Case Series

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Tuberculosis as a Complication of BCG in Treatment of Bladder Carcinoma: A Case Series Study

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ABSTRACT

Bacillus Calmette-Guérin (BCG) is a live attenuated strain of Mycobacterium bovis, and it is the essential constituent of the vaccine against tuberculosis (TB) and adjuvant treatment for bladder cancer. This vaccine has a potential pathogenic action; bacilli can cause recorded complications that can be located near the site of inoculation, and at a distance through the blood dissemination root. The BCG-related disease can represent a side effect of anti-TB vaccination in patients with acquired or congenital immunodeficiency or a complication of the therapeutic oncologic schedule in patients with malignancy. Here, we report three cases of BCG-related disease, who visited our national tuberculosis Iraqi center in 2022, among whom two of them presented with locally developed TB and the third presented with disseminated miliary TB.

Keywords: BCG, Extra-pulmonary Tuberculosis, Miliary TB, Bladder carcinoma

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INTRODUCTION

In 2021, an estimated 10.6 million people fell ill with TB. The TB incidence rate (new cases per, 100 000 population, per year) rose by 3.6 % between 2020 and 2021. The burden of drug-resistant TB (DR-TB) is estimated to be 450 000 new cases of rifampicin-resistant TB (RR-TB) in 2021.Globally, the success rate for people treated for TB, in 2020, was 86 %.[1]

Among extra-pulmonary TB, Genitourinary tuberculosis (GUTB) is the second most common in most developed countries (20 % to 40 %) and the third most common in most developing countries.[2]

Urinary bladder tuberculosis (UB-TB) is one of the gravest public health issues of renal TB, and it is diagnosed in < 50 % of urogenital TB. Unsatisfactory and delayed diagnosis, with imprudent medications, for bladder TB frequently resulted in several urinary complications including contraction of the UB.[3]

Miliary tuberculosis (TB) is one of the severest forms of TB. Despite effective treatment, it continues to have a high mortality rate, which is likely to be a consequence of the dissemination of Mycobacterium tuberculosis bacilli, via the lymph and blood, to the tissues.[4]

Bacillus Calmette-Guérin (BCG) is a live attenuated strain of Mycobacterium bovis, which is part of the Mycobacterium Tuberculosis Complex (MTC). BCG vaccine strain was obtained from an isolate of Mycobacterium bovis, and it was used for the first time as a human vaccine in 1921.[5,6]

World Health Organization (WHO) recommends, as part of childhood immunization programs, a single dose of BCG vaccine in countries with high TB burden.[1]

The diagnosis of BCG-related disease is usually done with the following criteria: contact with BCG in the patient's medical history and least compatible clinical symptoms not otherwise explained.[7]

BCG post-vaccination-disease, in the pediatric patient, has its onset weeks or months after the vaccination. It comes with various patterns that are classified into regional (persistent ulcer, abscess, fistula, or lymphadenopathy limited to the region of inoculation), extra-regional (osteitis or cutaneous abscess), and disseminated disease.[8,9]

In 1990, Food and Drug Administration (FDA) approved BCG adjuvant therapy for recurrent, Non-Muscle-Invasive-Bladder Cancer (NMIBC). BCG immunotherapy is the gold-standard adjuvant treatment for NMIBC with high progression risk (stage T1 tumors, high-grade carcinoma, carcinoma in situ, and multiple and recurring stage T1 tumors > 3 cm), and it is also recommended for intermediate-risk NMIBC.[10-12]

Intra-vesical instillation of Bacilli Calmette-Guérin (BCG) has been established as an efficient therapy for superficial bladder carcinoma. In short, intra-vesical BCG is well tolerated and results in complications of less than 5 %. However, adverse effects such as granulomatous prostatitis, pneumonitis, hepatitis, sepsis, and hypersensitivity reactions may also occur. The reported rate for tuberculosis orchitis, after BCG intra-vesical therapy, is 0.4 %.[13]

Immunotherapy, with BCG, is generally considered safe, but post-instillation disease could occur, which could be both localized and disseminated.[14,15]

The guidelines of the European Association of Urology (EAU) suggest 6-weekly instillations, during an induction phase, followed by a maintenance schedule for optimal efficacy. The Southwest Oncology Group (SWOG) found highly significant benefits regarding recurrence-free survival, for a standard induction, followed by a maintenance phase of BCG, weekly once for 3 weeks, and at 3, 6, 12, 18, 24, 30, and 36 months after BCG induction as compared with BCG induction alone.[16]

