Penile lesion with inguinal adenopathy after intravesical Bacillus Calmette-Guerin instillation therapy

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ABSTRACT

Intravesical Bacillus Calmette-Guérin (BCG) is widely used as an adjuvant therapy in the treatment of non-muscle-invasive bladder cancer. BCG is generally well tolerated, though localized and systemic infectious complications may occur. Infection of the glans and inguinal adenopathy are rare local complications of intravesical BCG therapy. Traumatic urethral catheterization is one of the main causes. We report the case of a 75-year-old male who developed granulomatous balanitis and enlarged inguinal lymph nodes after five cycles of intravesical BCG treatment for transitional cell carcinoma of the bladder. Histology revealed giant cell granuloma. Oral antituberculous treatment was initiated with subsequent full recovery of penile lesions and adenopathy. Physicians who administer BCG must be familiar with the possible complications and their adequate management and should inform patients about the side-effects accordingly.

Key words: Bladder cancer, Bacillus Calmette-Guerin, balanitis, complication, intravesical treatment

INTRODUCTION

Intravesical instillation of Bacillus Calmette-Guerin (BCG) is an established option for the treatment and prophylaxis of non-muscle-invasive bladder cancer. Complications with this therapy are not rare ranging from local reactions to sepsis. Low-grade fever and irritative bladder symptoms are common side-effects of intravesical BCG instillation therapy. Penile lesions or balanitis as complications of BCG treatment have been reported in a few cases. In this report, we present a patient who underwent intravesical treatment with BCG and subsequently developed penile lesions and bilateral inguinal lymphadenopathy.

CASE REPORT

A 75-year-old patient presented with complaint of hematuria. Ultrasonography revealed a solid 2-cm mass on right wall of the bladder. Cystoscopy confirmed bladder tumor and patient underwent transurethral resection of bladder tumor. The pathologic diagnosis was pTa, G2 transitional cell carcinoma and carcinoma in situ (WHO 1973). He was offered six weeks of BCG instillation (OncoTICE®, Tice Strain, administered intravesically after reconstitution in 50 ml saline). The patient was unable to complete the treatment cycles consecutively due to severe irritative symptoms; hence at the second and fourth week, treatment cycles were cancelled for a period of one week and his symptoms were treated with antibiotics and antispasmodics. Urine cultures were negative for bacterial colonization but pyuria was present at urine analysis. He had no gross hematuria, fever or chills. He was administered five cycles of BCG at full dose, atraumatically, by a staff urologist using a 12Fr hydrophilic Nelaton catheter. There was no external spillage during the administration of BCG. One week after the last instillation the patient reported penile swelling and tenderness, itching at suprapubic areas. Two days later, he presented with a penile lesion and indurated lesions at the suprapubic area. Physical examination demonstrated two areas of painless indurated lesions at the pubic area and shallow ulceration on the penil shaft (Figures 1a and b) and bilateral palpable inguinal lymphadenopathy. He had low-grade fever without chills. He had no history of tuberculosis, diabetes or immunodeficiency. Chest X-ray was unremarkable and computed tomography (CT) of abdomen revealed bilateral inguinal adenopathy (maximal...
length of diameter 1cm on the left and 1,5 on the right side). Laboratory data showed slight elevation of C-reactive protein and erythrocyte sedimentation rate, and otherwise blood chemistry was normal. Polymerase chain reaction (PCR) for urine tubercle bacilli was negative, and thereafter urine cultures were also negative for mycobacterium.

The patient underwent diagnostic biopsy from the papules of pubic areas and cystoscopy at the same time. Cystoscopy showed several erythematous areas in the bladder and cold-cut biopsy was obtained from these areas. Pathology of the bladder biopsies revealed acute and chronic inflammation with granulomatous changes; there was no evidence of malignancy. The pathologic examination of biopsy samples from endurated pubic lesions demonstrated granulomatous inflammation with caseous necroses [Figure 2] and multinucleated giant cells of Langhans type, which was compatible with BCG-induced granulomatous skin infection.

Intravesical BCG instillation therapy was discontinued and the patient was given a three-drug antitubercular regimen including rifampicin, isoniazid, and pyrazinamide. The total treatment course was six months, with discontinuation of pyrazinamide after two months. Complete resolution of penile, pubic lesions and inguinal adenopathy was achieved at six months of treatment [Figures 1c and d]. Follow-up cystoscopy showed no evidence of tumor recurrence and CT of abdomen and chest X-ray were unremarkable.

**DISCUSSION**

After BCG instillation systemic side-effects can occur. Side-effects of BCG usually occur when BCG is given immediately after transurethral resection of a bladder tumor, or when the patient had a traumatic catheterization or concurrent cystitis during intravesical instillation. Use of immunosuppressive agents or genetic factors may also play significant role. During the instillation cycles of BCG, our patient developed pain and cystitis symptoms. Urine culture was negative however this may not preclude urinary tract infection and may have predisposed to BCG side-effects. Although catheterization was atraumatic in the present case unnoticed trauma during catheterization could have played a role in the BCG toxicity determined in our patient. Although our patient had no co-morbidities such as diabetes or immunosuppression, his older age may have been a factor for the progression of side-effects.

Granulomatous reaction associated with BCG treatment is known to occur in the bladder, epididymis, prostate, kidney, lung and liver.\(^1\,^2\) However, occurrence of balanitis is uncommon and only a few cases of balanitis associated with BCG instillation have been reported.\(^3\) Granulomatous balanitis symptoms include penile edema, papules and ulcers, occasionally associated with inguinal lymphadenopathies as in our case. *Mycobacterium tuberculosis* complex may not be identified by cultures or by Ziehl–Nielsen stains in the granulomatous changes.\(^2\) Therefore, clinical diagnoses are made in the majority of cases by histopathology and by the history of BCG therapy. Although the stain and culture were negative for mycobacterium, given the recent history of intravesical instillation of BCG, these lesions likely represent dissemination of inoculums. The mechanism of infection presumably occurred via direct inoculation of the penis during the instillation of BCG, followed by dissemination to the superficial inguinal lymph nodes. Histological appearances of these changes typically show epithelioid granuloma with central necroses and giant cells of Langhans type as determined in our case.

As BCG-induced penile ulcer and adenopathy is a rare complication of intravesical BCG therapy, treatment for this disease is not yet standardized. However, modern short-course anti-tuberculosis drug regimens for genitourinary tuberculosis are also recommended for the treatment of such cases. According to the World Health Organization
anti-tuberculous drug treatment is based on an initial two-month intensive phase of treatment with three or four drugs with rifampicin, isoniazid, pyrazinamide, and ethambutol to destroy almost all tubercle bacilli. Treatment is followed by a four-month continuation phase with only two drugs, rifampicin and isoniazid. In our case, complete resolution of penile lesions and adenopathy were achieved at the end of treatment.

Adverse effects of BCG intravesical administration affect several organs in the genitourinary system and can disseminate to distant organs. The clinician must be alert to any complaints the patient has after treatment, and investigate accordingly. Physicians should be aware of the possibility of BCG-induced granulomatous balanitis and concomitant adenopathy. When these clinical features appear in patients, adequate therapy should be started as soon as possible. We consider that immediate antituberculous therapy should be commenced to achieve prompt resolution and management of clinical findings.

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How to cite this article: Aslan G, Sevinc C, Tuna B, Ozkal S, Yorukoglu K. Penile lesion with inguinal adenopathy after intravesical Bacillus Calmette-Guerin instillation therapy. Indian J Urol 2013;29:70-2.

Source of Support: Nil, Conflict of Interest: None declared.