spot and Quantiferon) were also negative. The treatment with a combination of rifampicin 600 mg daily (in the morning), isoniazide 300 mg daily (in the morning), and ethambutol 1200 mg daily (in the evening) was initiated in December 2021 with a planned treatment duration of 9 months. The treatment was tolerated well. At the time of writing this report in October 2022, the patient is well with no evidence of recurrent pulmonary infection or bladder cancer and continues therapy.

LITERATURE REVIEW AND DISCUSSION

Immunotherapy may be viewed as a form of targeted therapy aiming at activating the host response against the tumor[1,5]. Conceptually, immunotherapy has an advantage over cytotoxic chemotherapy, the medical treatment most commonly used in cases of malignant disease. It has a different mechanism of action resulting in greater efficacy in certain situation, and relative selectivity that is associated with fewer side effects[5]. Although the administration of immunotherapy is, in general, associated with better tolerance compared to cytotoxic agents, it has a peculiar set of toxicities that is specific for each modality of immunotherapy. Intravesical BCG therapy is unique in combining the selectivity of action aiming at activating the immune system with the anatomical selectivity associated with local intravesical application. Most side effects of anticancer agents are systemic, and local or regional administration of therapy significantly reduces systemic effects. Because live bacteria are used, an infection is induced that is mostly locoregionally confined[6]. Systemic infection represents a rare complication of intravesical BCG therapy[4] and in contrast to the situation when BCG is used as a vaccine in the prevention of tuberculosis[7].

BCG was originally introduced as a vaccine against tuberculosis, and the administration of the vaccine provides effective protection against severe miliary and meningeal tuberculosis[2]. Later it was discovered that locoregional administration of the vaccine may be effective in the control of early urinary bladder cancer and skin melanoma. Intravesical BCG administration remains a standard part of the management of patients with recurrent in situ or microinvasive bladder cancer.

The two cases of BCG pneumonia described here illustrate the wide range of presentations from symptomatic to completely asymptomatic illness. It may be speculated that in the second case BCG infection was suppressed by antibiotic therapy 4 years prior to the diagnosis which was a fortuitous finding during the examination of the resection specimen.

Given the rarity of this complication, systemic BCG infection after intravesical therapy has been described mostly as single case reports[8-32], or small retrospective series[33-35]. Some cases of systemic manifestations with pneumonitis or hepatitis were thought to be associated with a hypersensitivity response[13,33,36]. Cases of hypersensitivity pneumonitis after intravesical BCG therapy excluding other possible causes and responding to corticosteroids in the absence of antituberculosis therapy have been documented[37]. However, the distinction between hypersensitivity reaction and systemic infection may be difficult in individual cases[10,27,28]. The identification of mycobacteria in distant organs obviously supports the infectious etiology[33], but negative findings are more difficult to interpret[14]. The presence of granuloma is considered a hallmark of systemic infection even in the absence of positive microbiological findings. Positive PCR for Mycobacterium tuberculosis complex bacteria in the present two cases provided a definitive proof of disseminated infection. In

the literature, antituberculosis treatment has been used in several cases of patients with negative PCR or other microbiological investigation resulting in marked clinical improvement[18,21].

Interferon-gamma releasing assays are specific for Mycobacterium tuberculosis and should be negative in the case of infections with Mycobacterium bovis, including BCG, but positive results of interferon-gamma releasing assay have also been anecdotally reported in a patient with BCG pneumonitis, probably as a result of coincident tuberculosis infection that may not be exceptional in older individuals[18]. Given that antituberculosis therapy would be administered in any case under these circumstances, in patients with systemic BCG infection, the distinction between latent tuberculosis infection and active infection with Mycobacterium tuberculosis may not seem as important, although it could influence the selection of drug regimen.

The incidence of systemic BCG infection after intravesical therapy is probably below 1% (ref.[4]), and likely even lower. In a cohort of 2602 patients treated with intravesical BCG pneumonitis and/or hepatitis was observed in 18 cases (0.7%) (ref.[38]). In one prospective trial, lung infection was reported in 5 cases (0.4%). In a retrospective series of 200 patients, lung involvement was observed in a single case[39]. Only a single case was reported in another series of 106 patients[40]. In a small randomized trial comparing intravesical BCG with intravesical interferon-alpha, BCG pneumonitis was observed in one case out of 32 patients treated[41]. Compared to interferon-alpha, BCG markedly reduced the recurrence rate in that study. In other small cases series of patients treated with intravesical BCG, only individual cases of systemic BCG infection have been reported[42,43]. Among sites of systemic infection, lung involvement is the most common[24,44]. Granulomatous hepatitis has also been repeatedly reported[10,12,33], while the involvement of other organs like musculoskeletal system, aorta or other large vessels is even more rare and reported only anecdotally[15,16,44,45]. Cases involving both the lungs and the liver have been documented[32]. Manifestation of systemic infection range from asymptomatic to severe sepsis, and cases with fatal outcome have been reported[11,27]. Cases of multiple organ involvement including the lungs and the liver have been documented[17].

In the diagnostic evaluation, effort should be made to confirm the diagnosis by demonstrating the presence of BCG. Metastatic spread or complications of malignancy like pulmonary embolism should also be considered in the differential diagnosis[46]. In fact, one patient in the present series had both lung metastases and BCG granulomatous pneumonitis. Other rare disorders should also be considered. Selmi et al.[47] described a case of granulomatosis with polyangiitis in a patient after intravesical BCG treatment.

BCG is of low virulence in immunocompetent subjects. On the other hand, cancer is associated with secondary immune deficiency[48]. Moreover, cases of systemic BCG infection have been reported in patients with bladder carcinoma after kidney transplantation[22]. However, there are currently no clinical or laboratory parameters that would allow identification of individuals at risk of systemic BCG infection.

Combination of antituberculosis agents is recommended in the management of locoregional and systemic infection complicating intravesical BCG administration[6]. The use of corticosteroids has also been reported in the cases thought to be due to hypersensitivity response[13,49], in combination with antituberculosis agents[19,35,50], or after no improvement with standard antituberculosis therapy[51]. A case of acute eosinophilic pneumonia after intravesical BCG with a prompt response to corticosteroid therapy has been documented[52]. Standard combination regimen of antituberculosis agents was used to treat BCG infection in both cases described here. Spontaneous resolution of granulomatous pneumonitis after intravesical BCG therapy has been reported[23], but this approach is risky and the overwhelming body of literature supports active treatment. For obvious reason, prospective trials will probably never be performed in this rare situation and very heterogeneous patient populations, and case reports and review articles will remain the only source of information on the management. The patients described in the present report had a rare complication of BCG therapy that was manageable. At the same time the experience in both of these cases illustrates that tumor recurrence should be the most feared event in patients undergoing this treatment.

CONCLUSION

Systemic infection represents a rare, but potentially serious complication of intravesical BCG therapy for urinary tract cancer. This complication should be considered in all patients with a history of intravesical BCG therapy presenting with prolonged unexplained fever or other symptoms, and the patient should be promptly referred to further evaluation and treatment.

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