The absolute contra-indications of BCG intra-vesical instillation are recent Trans-Urethral Resection (less than fourteen days), macroscopic hematuria, urinary tract infection, and traumatic bladdercatheterization.[17]

Gene-Xpert MTB/RIF® (Ultra) is a real-time polymerase chain reaction (PCR) assay (molecular assay) that was a major step forward in improving the diagnosis of TB and the detection of rifampicin resistance, and it was intended as the initial test for diagnosis of TB.[18]

About one-fourth of the world population has latent TB infection (LTBI); the majority of it is distributed in 22 high-burden countries & (90 %–95 %) of those who are infected with mycobacterium tuberculosis (MTB) remain healthy otherwise. These people are classified as "latent tuberculosis infected" (LTBI), and they remain a reservoir from which active TB cases will continue to develop "reactivation tuberculosis". Latent infection is defined by the absence of clinical symptoms of TB in addition to a delayed hypersensitivity reaction to the purified protein derivative of MTB used in tuberculin skin test or a T-cell response to MTB-specific antigens.[19]

There is no gold standard test to diagnose LTBI. Both currently available tests—TST and IGRA—are indirect and require a competent immune response to identify people infected with TB.[20]

Early diagnosis and treatment of active TB remain the top priority in resource-poor countries with high TB prevalence. Notwithstanding, because LTBI significantly contributes to the pool of active TB cases later on, its diagnosis and treatment are essential, especially in high-risk groups. The lack of a gold standard and several limitations of available tools, namely the tuberculin skin test and interferon-γ release assays, are major constraints for LTBI diagnosis.[21]

People who should receive treatment for LTBI include patients who initiate anti-Tumor Necrosis Factor (TNF) treatment, patients receiving dialysis or preparing for an organ transplant, silicosis patients, prisoners, health workers, immigrants from countries with height burdens, and homeless people.[22]

CASES PRESENTATION

CASE 1

Sixty-year-old female, diagnosed with urinary bladder papillary transitional cell carcinoma, in Baghdad Teaching Hospital, two years ago, subsequently received a four-week course of intra-vesical BCG (one dose per week). The last instillation was administered one week before she visited our center. The report sent by her urologist showed that she had a fever preceded by shivering, malaise, anorexia, irritative lower urinary tract symptoms, and severe hypotension leading to syncope. Physical examination revealed an increase in pulse rate, blood pressure, and respiratory rate. Investigatory

markers were in the normal range, and supportive treatment had been given to her in the hospital.

A recent Magnetic Resonance Imaging (MRI) report showed irregular asymmetrical thickening of the urinary bladder wall, to a maximum of 9 mm, with a focus of hypo-tense signal in T1, and it was seen at the anterior superior wall, measuring 12×5 mm, with surrounding soft tissue stranding mainly at the superior part of the urinary bladder.

The Quantiferon TB test was positive.

Histo-pathological biopsy showed transitional cell carcinoma high-grade infiltration in the underlying stroma stage, according to the American Joint Committee on Cancer (AJCC) staging manual of 2017.

Her medical history revealed that she had been vaccinated with BCG at birth.

A part of the biopsy, sent for Gene-Xpert, was positive.

Treatment was started with Isoniazid 300 mg, Rifampicin 600 mg, Ethambutol 1100 mg, and Pyrazinamide 1600 mg, daily once, and was continued for two months. Isoniazid 300 mg and Rifampicin 600 mg, daily once, were kept up for another four months, till the following visit, and all the symptoms improved smoothly within two months of treatment.

CASE 2

The second case was a sixty-eight-year-old male who was diagnosed with bladder papillary transitional cell carcinoma, at Al-Kindy Teaching Hospital, three years ago. He received six doses of the BCG vaccine one week apart. Two months after the sixth dose, the patient developed a low-grade fever, anorexia, and genitourinary tract symptoms including lower abdominal pain, urgency, frequency, and intermittent urination. He consulted his doctor, and a cystoscopy was done as an exploration, and a biopsy was taken. The results were as follows: urethral mucosa with mucosal ulceration, dense chronic inflammation by lymphocytes, epithelioid histiocytes with caseation granuloma, and scattered multinucleated Langerhans giant cell. The patient had a medical history of type 2 diabetes mellitus and uncontrolled hypertension.

