A Rare Case Report of BCG Induced Balanitis in a Patient with Transitional Cell Carcinoma of Urinary Bladder

Abstract
Primary Bacillus Calmette–Guérin (BCG) infection of the glans penis is not a very common entity and has been rarely reported in literature. BCG has been used as an adjuvant therapy in patients of transitional cell urinary bladder carcinoma following transurethral resection of bladder tumor. We report a 66-year-old male patient who was being managed for urinary bladder carcinoma with nine sittings of adjuvant BCG therapy. He developed painless swelling with multiple pustules over glans penis and prepuce along with inguinal lymphadenopathy. He had a BCG inoculation scar over his arm and his chest X-ray was within normal limits. His workup for sexually transmitted disease was negative. The biopsy from the nodule on prepuce revealed mixed inflammatory infiltrate comprising of neutrophils, lymphocytes, and eosinophils along with numerous congested blood vessels and hemosiderin macrophages. Mycobacterium tuberculosis gene expert from tissue was positive for acid fast bacilli (AFB). Fine-needle aspiration cytology from the right inguinal lymph node also revealed AFB on Ziehl–Neelsen stain. The BCG immunotherapy was stopped and the patient was started on a standard four-drug antitubercular therapy comprising isoniazid, rifampicin, ethambutol, and pyrazinamide along with daily doses of pyridoxine. The edema resolved and papules subsided within 2 weeks after starting antitubercular therapy. This is a very rare presentation although intravesical BCG therapy is a very common treatment modality, hence this report is intended to increase awareness of this condition in dermatologists and venereologists.

Keywords: Bacillus Calmette–Guérin, balanitis, Mycobacterium tuberculosis

Introduction
In 1921, Bacillus Calmette–Guérin (BCG) vaccine was first introduced in humans.[1] It is a live attenuated strain of Mycobacterium bovis. In 1976, Marales used BCG intravesically for treating superficial transitional cell carcinoma of the urinary bladder.[2] BCG as an immunotherapy agent led to variable complications, out of which the rarest is the development of disseminated BCG disease. It manifests in the form of sepsis, soft-tissue infections, miliary pneumonitis, granulomatous hepatitis, and bone marrow involvement.[3] Symptoms related to the above-mentioned complications after BCG therapy were seen at variable periods, some of them presenting early while a few were presenting late. Primary BCG infection of the glans penis is not a very common entity and has been reported in the literature.[3,14]

The exact mechanism of action of use of BCG in bladder carcinoma is not fully understood, however, BCG-induced T-lymphocytes-dependent antitumor effect has been proposed as the modality of action.[2] Transurethral resection of bladder tumor (TURBT) is the standard mode of treatment for transitional bladder carcinoma but it has a high recurrence rate which ranges from 48 to 70%.[1] Intravesical BCG is now considered as an adjuvant therapy in patients of carcinoma bladder following TURBT which certainly reduces the tumor recurrence. The primary infection of the glans penis with BCG following its intravesical spray is extremely rare and we report one such case in a patient with bladder carcinoma being managed with intravesical BCG therapy following TURBT. We took informed consent from our patient before publication of this report.

Case Report
A 66-year-old male who was diagnosed as a case of transitional cell carcinoma of the urinary bladder was managed with TURBT...
about 1 year back. This was followed by 6 weekly doses of intravesical injections of Bacillus Calmette Guérin (BCG) vaccine (80 mg). Following a gap of 6 months after the first cycle, the next cycle of BCG vaccines was initiated. After 10 days of his last BCG injection (ninth dose), the patient developed painless swelling and pus-filled lesions over the glans penis and prepuce. During this last therapy, there was difficulty in inserting the urinary catheter due to the diffuse prepucial edema. Over the next 2–3 days, he developed multiple asymptomatic yellowish pustules, tiny raised red lesions, and deep-seated nodules over the penis. An examination revealed diffuse edema over the entire penis including the glans. There were multiple, firm, indurated, nontender papules, and a few deeper nodules and pustules on the proximal part of glans penis [Figures 1 and 2]. He had multiple nontender non-matted bilateral enlarged inguinal lymph nodes with the largest measuring about 5 cm on the right side. There was no urethral discharge and no generalized lymphadenopathy. He had a BCG inoculation scar over the left arm.

There was no history suggestive of tuberculosis, sexually transmitted diseases, or high-risk sexual behavior. The patient had low-grade fever and generalized malaise on presentation but there was no history of cough or weight loss. Chest X-ray and Mantoux were within normal limits. HIV antibody and Venereal Disease Research Laboratory (VDRL) tests were negative. His RT-PCR for COVID-19 was negative. The biopsy from nodule on prepuce revealed mixed inflammatory infiltrate comprising of neutrophils, lymphocytes, and eosinophils along with numerous congested blood vessels and hemosiderin macrophages [Figure 3]. No mycobacterium was visualized in the Ziehl–Neelsen staining of the histopathology specimen. MTb gene expert from tissue was positive for the Mycobacterium tuberculosis complex. Fine-needle aspiration cytology from the right inguinal lymph node also revealed AFB on Ziehl–Neelsen stain along with some scattered macrophages in the background of the hemorrhage.

The BCG immunotherapy was stopped and the patient was started on standard four-drug antitubercular therapy comprising isoniazid, rifampicin, ethambutol, and pyrazinamide along with daily doses of pyridoxine. The edema resolved and the papules started subsiding within 2 weeks after starting antitubercular therapy [Figure 4].