Investigatory markers were in the normal range except for a decrease in hemoglobin, which was 10 g/dl.

The Quantiferon TB test was positive.

The patient started a full course of anti-TB drugs for six months, the fever subsided only after two weeks, and the other symptom improved gradually.

CASE 3

The third case was a fifty-five-year-old male who has been diagnosed with bladder papillary transitional cell carcinoma in a Baghdad Teaching Hospital. He received five doses of the BCG vaccine one week apart. After the last dose, the patient developed a low-grade fever, chills, fatigue, malaise, and night sweats associated with shortness of breath. The patient had a history of uncontrolled DM and hypertension for ten years.

Apart from general examination, nothing was relevant except for fever and increased respiratory rate.

X-ray was done for the patient, which showed a miliary pattern of the lesion (small nodular opacities measuring 1–2 mm in diameter) scattered throughout both lungs; the same finding of diffuse miliary infiltrate was found on chest high-resolution computed tomography and sputum examination for cytology, and the Acid-Fast Bacilli (AFB) was negative.

Investigatory markers were in the normal range except for elevation in erythrocyte sedimentation rate (ESR), which was 100 mm/hr.

The patient was diagnosed with a case of military TB and received anti-TB medication for six months. The patient showed a dramatic response within three weeks of starting the medication.

DISCUSSION

There is a large body of evidence demonstrating the superior efficacy of BCG in the treatment of bladder cancer when compared with Trans-Urethral Resection (TUR) alone or TUR and chemotherapy. The European Association of Urology (EAU) guidelines, in 2013, reported a total of five meta-analyses to substantiate this claim.[23]

The mechanism of the action of BCG, in bladder cancer, is still unclear and probably is specific to anti-BCG cell-mediated immunity. BCG triggers a variety of local immune responses that appear to correlate with antitumor activity. Studies of the immunological mechanism of BCG therapy showed that an intact immune system, particularly the cellular system, is required for anti-tumor activity because mycobacterial antigen presentation, by phagocytes to T helper cells, is the pivotal interaction.[24]

Thirty nine percent of the infection, post-BCG installation, presented as systemic, and 61% were in the genitourinary tract.[25]

Two of our cases were tuberculosis cystitis and one was miliary tuberculosis.

Urogenital tuberculosis affected more men, than women (2:1), with a mean age of 40.7 years (range 5–88 years).[21] Two of our cases were male and one was female. All of them were with a mean age of 50–70.

We recorded the medical history of each patient and performed microbiological and immunological tests. To prove the mycobacterial infection, we obtained specimens for staining for acid-fast bacilli, culture, and Polymerase Chain Reaction (PCR) testing for mycobacterial DNA. The results were positive, for staining, for acid-fast bacilli (Ziehl-Neelsen), PCR, and granulomatous inflammation with or without caseous necrosis.

The two cases, with tuberculosis cystitis, were clinically diagnosed by biopsy and Quantiferon TB test, and the case of military TB was clinically diagnosed by chest X-ray.

The predisposing factors for developing BCG infection, after intra-vesical instillation, are still unclear, but it is supposed that trauma on the bladder mucosa, during the procedure and its previous state, concurrent urinary infections, and catheterization are more likely to play a major role rather than other factors such as the BCG dose, the number of treatment courses, or the interval that elapsed since the last preceding Trans-Urethral Resection (TUR).[26]

The optimum number of BCG instillations, during the induction period, is unknown. Four, rather than six, weekly instillations of BCG might be sufficient to maximize the peripheral response in patients previously immune to mycobacterial antigens. However, patients not previously immunized against mycobacterial antigens might require the full six weekly instillations to achieve a maximum level of stimulation.[27]

The first case developed tuberculosis cystitis after one week from the fourth dose, while the second case developed the disease one month from the sixth dose, and the third case developed TB after the fifth dose of the BCG vaccine.

The key to appropriate management of complications of BCG therapy is awareness of their possibility even months or years after the therapy has been given. Appropriate empirical therapy, in acute situations, and mycobacterial culture in chronic situations can then be performed.[28]

CONCLUSIONS

Intra-vesical instillation of the BCG vaccine should be considered, according to the disease state and patient basis, with full patient knowledge of the potentially significant risks. Screening with a Quantiferone TB test, before starting the first dose of BCG vaccine instillation, should be recommended and Isoniazid with Rifampicin could be indicated as the treatment for latent tuberculosis infection.

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