**Discussion**

BCG is a live, attenuated intradermal vaccine primarily used to provide protective immunity against tuberculosis. Although BCG vaccine is usually a safe vaccine in children, many complications have been reported, such as adverse
local reactions, regional lymphadenitis, osteomyelitis, and disseminated infection in immunocompromised children, with lymphadenitis being one of the most common complications. Intravesical instillation of BCG is widely accepted as an adjuvant immunotherapeutic modality of in situ and superficial transitional cell carcinoma of the urinary bladder. Literature reports also suggest the use of BCG immunotherapy for the treatment of malignant melanoma. A large number of local and generalized adverse effects have been reported following its use in bladder carcinoma. Nonspecific dermatological manifestations include generalized maculopapular eruption, erythema multiforme, urticaria, and protracted ulceration. Specific dermatoses include lupus vulgaris, papulonecrotic tuberculosis, lichen scrofulosorum, development of basal cell carcinomas, and disseminated cutaneous tuberculid granulomas. Systemic side effects include minor reactions like low-grade fever, cystitis, hematuria, malaise, and vomiting. Major side effects include high-grade fever, hepatitis, granulomatous pneumonitis, bladder contracture, renal abscess, and fatal sepsis. Presentation of balanitis with penile papules and ulcers is an extremely rare occurrence. Konohana et al. in 1992 first reported a case of balanitis post intravesical BCG therapy and they could isolate Mycobacterium tuberculosis on culture, and since then, 13 cases have been reported in the literature. The summary of the patients and the clinical response is summarized in Table 1. This is just the second patient reported in Indian literature despite the high prevalence of tuberculosis and a large number of cases of urinary bladder carcinoma being managed with adjuvant BCG therapy in India since 1988. Most of the patients reported in the literature developed these lesions after 3–16 sittings of intravesical BCG therapy and granulomatous histopathology was the most common presentation as was noted in our case. Our patient also had presented with lesions similar to the ones reported in the literature and had inguinal lymphadenopathy. French et al. postulated these lesions as papulonecrotic tuberculids, however, in our case, positive gene expert result strongly suggests these cases as inoculation tuberculosis rather than a tuberculid. Response of treatment to anti-tubercular therapy and localized swelling and induration suggests a primary tubercular infection with regional inguinal lymphadenopathy. Patients with bladder carcinoma have an underlying immunodeficiency which predisposes them to this presentation and the route of inoculation is most likely the outward flow of urine from the bladder. Traumatic catheterization has also been suggested as a mechanism for direct inoculation of BCG, however, in our case, traumatic catheterization was secondary to prepucial edema which developed after the development of pustules over the glans along with inguinal lymphadenopathy. This case highlights the presentation of BCG inoculation tuberculosis as a rare entity and dermatologists and venereologists should be aware of this clinical scenario in patients with urinary bladder carcinoma treated with adjuvant BCG chemotherapy. Granulomatous balanitis is the most widely reported penile complication, after multiple cycles of BCG used as an immunotherapy intravesically in transitional cell carcinoma, presenting with symptoms like penile edema, papules, nodule, and ulcers, along with inguinal lymphadenopathies. The occurrence of skin lesions has a variable timeline ranging from early to 1 year after the last BCG instillation. There is no definite mechanism identified for the dissemination of infection. However, trauma while urethral catheterization prior to BCG instillation has been thought to be the most likely cause of
Table 1: Profile of patients with Bacillus Calmette Guérin-induced granulomatous balanoposthitis following intravesical therapy

| Ref No | Age of patient (years) | Total BCG sitings | Difficulty in catheterization | Inguinal lymph node | Acid fast bacilli | Treatment | Time of response |
|--------|-----------------------|-------------------|-------------------------------|--------------------|------------------|-----------|-----------------|
| 3      | 63                    | --                | Enlarged                      | Positive           | Rifampicin + Isoniazid: 6 months | 6 months |
| 6      | 29                    | 16                | Present                       | Enlarged           | Rifampicin + Isoniazid + Ethambutol: 9 months | 2 months |
| 7      | 52                    | 6                 | --                            | Positive           | Rifampicin + Isoniazid + Ethambutol: 3 months | Quick |
| 8      | 60                    | 3                 | Absent                        | --                 | Isoniazid 3 months | 6 weeks |
| 8      | 67                    | 4                 | Absent                        | --                 | Rifampicin + Isoniazid: 3 months | 6 weeks |
| 9      | 65                    | 6                 | Absent                        | Positive           | Isoniazid + Ethambutol: 6 months | 6 months |
| 10     | 67                    | 5                 | Present                       | --                 | Rifampicin + Isoniazid: 3 months | 3 months |
| 11     | 77                    | 7                 | Absent                        | --                 | Rifampicin + Isoniazid: 12 months | 1 year |
| 11     | 61                    | 6                 | Present                       | --                 | Rifampicin + Isoniazid + Ethambutol: 3 months | 6 weeks |
| 12     | 69                    | 6                 | Absent                        | Not Enlarged       | Negative         | Isoniazid 12 months | 1 week |
| 13     | 58                    | 7                 | Present                       | Enlarged           | Positive         | Rifampicin + Isoniazid + Ethambutol: 6 months | 2 weeks |
| 14     | 75                    | 10                | Absent                        | Enlarged           | Positive         | Rifampicin + Isoniazid + Ethambutol + Pyrazinamide: 6 months | -- |
| 16     | 55                    | 6                 | Present                       | Enlarged           | Positive         | Rifampicin + Isoniazid + Ethambutol + Pyrazinamide: 2 months followed by 4 months of Rifampicin + Isoniazid | Presently recovering after 4 weeks |

infection. In our patient also there was pain and difficulty while insertion of catheter prior to the BCG instillation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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